A poor sleep-wake cycle is associated not only with low testosterone but also with abnormalities in progesterone, prolactin, cortisol, dopamine, norepinephrine, and adrenocorticotropic hormone. Improving the sleep-wake cycle is vital in improving hormone balance.

Nutrition

Following a diet focused on limiting insulin resistance is important. As previously described, low testosterone is closely associated with insulin resistance, metabolic syndrome, and type 2 diabetes. I recommend that my patients eat smaller meals every 2 to 3 hours to maintain a steady blood glucose level. The meals and snacks should consist of lean proteins (e.g., poultry, fish, beef, nuts, eggs, and beans), vegetables and high-fiber fruits, and monosaturated and polyunsaturated fats. To avoid pesticide, antibiotic, and xenohormone exposure, consumption of organic foods is important.

In addition, patients should avoid refined carbohydrates and sugar as found in sweets, soft drinks, cookies, breads, and pastas (see Chapter 85, The Glycemic Index/Load). Ethanol is known to increase cortisol, reduce LH, and reduce testosterone production. It was originally thought to do so by directly affecting the hypothalamic-pituitary axis.[119,120] However, a study by Emanuele et al[121] demonstrated that the suppression of the reproductive axis is independent of the hypothalamic-pituitary axis. Therefore, limitation of alcohol also optimizes testosterone therapy and treatment.

Exercise

Exercise, especially resistance training, is an important adjunct to testosterone therapy and prevention of osteoporosis. Testosterone is one of the most potent androgenic-anabolic hormones, and its biologic effects include promotion of muscle growth. In general, testosterone concentration is elevated directly following heavy resistance exercise in men.[122] Resistance exercise has been shown to elicit a significant acute hormonal response. Anabolic hormones such as testosterone and growth hormone have been shown to be elevated 15 to 30 minutes after exercise as long as adequate stimulus has been given. Protocols high in volume, moderate to high in intensity, with easy short rest intervals and stress in a large muscle mass, tend to produce the greatest acute hormone elevations.[123] Specifically, training involves frequent repetitions of moderate weight, and the dynamic components tend to produce its beneficial results.[124]

One of the most efficient ways to increase endogenous testosterone is through regular resistance exercise.

Kraemer et al[125] were able to show that trained individuals could exhibit early-phase endocrine adaptations during a resistance training program. Their protocol consisted of 1 week of preconditioning orientation followed by 8 weeks of heavy resistance training. Serum total testosterone concentrations were significantly higher for men at all points measured, and exercise-induced increases in growth hormone over the preexercise values were observed at all phases of training.[125] Another study looked at the effect of circadian rhythm in the interactions of cortisol and testosterone with resistance training.[126] Elevated postexercise testosterone concentrations can be modulated by dietary nutrients such as adequate fat and an appropriate protein-to-carbohydrate ratio.[127,128]

Pharmaceuticals: Hormonal Therapy

Testosterone Therapy Overview

Testosterone therapy has been shown to alleviate certain symptoms associated with low testosterone. Before prescribing testosterone therapy, the clinician should document the diagnosis of hypogonadism, make a list of signs and symptoms to support a diagnosis, and evaluate the patient for possible causes and complications of hypogonadism. A complete hormone profile and general health panel should also be reviewed, and attention should be paid to balancing all hormones, especially cortisol and insulin. Pay close attention to the prolactin level because a prolactinoma can cause low testosterone. In addition, as previously described, the patient must optimize lifestyle factors to support testosterone therapy further.

Box 34-6 lists considerations before initiating testosterone therapy. The clinician should discuss with the patient the possible therapeutic modalities including creams, gels, patches, injections, and so on, to determine which modality he wishes to use. If the patient wishes to maintain his fertility, hCG must be used to stimulate his natural production of testosterone. Testosterone replacement will reduce sperm count and inhibit fertility. For hCG to work, testicular function must be intact. Therefore, the LH level should be in the normal range. Contraindications to therapy are listed later in this chapter. Obviously, it is prudent not to start testosterone therapy in a patient with a contraindication.

Testosterone Cypionate, Propionate, and Enathenate Esters

The most commonly used forms of androgen replacement therapy include 17β-hydroxyl esters of testosterone administered with slow-release, oil-based vehicles. Commonly used intramuscular injectable testosterone esters are testosterone enanthate, propionate, and cypionate.[129–131] The different esters absorb at various rates and have different half-lives.

BOX 34-6. Considerations for Initiating Testosterone Therapy

What form will the patient use (gel, injection, pellet, patch)?
Does the patient wish to maintain his fertility?
What is the testicular function?
What lifestyle changes does the patient need to make?
Does the patient have a contraindication to therapy? (see Box 34-8)

Dosage

Testosterone cypionate is one of the most widely used intramuscular testosterone esters. At a dose of 200 to 250 mg, the optimal injection interval is 2 to 3 weeks, but peak and trough values are clearly higher and lower than the normal range.[129] More often, it is dosed more frequently at 50 to 100 mg once or twice a week, to avoid the high peaks and troughs. In addition, it can be dosed subcutaneously at 30 to 50 mg twice a week. Many of my patients tolerate subcutaneous administration well. It is easy for them to self-administer and does not cause significant peak or trough symptoms.

Topical Testosterone Creams and Gels

Commercially available testosterone products on the market include testosterone gels, AndroGel and Testim, and the Androderm testosterone patch. Transdermal administration delivers testosterone at a controlled rate into the systemic circulation by avoiding hepatic first pass and reproducing the diurnal rhythm of testosterone secretion, without the peak and trough levels observed in long-acting testosterone injections.[132] These patches have a reservoir containing testosterone with a permeation-enhancing vehicle and gelling agents. Clinical efficacy is as good as with conventional testosterone ester injections.

Dosage

Testosterone gels and creams can be made by compounding pharmacies in any dosage requested. I find that my compounded dosages are much lower than those currently available on the market. Transdermal creams are well absorbed in most men and are easy to apply. These creams should be applied to the upper torso in areas with a reduced amount of hair. Because hair follicles and the skin of the scrotum contain 5-alpha-reductase, keeping cream or gel application away from those areas will limit testosterone conversion to DHT. I usually compound testosterone creams and gels in dosages from 10 to 30 mg per day. However, dosages reported in the literature range from 10 to 300 mg per day.[133]

Patients should be counseled to rub cream or gel in carefully for maximal skin absorption. In addition, they should avoid putting creams, lotions, or bath oils over the area where the testosterone has been applied, so these substances do not interfere with absorption. Special consideration should be given to men who have small children or animals in the house because the testosterone creams and gels can be transferred to others. He should avoid applying the testosterone to the skin areas with a large potential for contact with others. It is best to apply it to the upper chest and arms, immediately put a shirt on to cover the area, wash hands with soap, and use a separate hand towel.

Precautions

The most common adverse effect is local skin reactions. Fifty percent of men participating in a clinical trial reported transient, mild to moderate erythema at some time during therapy.[134]

Testosterone Pellets

Subdermal pellet implantation was among the earliest effective treatment modalities for clinical use of testosterone and became an established form of androgen replacement by 1940. Testosterone pellets, or subdermal implants, offer the longest duration of action with prolonged, zero order, steady-state characteristics. Implantation requires a minor office procedure, and, once implanted, the pellets last 4 to 7 months, depending on activity and stress level.

Dosage

The standard dosage is 800 to 1000 mg subdermally every 4 to 7 months.

Precautions

Potential drawbacks of the pellet include the need for the physician to be trained in its insertion, the risk of infection from the procedure, the inconvenience of pellet extrusion, and the inability to remove the pellet if a contraindication to testosterone therapy develops.[135]

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a polypeptide hormone produced by the placenta, containing an alpha and a beta subunit. The alpha subunit is essentially identical to the alpha subunits of LH and FSH, so it has the ability to stimulate the testes to produce more testosterone. In addition, because exogenous testosterone is not being given, it can avoid the testosterone replacement side effects of lower sperm count and loss of testicular volume. hCG alone, with no exogenous testosterone, is the preferred therapy for hypogonadal men younger than 40 years old who have adequate testicular function. Tsujimura et al[136] discussed a testosterone replacement method using 3000 units subcutaneously every 2 weeks. These investigators noted that total, free, and bioavailable testosterone increased by 25%, and symptoms improved.[136] Saez et al[137] showed that after the administration of hCG, plasma testosterone increased sharply within 4 hours and then decreased slightly and remained at a plateau for least 24 hours. A delayed peak of testosterone was seen between 70 and 96 hours. Thereafter, testosterone declined to the initial levels at 144 hours.[137]

Dosage

The most common dosages used are between 2000 and 5000 units subcutaneously per week. I usually use approximately 1000 units subcutaneously once to twice per week.

Precautions

Although hCG can increase testosterone and avoids the side effects of testicular atrophy and low sperm count, the long-term risks of giving men a female pregnancy hormone is unknown, and precaution should be taken.

Progesterone

Progesterone has not been as thoroughly studied in men as it has in women. Progesterone is the third hormone in the cascade starting from cholesterol and is the precursor to cortisol, testosterone, and estrogen. In healthy men, progesterone production is approximately 1.5 to 3 mg per day, and the hormone is produced almost entirely by the adrenal glands. As men age, progesterone production decreases.[138] However, it does not decline as rapidly as DHEA or pregnenolone. Progesterone helps reduce the level of estradiol in the blood by increasing the conversion of estradiol and estrone, which is 10 to 12 times less active than estradiol.[139] Thus, progesterone deficiency can be seen in diseases that are associated

with estrogen excess such as gynecomastia, ischemic heart disease, BPH, and, possibly, prostate cancer.[140]

Progesterone is also known to reduce the level of DHT in the blood and the prostate by competing for the 5-alpha-reductase enzymes where it is converted into 5-alpha-dihydroprogesterone. This, in turn, limits the ability of 5-alpha-reductase to turn testosterone into DHT.[141] Progesterone also has a calming effect on the body. When it is given orally, its metabolites, pregnenolone and allopregnenolone, increase relaxation by stimulating the gamma-aminobutyric acid receptors. Progesterone has been used in men to help reduce insomnia.[142]

Possible Side Effects of Testosterone Therapy

The clinician must follow up the patient for the potential risks of testosterone therapy. Gynecomastia may occur if conversion of testosterone to estradiol is high. Therefore, clinicians should monitor estradiol levels, and as gynecomastia occurs, consider reducing testosterone dose, inhibiting aromatase (weight loss, quercitin, zinc, resveratrol, progesterone), and evaluating for other possible reasons of elevated estrogen such as alcohol use. Polycythemia is more likely to occur with injections. Hemoglobin and hematocrit should also be monitored, especially earlier in therapy. If the patient has a hematocrit greater than 55, testosterone therapy should be stopped, or therapeutic phlebotomy should be recommended (donate 1 unit of blood). This situation is more often seen in men with chronic obstructive pulmonary disease or sleep apnea and in smokers. Rhoden and Morgentaler[143] noted that "it is reassuring that as far as we can determine, no testosterone associated thromboembolic event has been reported to date." Reduced testicular volume may be a cosmetic issue to some men but is reversible with cessation of therapy (Boxes 34-7 and 34-8).

Prostate-Specific Antigen

PSA is a 34-kDa glycoprotein manufactured almost exclusively by the prostate gland. PSA is produced for the ejaculate, in which it is thought to help with the liquefaction of the semen in the seminal coagulum, which allows sperm to swim freely.[144] PSA is also believed to be useful in dissolving the cervical mucus cap, thus allowing the entry of sperm. It is present in small quantities in the serum of men with healthy prostates, but it is often elevated in prostate cancer and in other prostate disorders. PSA levels can increase with prostatitis, irritation, BPH, and recent ejaculation, thereby producing a falsely elevated result.[145]

BOX 34-7. Potential Adverse Effects of Testosterone Therapy

Polycythemia
Gynecomastia
Fluid retention
Reduced testicular volume
Decreased sperm count
Elevated prostate-specific antigen
Stimulated prolactinoma growth

BOX 34-8. Contraindications to Testosterone Therapy

Active prostate carcinoma
Breast cancer
Prostatic nodules or indurations
Unexplained prostate-specific antigen (PSA) elevation
Erythrocytosis (hematocrit greater than 50)
Unstable congestive heart failure
Severe, untreated sleep apnea

From Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag.* 2009;5:427–448.

PSA should not rise significantly as a result of testosterone therapy. With the start of therapy, patients may have a small increase of approximately 0.2 ng/mL. The first 3 to 6 months after initiating testosterone therapy is the most critical time for moderate effects on the prostate. Therefore, PSA levels should be monitored every 3 months for the first year of treatment. The clinician must also be mindful when comparing PSA levels from different laboratories or different techniques of measure.

Benign Prostatic Hypertrophy, Prostate Cancer, and Testosterone Therapy

BPH, a common disease in older men, is believed to be related to the androgens DHT and estrogens. The incidence tends to increase when serum testosterone levels fall and estrogens increase. Testosterone replacement therapy appears to have little effect on prostate tissue androgen levels and cellular function and causes no significant adverse effects on the prostate. At the present time no conclusive evidence indicates that testosterone therapy increases the risk of prostate cancer or BPH.[67,143]

Today, as documented in many reviews, nothing has been found to support the evidence that restoring testosterone levels within normal range increases the incidence of prostate cancer. In fact, the incidence of prostate cancer in men with primary or secondary hypogonadism who are treated with testosterone is lower than the incidence observed in the untreated eugonadal population.[146] Mounting evidence demonstrates a lack of association between testosterone therapy and prostate cancer progression.[147,148] Gould and Kirby[149] looked at the risk of testosterone therapy inducing prostate cancer as they reviewed 16 studies, some of which were placebo controlled. These investigators found no increased risk of prostate cancer over the background prevalence with up to 15 years of follow-up.[149] Rhoden and Morgentaler[143] concluded that there is "no compelling evidence at present to suggest men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases the risk. In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time in a man's life when testosterone levels decline."

Monitoring Therapy

Before starting testosterone therapy, clinicians must adequately diagnose and document male hypogonadism, with documentation of symptoms and physical examination with a digital rectal examination. In addition, clinicians should obtain necessary laboratory tests (see Box 34-5), and discuss lifestyle factors. Once therapy has started, I have follow-up in 1 month to discuss symptom improvement, potential side effects, lifestyle issues, and any other concerns. Patients then come in for a follow-up visit every 3 to 6 months until they are stable. After that time, they follow up every 6 months. During their follow-up visits, we review laboratory test results for total and free testosterone, complete blood cell count, PSA, estradiol, DHT, and any other laboratory abnormalities that are specific for the patient. I titrate testosterone and estradiol to stay within the physiologic range. I recommend that the patients undergo digital rectal examination every 6 months to monitor prostate health (Box 34-9).

Low free testosterone with a high estradiol level (greater than 30 pg/mL) suggests excess aromatase activity with conversion of testosterone to estradiol. Because most aromatase is found in fat cells, weight loss in the overweight patient is a key therapeutic tool (see also Box 34-2 for a list of aromatase inhibitors).

BOX 34-9. Recommend Urologic Consultation

Verified serum prostate-specific antigen (PSA) greater than 4.0 ng/mL
Increase in serum PSA concentration more than 1.4 ng/mL within any 12-month period of testosterone therapy
PSA velocity greater than 0.4 mg/mL/year using PSA after the first 6 months of testosterone therapy
Detection of prostate abnormality on digital rectal examination
American Urological Association prostate symptom score higher than 19

From Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag.* 2009;5:427–448.

Prevention Prescription

- Manage stress levels (see Chapter 93, Relaxation Techniques).
- Avoid sugars and refined carbohydrates to maintain insulin sensitivity.
- Eliminate food additives such as trans fats and high-fructose corn syrup.
- Eat whole foods every 3 hours by consuming lean proteins, vegetables, high-fiber fruits, and healthy fats.
- Get adequate sleep every night.
- Maintain ideal weight.
- Engage in interval and strength training exercises.
- Limit consumption of alcohol, which can increase the conversion of testosterone to estradiol.
- Avoid pesticides and environmental toxins: bisphenol A.
  - Do not microwave in plastic containers.
  - Use only containers marked with number 2, 4, or 5.
  - Do not use containers marked with number 3, 6, or 7 (PC).
  - Use number 7 (PLA) bottles when available.
  - Drink filtered water from BPA-free bottles or from ceramic or stainless steel bottles.
  - Limit canned soups, juices, and sauces; buy them in glass containers.
  - Do not drink or eat out of Styrofoam containers.
- Avoid pesticides and environmental toxins: phthalates.
  - The best way to avoid phthalates is to locate less toxic products and begin to use them.
  - A number of Web sites (e.g., www.LessToxicGuide.ca) provide information on phthalate-free products including cosmetics, shampoos, soaps, and household cleaning ingredients.

Therapeutic Review

Lifestyle

- Avoidance of toxin exposure A1
  - Encourage organic food consumption to reduce exposure to pesticides and persistent organic pollutants.
  - Encourage reduction in exposure to bisphenol A and phthalates.
- Stress reduction A1
  - Encourage the patient to practice the stress reduction techniques in Chapter 93, Relaxation Techniques.
- Maintenance of ideal weight
  - Specifically avoid buildup of abdominal and visceral fat that increases conversion of testosterone to estradiol. A1
- Adequate sleep A1

- Encourage the patient to get at least 7 hours of sleep at night.

- Diet 
  - Encourage the patient to eliminate refined carbohydrates and sugars.
  - Encourage the patient to eat smaller meals and snacks every 2 to 3 hours consisting of lean proteins, vegetables, high-fiber fruits, and healthy fats to maintain stable blood glucose levels.
- Exercise 
  - Encourage regular resistance training.

Note: If the patient is successful with the foregoing recommendations, replacement therapy is often not necessary.

Supplements

- Zinc: 25 to 50 mg per day (balance with 2 mg copper per day) 
- Saw palmetto: 160 mg once or twice per day 
- Chrysin: 1000 to 2000 mg per day orally; 100 to 200 mg per day transdermally 

Hormonal Therapy

- Testosterone 
  - Testosterone cypionate injections: 50 to 100 mg once or twice per week intramuscularly; 30 to 50 mg once or twice per week subcutaneously
  - Testosterone creams and gels: 10 to 30 mg per day (literature ranges from 10 to 300 mg per day)
  - Testosterone patch (commercial products more expensive than compounded products): Androderm, 2.5- to 5-mg patch each evening, starting with the 2.5-mg patch to the back, abdomen, thigh, or arm; AndroGel, 25 to 50 mg (25 mg/2.5 g, 50 mg/5 g) each morning; Testim, 50 mg/5 g applied each morning
  - Testosterone pellets: 800 to 1000 mg every 4 to 7 months (depending on symptoms and levels of testosterone)
- Human chorionic gonadotropin: 1000 units once or twice per week (as a single therapy); 250 units once or twice per week (when used as an adjunct to testosterone therapy) 
- Progesterone: 25 mg at night orally 
- Follow-up
  - Follow-up visits are scheduled every 3 months until levels are stable and then every 6 months.
  - Laboratory tests include total and free testosterone (bring up to physiologic levels), estradiol (bring down to physiologic levels), complete blood cell count (watch for polycythemia, hematocrit greater than 50), prostate-specific antigen (watch for elevation greater than 1.4 ng/mL in 12 months while on testosterone therapy), DHT (if elevated, reduce testosterone dose or increase 5-alpha-reductase inhibition [see Box 34-1]).
  - Titrate testosterone to stay within the physiologic range.
  - If estradiol is high, encourage therapies that inhibit aromatase (weight loss, progesterone, zinc, grape seed extract) or reduce the testosterone dose if levels are elevated.
  - Patients should undergo digital rectal examination every 6 months to monitor prostate health.
- Contraindications to testosterone therapy
  - Active prostate carcinoma
  - Breast cancer
  - Prostatic nodules or indurations
  - Unexplained prostate-specific antigen elevation
  - Erythrocytosis (hematocrit greater than 50)
  - Unstable congestive heart failure
  - Severe, untreated sleep apnea

KEY WEB RESOURCES

WorldHealth.net information on testosterone: www.WorldHealth.net/list/news/testosterone

The American Academy of Anti-Aging Medicine is dedicated to the advancement of technology to detect, prevent, and treat aging-related disease and to promote research into methods to retard and optimize the human aging process. The section of this Web site on testosterone offers some articles and insights from leaders in the field.

Endocrine Society: www.endo-society.org

Founded in 1916, this group is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. Members of the Endocrine Society represent the full range of disciplines associated with endocrinologists: clinicians, researchers, educators, fellows and students, industry professionals, and health professionals who are involved in the field of endocrinology.

American Urological Society: www.auanet.org.	This organization, founded in 1902, is the premier professional association for the advancement of urologic patient care. It works to ensure that its more than 17,000 members are current on the latest research and practices in urology. If you search "testosterone" on the Web site, you gain access to articles and other information.
Harvard Newsletter on Male Hormone Replacement: http://www.health.harvard.edu/newsweek/Hormone-replacement-the-male-version.htm.	Harvard Health Publications is the publishing division of the Harvard Medical School of Harvard University. The goal is to bring people around the world the most current health information that is authoritative, trustworthy, and accessible, by drawing on the expertise of the 9000 faculty physicians at Harvard Medical School in Boston.
Environmental Working Group: www.EWG.org.	This organization's mission is to use the power of public information to protect public health and the environment. The group specializes in providing useful resources to consumers while simultaneously pushing for national policy change.

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Chapter 35

Hormone Replacement in Women

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A woman's hormonal response is as unique to her as her own fingerprints. Hormonal replacement at any age should not be considered without a thorough understanding of all the hormones in a body. The hormones are part of a symphony, and everything needs to be playing in tune. If one hormone is not in concert, then the patient will have a difficult time achieving optimal health. This chapter discusses the functions, symptoms of hormone deficiency, and symptoms of hormone excess with regard to estrogen, progesterone, and testosterone. Hormone replacement of estrogen, progesterone, and testosterone is also examined. Other hormones such as dehydroepiandrosterone (DHEA), cortisol, insulin, pregnenolone, prolactin, and thyroid are also part of the hormonal web but because of space constraints are not discussed in this chapter. Hormonal dysfunction can occur at any age. This chapter focuses on hormone replacement therapy (HRT) for women in the perimenopausal and menopausal years.

Perimenopause and Menopause

Menopause is defined as no menstrual cycle for 12 months. If a woman's hormones are out of balance, symptoms may begin many years before menopause. The symptoms of both perimenopause and menopause are similar (Box 35-1).

The normal age for a woman to go through menopause ranges from 35 to 55 years. Therefore, a woman may easily live one half of her life without a menstrual cycle. Some women have premature ovarian failure, which occurs when their ovaries stop producing an adequate amount of sex hormones before the age of 35 years (Box 35-1e).[1]

Box 35-1e, which lists causes of premature ovarian failure, can be found online at expertconsult.com.

Estrogen

Estrogen has 400 crucial functions in the body (Box 35-2).[2–54] The body has receptor sites for estrogen in many locations: brain, muscles, bone, bladder, gut, uterus, ovaries, vagina, breast, eyes, heart, lungs, and blood vessels (Box 35-2e).

Box 35-2e, which identifies symptoms of low estrogen, can be found online at expertconsult.com.

The patient can have excess estrogen levels in the body in relation to progesterone. This condition is called estrogen dominance. Estrogen dominance can result from the overproduction of estrogen or from an imbalance of progesterone to estrogen ratio. The symptoms of estrogen excess may also be the result of estrogen transformation, rather than the absolute amount of estrogen in the system (see the section on estrogen metabolism) (Box 35-3).[55]

Integrative Therapy (Hormones)

Synthetic Estrogens

Synthetic estrogens do not have the same chemical structure as hormones produced by the body and consequently do not fit into the estrogen receptors exactly as do natural estrogens.[56] Estradiol (E_2) that is produced naturally in a woman's body is eliminated within a few hours. Conversely, some synthetic estrogens (conjugated equine estrogen [Premarin]) have been shown to stay in the body for up to 13 weeks because the enzymes designed to metabolize the body's own estrogen do not break down synthetic estrogens as effectively.[57] Furthermore, the potency of synthetic estrogen is approximately 200 times that of natural E_2.[58]

BOX 35-1e. Causes of Premature Ovarian Failure

- Chronic dieting and eating disorders (anorexia, bulimia)
- Compulsive exercise
- Cigarette smoking
- Tubal ligation
- Hysterectomy without removal of ovaries
- Thyroid disorders
- Polycystic ovarian syndrome
- Viral oophoritis
- Postpartum status (may happen to women who are older when they deliver)
- Cessation of birth control pills after long-term use
- Toxic exposures: black widow spider bites, Lyme disease, pesticides
- High intake of soy
- High intake of excitatory amino acids (glutamate, monosodium glutamate, aspartame)
- Thin body structure (thinner women may have earlier onset)
- Vegetarian diet
- Malnutrition
- Living at high altitudes
- No history of pregnancy
- Genetic abnormalities
- Damage in utero from smoking, alcohol, pesticides, and other chemicals
- Recreational drug use (marijuana, cocaine, ecstasy)
- Chemotherapy
- Autoimmune diseases
- Radiation exposure
- Medications that disrupt the hypothalamic-pituitary-ovarian pathways (e.g., antidepressants, antipsychotics, and anticonvulsants)

Data from Vliet E. *It's My Ovaries, Stupid!* New York: Scribner; 2003:60–61.

BOX 35-2e. Symptoms of Low Estrogen

- Thin and aging skin
- Decrease in breast size
- Stress incontinence
- Oily skin
- Joint pain
- Elevated blood pressure
- Brittle hair and nails
- Acne
- Decreased sexual interest
- Decreased dexterity
- Increase in insulin resistance and possible diabetes
- Vaginal dryness
- Decreased memory
- Osteoporosis/osteopenia
- Urinary tract infections
- Increased cholesterol
- Restless sleep
- Low energy, especially at the end of the day
- Increase in tension headaches
- Dry eyes
- Increase in facial hair
- Bladder problems (more infections, urinary leakage)
- Thinning hair
- Weight gain around the middle
- Food cravings
- Difficulty losing weight even with exercise and diet
- Anxiety
- More frequent migraines

Data from Vliet E. *It's My Ovaries, Stupid!* New York: Scribner; 2003:60–61.

BOX 35-1. Symptoms of Perimenopause and Menopause

- Hot flashes
- Night sweats
- Vaginal dryness
- Vaginal odor
- Mood swings
- Irritability
- Insomnia
- Depression
- Loss of sexual interest
- Hair growth on face
- Painful intercourse
- Panic attacks
- Excessive dreaming
- Urinary tract infections
- Vaginal itching
- Lower back pain
- Bloating
- Flatulence
- Indigestion
- Osteoporosis or osteopenia
- Aching ankles, knees, wrists, shoulders, or heels
- Hair loss
- Frequent urination
- Snoring
- Sore breasts
- Palpitations
- Varicose veins
- Urinary leakage
- Dizzy spells
- Panic attacks
- Skin feeling crawly
- Migraine headaches
- Weight gain
- Memory lapses or lack of focus and concentration

Natural Estrogens

The body makes many kinds of estrogens. The three main estrogens are as follows:

- E_1, called estrone
- E_2, called estradiol
- E_3, called estriol

Estrone (E_1)

E_1 is the main estrogen the body makes postmenopausally. It is derived from E_2. High levels stimulate breast and uterine tissue, and many researchers believe it may be related to an increased risk of breast and uterine cancer.[42,59]

Before menopause, E_1 is made by the ovaries, adrenal glands, liver, and fat cells. Premenopausally, E_1 is converted to E_2 in the ovaries. Postmenopausally, little E_1 becomes E_2 because the ovaries stop working. In later years, E_1 is then made in the fat cells and, to a lesser degree, in the liver and adrenal glands.[42] Therefore, the more body fat one has the more E_1 will be manufactured. Consequently, obese women have an increased E_1:E_2 ratio.[60] In addition, routine alcohol consumption shifts the estrogen production to E_1.[61,62]

BOX 35-2. Functions of Estrogen

- Stimulates the production of choline acetyltransferase[7–11]
- Increases metabolic rate[12]
- Improves insulin sensitivity[13–16]
- Regulates body temperature
- Helps prevent muscle damage[17]
- Helps maintain muscle[18,19]
- Helps one sleep deeply[20]
- Reduces the risk of cataracts[21]
- Helps maintain the elasticity of arteries[22]
- Dilates small arteries[22,23]
- Increases blood flow[22–25]
- Inhibits platelet stickiness[22]
- Decreases the accumulation of plaque on the arteries[22]
- Enhances magnesium uptake and use[26]
- Maintains the amount of collagen in the skin
- Reduces vascular proliferation and inflammatory responses and thereby decreases heart disease risk[27]
- Lowers blood pressure[28]
- Decreases low-density lipoprotein and prevents its oxidation[29,30]
- Helps maintain memory[31–36]
- Increases reasoning and new ideas[24,37]
- Helps with fine motor skills[24,37]
- Increases the water content of the skin and is responsible for its thickness and softness[38]
- Enhances the production of nerve growth factor[39]
- Increases high-density lipoprotein by 10% to 15%[40]
- Reduces the overall risk of heart disease by 40% to 50%[40]
- Decreases lipoprotein (a)[40]
- Acts as a natural calcium channel blocker to keep the arteries open[41]
- Enhances energy[42]
- Improves mood[43–47]
- Increases concentration[43]
- Maintains bone density[43,49]
- Increases sexual interest[43]
- Reduces homocysteine[49,50]
- Decreases wrinkles[51]
- Protects against macular degeneration[51]
- Decreases the risk of colon cancer[51]
- Helps prevent tooth loss[51]
- Aids in the formation of neurotransmitters in the brain such as serotonin[43,52]

Obesity and alcohol increase estrone-to-estradiol ratio and may thus increase the risk of breast and uterine cancer.

Estradiol (E_2)

E_2 is the strongest estrogen. It is 12 times stronger than E_1 and 80 times stronger than E_3. It is the main estrogen the body produces before menopause. Most E_2 is made in the ovaries. High levels of E_2 are associated with an increased risk of breast and uterine cancer. E_2 is the main estrogen the patient loses at menopause. However, two thirds of postmenopausal women up to the age of 80 years continue to make some E_2.[54] E_2 levels are lower in women who have had a surgical procedure that affected their ovaries. Even

BOX 35-3. Causes of Estrogen Dominance

- Impaired elimination of estrogen
- Lack of exercise
- Administration of too much estrogen
- Diet low in grains and fiber
- Environmental estrogens (see the section on estrogen metabolism)
- Elevation of 16-hydroxyestrone metabolism (see estrogen metabolism)

Data from Adlercreutz J. Western diet and Western diseases: some hormonal and biochemical mechanisms and associations. *Scand J Clin Lab Invest Suppl.* 1990;201:3–23.

with one or both ovaries remaining, these patients may still have a decrease in hormonal function and may have menopausal symptoms[63] (Box 35-3e).[64–66].

Box 35-3e, which lists the functions of estradiol in the body, can be found online at expertconsult.com.

Estriol (E_3)

E_3 has a much less stimulating effect on the breast and uterine lining than does E_1 or E_2. E_3 has been shown not to promote breast cancer, and considerable evidence indicates that it protects against the disease.[67] In Western Europe, E_3 estrogen has been used for decades.[68–73]

E_3 is an adaptogen, meaning that it adapts in the body to the ambient environment. E_3 given by itself has few estrogenic effects.[74–77] When given in a tenfold amount in relation to E_2 (biest; see later), E_3 antagonizes the effect of E_2.[78] Studies of E_3 since the 1970s revealed that E_3 given experimentally to women with breast cancer decreased disease recurrence. This group includes one study in the 1970s in which women with metastatic breast cancer were given E_3. Thirty-seven percent of the women had remission of the metastatic lesions or their cancer spread no further.[70] More research is needed in this area before E_3 can be recommended for women with a history of hormonally related breast cancer (Box 35-4).[72,79–83] Asian and vegetarian women have high levels of E_3 and much lower rates of breast cancer.[84]

Although E_3 does not have the major bone, heart, or brain protection of E_2,[42,85] it does have some minor positive effects on bone[72] and heart health by lowering cholesterol.[86,87]

Estrogen prescribed for HRT should be applied transdermally and not orally. In part because of the first-pass effect through the liver, estrogen given by mouth can have the following effects[88,89]:

- Elevate blood pressure
- Increase prothrombic effects[90]
- Increase triglycerides
- Increase E_1
- Cause gallstones
- Elevate liver enzymes

BOX 35-4. Functions of Estriol in the Body

- Helps to control menopausal symptoms including hot flashes, insomnia, and vaginal dryness[72,79,80]
- Helps the gut maintain a favorable environment for the growth of good bacteria (lactobacilli) and helps reduce pathogenic bacteria[77]
- Benefits the vaginal lining[81]
- Increases high-density lipoprotein and lowers low-density lipoprotein[82]
- May help restore the proper pH of the vagina and consequently helps prevent urinary tract infections[83]
- Blocks estrone by occupying the estrogen receptor sites on the breast cells
- Decrease growth hormone
- Interrupt tryptophan metabolism and consequently serotonin metabolism[91]
- Increase C-reactive protein[44]
- Increase sex hormone–binding globulin (which can decrease testosterone)
- Increase carbohydrate craving[92]
- Increase weight gain[92]

Estrogen replacement therapy should be administered by the transdermal route. Oral dosing can increase the risk of heart disease, a finding that may help explain the elevated risk in the Women's Health Initiative study.

Consequently, as HRT, estrogens should be applied transdermally. Many studies have been conducted on transdermal application of E_2. Transdermally given E_2 has been shown to have the following effects[90]:

- Does not have the same impact on liver synthesis of proteins as estrogen given by mouth[93–95]
- Does not have negative effects on the health of the heart
- Does not negatively affect blood clotting[96–98]
- Lowers triglycerides and thus decreases the risk of heart disease in women[99]

Estrogen Receptor Sites

Estrogen has two main receptor sites to which it binds in the body: estrogen receptor alpha, which can increase cell growth; and estrogen receptor beta, which decreases cell growth and helps prevent breast cancer development. E_2 equally activates estrogen receptors alpha and beta. E_1 selectively activates estrogen receptor alpha sites in a ratio of 5:1, which can increase cell proliferation. E_3 binds preferentially to estrogen receptor beta in a 3:1 ratio, which may be one of the reasons that E_3 may help prevent breast cancer development.

Estrone (E_1) selectively activates estrogen receptor sites that increase cell proliferation and has the greatest risk of stimulating breast cancer.

BOX 35-3e. Functions of Estradiol in the Body

- Helps maintain potassium levels
- Helps absorption of calcium, magnesium, and zinc
- Increases high-density lipoprotein
- Decreases low-density lipoprotein
- Decreases total cholesterol
- Decreases triglycerides (transdermal administration only)
- Decreases platelet stickiness
- Increases growth hormone[65]
- Increases serotonin
- Helps maintain bone structure
- Increases endorphins
- Improves sleep
- Decreases fatigue
- Works as an antioxidant[66]
- Helps maintain memory

Data from Vliet E. *It's My Ovaries, Stupid!* New York: Scribner; 2003:85.

Estrogen Metabolism

A growing body of research shows that it is not simply the amount of total estrogen circulating in the body that is critical to women's health. How estrogen is metabolized in the body may also play an important role in causing various estrogen-dependent conditions, including osteoporosis, autoimmune disorders, and cancer.

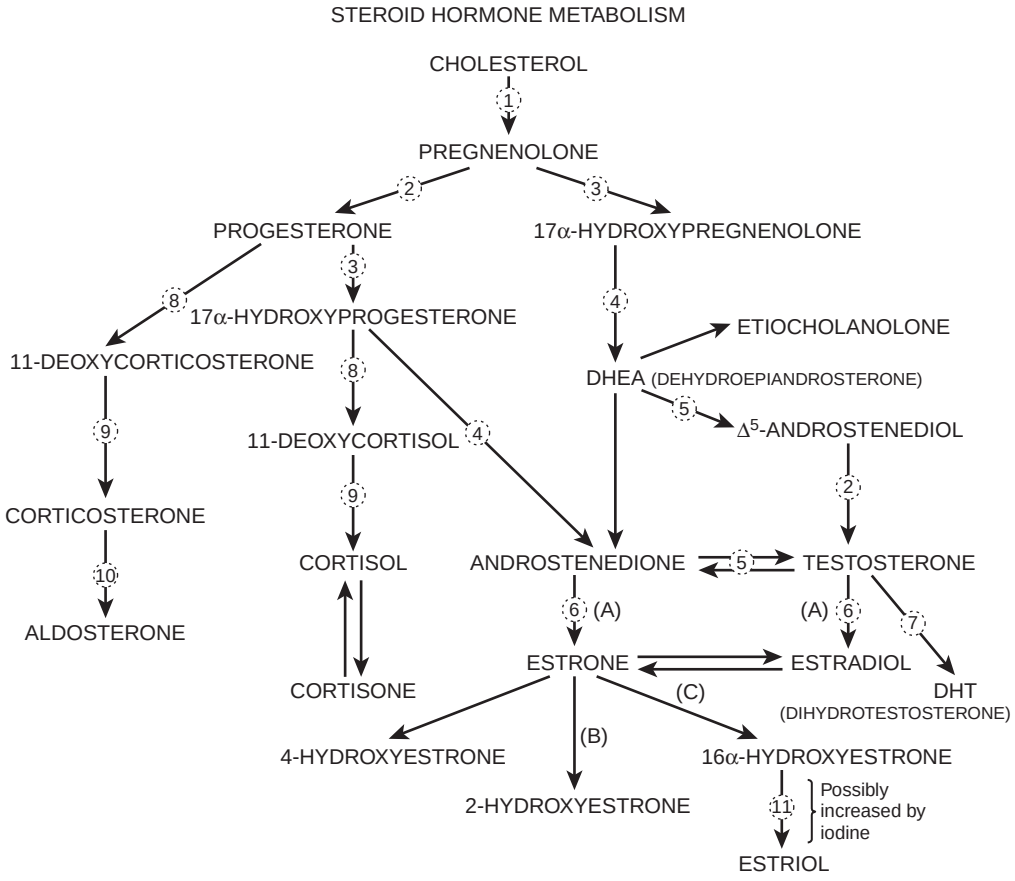
After menopause, the metabolism of estrogen can change. Consequently, a woman may respond differently to exogenous estrogen.[100]

Estrogen is metabolized in the body in the following ways (Fig. 35-1):

- Two major competing pathways
  - 2-Hydroxyestrone
  - 16-Hydroxyestrone
- One minor pathway
  - 4-Hydroxyestrone

2-Hydroxyestrone is sometimes called the good estrogen.[101] It does not stimulate the cells to divide, which can cause damage to DNA and cause tumor growth.[101] Furthermore, by latching onto available estrogen cell receptors, 2-hydroxyestrone may exhibit a blocking action that

FIGURE 35-1
Steroid hormone metabolism. (Courtesy of Sahar Swidan, PharD, BCPS.)



ENZYMES

1 Cholesterol side chain cleavage (CSCC)
2 3β-Hydroxysteroid Dehydrogenase (3β-OHSD) AND $\Delta^{5,4}$ Isomerase (reside on same protein)
3 17α-Hydroxylase**
4 C17,20-Lysase**
5 17β-Hydroxysteroid Dehydrogenase (17β-OHSD)
6 Aromatase
7 5α-Reductase AND NADPH
8 21-Hydrolase
9 11β-Hydroxylase
10 18-Hydroxylase AND 18-Hydroxydehydrogenase
11 16α-Hydroxylase
(A) Inhibited by Chrysin
(B) Increased by cruciferous vegetables (Indole-3-Carbinol) and flaxseed
(C) Decreased by cruciferous vegetables (Indole-3-Carbinol) and flaxseed

** NOTE: 17α-Hydroxylase and C17,20 - Lysase activities reside on a single protein (designated $P450_{C17}$)

prevents stronger estrogen products from gaining a foothold into the cells. Therefore, 2-hydroxyestrone is suggested to be anticancerous.[102]

The other major pathway of estrogen metabolism is 16-hydroxyestrone. This metabolite is much more active and has a strong stimulatory effect. 16-Hydroxyestrone binds to special receptors inside the cells that can increase the rate of DNA synthesis and cell multiplication.[103] Consequently, 16-hydroxyestrone is proposed to have significant estrogenic activity and to be associated with an increased risk of breast cancer. [104–113] Furthermore, 16-hydroxyestrone permanently binds to the estrogen receptor. Other estrogens attach briefly and then are released.[114] Other reasons may also exist for the association of 16-hydroxyestrone with a higher rate of cancer. High levels of 16-hydroxyestrone are associated with obesity, hypothyroidism, pesticide toxicity (organochlorines), omega-6 fatty acid excess, and inflammatory cytokine production. For the body to make a small amount of 16-hydroxyestrogen is advantageous, however, because 16-hydroxyestrone decreases the risk of osteoporosis. Therefore, a small amount of 16-hydroxyestrone production is desirable. Extensive endogenous and exogenous estrogen production through the 16-hydroxy pathway may put the patient at higher risk for breast cancer than when the 2-hydroxy pathway breaks down more estrogen.[115]

Studies have shown that low 2:16 hydroxyestrogen ratios are associated with elevated breast cancer risk. One study of postmenopausal women who went on to develop breast cancer had a 15% lower 2:16 hydroxyestrogen ratio than did women in control groups.[111] Similarly, in women who already have breast cancer, the survival rate is greater in women with higher ratios.[116,117] 2-Hydroxyestrone is protective against cancer only when this substance is methylated by catechol-O-methyltransferase (COMT) into 2-methoxyestrone. The ratio of 2-methoxyestone to 2-hydroxyestrone can be measured in the urine and is a good gauge of the body's ability to methylate. Another way of evaluating the body's ability to methylate is by measuring the serum homocysteine level. If it is elevated, this suggests poor methylation. Low ratios of 2:16 hydroxyestrogen are also associated with an increased rate of developing lupus.

Factors that support methylation are numerous:

- *S*-Adenosyl-L-methionine (SAMe)
- Methionine
- Vitamins B_2, B_6, and B_{12}
- Folic acid (also as folinic acid, 5-formyl THF, or 5-methyltetrahydrofolate)
- Trimethylglycine (TMG)
- Reducing catecholamine production by decreasing stress

A minor pathway of estrogen metabolism is 4-hydroxyestrone. It may also enhance cancer development. 4-Hydroxyestrone may directly damage DNA by causing breaks in the molecular strands of DNA.[118] Furthermore, the 4-hydroxyestrogens have the ability to convert to metabolites that react with DNA and cause mutations that can be carcinogenic.[119] In addition, 4-hydroxyestrone is present in greater quantities in patients deficient in methionine and folic acid. Women who have uterine fibroids also may have increased levels of 4-hydroxyestrone.

Equine estrogens increase metabolism to 4-hydroxyestrones.[120,121] Studies have shown that 4-hydroxyestrone from equine estrogen causes mutagenic damage five times more rapidly than do other forms of 4-hydroxyestrogens.[122]

Therefore, the metabolism of estrogen through the 2-hydroxy pathway is of critical importance in lowering the risk of cellular damage and possible development of cancer. It is consequently very important to measure the patient's levels of 2-hydroxyestrone and 16-hydroxyestrone, as well as the ratio between these two metabolites. Equally important is to measure 4-hydroxyestrone levels. The goal is to normalize estrogen metabolism. Follow-up testing is also suggested to assess the clinical impact of dietary and lifestyle changes, as well as HRT.[123] Even patients not receiving HRT should have an estrogen metabolism test, particularly if they have a family history of breast cancer.

What can elevate 2-hydroxyestrone levels?

- Moderate exercise[124,125]
- Cruciferous vegetables[105,126–135]
- Flax[136,137]
- Soy[138]
- Kudzu (source of isoflavones)
- Rosemary, turmeric
- Exercise
- Weight loss
- Broccoli derivatives[130,139–146]
  - Indole-3-carbinol
  - Diindolylmethane (DIM), a breakdown product of indole-3-carbinol
  - Sulforaphane glucosinolate
- High-protein diet[147]
- Omega-3 fatty acids[101,108,148]
- Vitamins B_6 and B_{12} and folate[149,150]

All the foregoing have been shown to increase the 2:16 ratio significantly and decrease 4-hydroxyestrone production, thus reducing the risk of estrogen-dependent health problems by shifting estrogen metabolism toward the less active 2-hydroxyestrone pathway.

Other factors affect how the body metabolizes estrogen. The first is obesity, which increases the action of estrogens in three ways[151]:

- Estrogen production and storage occur in fat cells.[152,153]
- Concentrations of sex hormone–binding globulin are decreased in obese patients. This change increases the amount of unbound estrogen available for use by the body.[154]
- Obesity decreases 2-hydroxyestrone and increases 16-hydroxyestrone production.[139,155]

The second factor is the presence of xenoestrogens. Researchers have identified 50 chemicals that imitate estrogen.[101,156–159]

Third, excessive alcohol intake interferes with the body's ability to detoxify estrogen and increases E_2 levels and, consequently, the risk of breast cancer.[160]

Finally, even antibiotics found in the food may be associated with an elevated risk of breast cancer development by changing the gut flora involved in the enterohepatic circulation of estrogens.[161]

Measuring estrogen metabolism (the 2-hydroxyestrone-to-16 alpha-hydroxyestrone ratio, 4-hydroxyesterone) is a key component to therapy.

Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are also a type of HRT. SERMs decrease total cholesterol by 5% and low-density lipoprotein (LDL) by 10%. They are not as effective in lowering triglycerides, however, and they do not increase high-density lipoprotein (HDL) as effectively as does standard HRT.[162] Furthermore, because estrogen receptor modulators are not neuroprotective, they do not have the same positive effect on memory and mood as does natural estrogen.[163]

Progesterone

Progesterone is made in the ovaries before menopause. After menopause, some progesterone is made in the adrenal glands (Box 35-5 and Box 35-4e).[164–169]

Box 35-4e, which identifies the causes of low progesterone levels, can be found online at expertconsult.com.

Natural progesterone is biologically identical to what the patient's own body produces. Synthetic progesterone, called progestin, is very different from natural progesterone because it does not have the same chemical structure. Consequently, progestins do not reproduce the actions of natural progesterone.[170] Further information on progesterone is available in the literature.[171–189]

One study showed that the use of synthetic progesterone increased the risk of breast cancer by 800% as compared with the use of estrogen alone.[190–193] Furthermore, an article published in *JAMA* (the official journal of the American Medical Association) discussed a risk of breast cancer that was predicted to rise by nearly 80% after 10 years of use of estrogen-progestin HRT and 160% after 20 years.[192] Similarly, Dr. Stephen Sinatra, a well-known cardiologist, found that synthetic progestins can lead to serious cardiac side effects in patients, including shortness of breath, fatigue, chest pain, and high blood pressure.[177] Progesterone (bio-identical) does not share the same risk seen with progestins (Box 35-6).[67,164,187,188,194–217]

BOX 35-5. Symptoms of Decreased Progesterone Levels

- Anxiety
- Depression
- Irritability
- Mood swings
- Insomnia
- Pain and inflammation
- Osteoporosis
- Decreased high-density lipoprotein
- Excessive menstruation
- Hypersensitivity
- Nervousness
- Migraine headaches before cycles
- Weight gain
- Decreased libido

Data from Smith P. *What You Must Know About Women's Hormones.* Garden City Park, NY: Square One Publishers; 2010:20.

BOX 35-6. Effects of Bio-Identical Progesterone

- Helps balance estrogen
- Leaves the body quickly
- Improves sleep hygiene
- Stimulates the production of new bone
- Has a natural calming effect[205]
- Lowers high blood pressure
- Helps the body use and eliminate fats
- Lowers cholesterol
- May protect against breast cancer by inhibiting breast tissue overgrowth
- Increases scalp hair
- Normalizes libido
- Helps balance fluids in the cells
- Increases the beneficial effects of estrogens on blood vessel dilation in atherosclerotic plaques[206–208]
- Has an anti-proliferative effect on all progesterone receptors, not just receptors in the uterus[187,188]
- Does not change the good effect of estrogen on blood flow[177]
- Increases metabolic rate[209]
- Is a natural diuretic
- Enhances the action of thyroid hormones
- Prevents migraine headaches that are cycle related
- Is a natural antidepressant
- Improves libido
- Helps restore proper cell oxygen levels
- Induces conversion of estrone (E_1) to the inactive E_{1S} form
- Promotes helper T-cell (Th2) immunity
- Is neuroprotective by promoting myelination
- Is antiinflammatory
- Relaxes smooth muscle
- Promotes bone formation or turnover[210]

The hormonal symphony is very important. If the body has too much synthetic or natural progesterone, then some of the following effects can occur[206,211,212]:

- Increases fat storage
- Decreases glucose tolerance and increases insulin levels, which may lead to insulin resistance
- Increases cortisol
- Increases appetite
- Increases carbohydrate cravings
- Relaxes the smooth muscles of the gut and thus can cause bloating, fullness, and constipation; can also contribute to gallstone formation[213]
- Suppresses the immune system[214]
- Causes incontinence[215]
- Causes ligaments to relax and can cause backaches, leg aches, and achy hips[216]
- Decreases growth hormone levels[217]

BOX 35-4e. Causes of Low Progesterone Levels

- Impaired production
- Low luteinizing hormone
- Increased prolactin production
- Stress[165]
- Antidepressants[166]
- Excessive arginine consumption[167]
- Sugar consumption[167]
- Saturated fat consumption[167]
- Deficiency of vitamins A, B_6, and C and zinc[168,169]
- Decreased thyroid hormone

This discussion clearly shows that natural (bioidentical) progesterone offers a safer approach than synthetic progesterone (progestin).[187] Moreover, the level of progesterone must be measured before the patient begins HRT and then again on a regular basis to confirm that the patient is receiving an optimal dose in balance with other hormones.

Progesterone can be prescribed as a pill or a topical cream. If the patient has insomnia, then oral progesterone is the preferred route of administration because it crosses the blood-brain barrier and affects the gamma-aminobutyric acid receptors in the brain to produce a calming effect that helps the patient sleep.[205,214] Prometrium is a natural progesterone preparation available from a pharmaceutical company. This preparation is made from peanut oil. More commonly, natural progesterone is prescribed by a health care practitioner and is then made by a compounding pharmacy, to facilitate customizing the patient's dosage. This form of natural progesterone is made from an extract of yams. The compounded formulation of progesterone has an enzyme added to convert the diosgenin in the yam into progesterone. Over-the-counter progesterone frequently does not contain this enzyme unless it appears on the label.[218] The absorption rate of oral progesterone increases as one ages; consequently, patients may need less medication as they grow older.[219] Some women have side effects of oral progesterone such as nausea, breast swelling, dizziness, drowsiness, and depression resulting from first-pass effects on the liver and gastrointestinal tract.[220,221] Lowering the dose or optimizing gastrointestinal tract health usually resolves these symptoms. Progesterone may be given transdermally, although no studies have shown that transdermal administration of progesterone aids in the prevention of endometrial hyperplasia.

Finally, epinephrine also interacts with progesterone as part of the hormonal symphony. Epinephrine surges, which occur with stress, can block progesterone receptors and can prevent progesterone from being used effectively in the body.[222]

Estrogen-to-Progesterone Ratio

As discussed, the risk of breast cancer is increased when estrogen metabolism favors the 16-hydroxyestrone or 4-hydroxyestrone pathway. Patients with a low progesterone-to-estrogen ratio, otherwise known as estrogen dominance, also have a higher risk of breast cancer.[223]

Important facts about the estrogen-to-progesterone ratio are as follows:

- Progesterone and E_2 (estrogen) work together in the body. E_2 lowers body fat by decreasing lipoprotein lipase. Progesterone increases body fat storage by increasing lipoprotein lipase.[224]
- Estrogen and progesterone work together to control the body's release of insulin. Women with diabetes must be prescribed the smallest amount of progesterone that will balance E_2.[225] E_2 increases insulin sensitivity and improves glucose tolerance, whereas excess progesterone decreases insulin sensitivity.
- A progesterone-to-estrogen ratio that is too high in progesterone breaks down protein and muscle tissue.[226] This process may worsen symptoms of diseases such as fibromyalgia.

Prolonged use of progesterone without adequate estrogen can have the following effects[226]:

- Increased weight gain
- Increased total cholesterol
- Decreased HDL
- Increased LDL
- Increased triglycerides
- Increased risk of developing insulin resistance
- Depression
- Fatigue
- Decreased libido

Progesterone must balance with estrogen in the body.

Testosterone

Testosterone is made in the adrenal glands and ovaries. As women age, their ovaries produce less testosterone. Of testosterone women produce, 1% is unbound, and the remainder is bound to sex hormone–binding globulin. Women with increased androgens have more free testosterone available for the body to use. Therefore, measuring hormone levels is important (Box 35-7).[227–233]

Research is showing that for testosterone to work well, E_2 must also be optimized. Without enough estrogen, testosterone cannot attach to brain receptors.[232] Testosterone given

BOX 35-7. Functions of Testosterone in Women

- Increases sexual interest (86% of women state they have a decrease in sexual interest with menopause.)[227]
- Increases sense of emotional well-being, self-confidence, and motivation[228]
- Increases muscle mass and strength
- Helps maintain memory[229]
- Stimulates the growth of pubic hair and underarm hair at puberty
- Increases muscle tone so the skin does not sag[230]
- Decreases excess body fat
- Decreases bone deterioration and helps maintain bone strength[231]
- Elevates norepinephrine in the brain[232]
- Has cardiovascular benefits[233]

Low testosterone levels can occur at any age and can be caused by the following:

- Menopause
- Childbirth
- Chemotherapy
- Surgical menopause[234]
- Adrenal stress or burnout
- Endometriosis
- Depression
- Psychological trauma
- Birth control pills (increases sex hormone–binding globulin)
- Cholesterol-lowering medications[235]

with E_2 lowers cardiac risk.[232,236] If given alone (and a women's own estrogen level is low), testosterone increases plaque formation in the coronary vessels and thereby increases the patient's risk of myocardial infarction. If testosterone is given with estrogen, it has a beneficial effect on the arterial walls.[237]

Testosterone increases plaque formation in the coronary vessels unless it is balanced with estrogen.

Prescription natural testosterone is the preferred method of testosterone replacement. Methyltestosterone (synthetic) use may increase the risk of liver cancer in women.[238–240] Testosterone should be applied transdermally to decrease negative effects on the liver. The patient should be instructed to rotate application sites. If the patient applies testosterone to the same location daily, she will have an increase in hair growth at the site of application.

A woman can have excess testosterone levels. Excess androgen production may come from the ovaries or the adrenals. Almost 10% of women have had some kind of androgen imbalance in their lifetime (Box 35-5e).[67,241,242]

Box 35-5e, which lists the symptoms of increased testosterone production, can be found online at expertconsult.com.

For the patient to have optimal health, her level of testosterone should be in balance with all the other hormones. Levels that are too high or too low are not desirable (Table 35-1).

Prevention Prescription

The body is designed not to need HRT postmenopausally. The adrenal glands produce enough dehydroepiandrosterone (DHEA) to make sufficient estrogen and testosterone to maintain function. Similarly, pregnenolone makes adequate progesterone, estrogen, testosterone, DHEA, and cortisol to maintain function in most patients. This function can be maintained best by the following recommendations:

- Encourage regular exercise.
- Maintain optimal weight.
- Maintain an adequate sleep-wake cycle with 7 to 8 hours of uninterrupted sleep each night.
- Decrease exposure to xenobiotics that can have hormonal influences by eating organic foods, drinking filtered water, avoiding petroleum-based cosmetics, storing food in glass (not plastic), avoiding eating animal fat, and avoiding diesel exhaust.
- Make changes to avoid chronic emotional stress (see Chapter 93, Relaxation Techniques).
- Eat a diet rich in protein, ground flaxseed, green tea, omega-3 fatty acids, and cruciferous vegetables. Obtain protein from plant sources (beans, nuts) more than from animal sources (see Chapter 86, The Antiinflammatory Diet).

TABLE 35-1. Twenty-four–Hour Production Rates of Sex Steroids in Women at Different Stages of the Menstrual Cycle

SEX STEROIDS	EARLY FOLLICULAR	PREOVULATORY	MIDLUTEAL
Progesterone (mg)	1.0	4.0	25.0
17-Hydroxyprogesterone (mg)	0.5	4.0	4.0
Dehydroepiandrosterone (mg)	7.0	7.0	7.0
Androstenedione (mg)	2.6	4.7	3.4
Testosterone (mcg)	144.0	171.0	126.0
Estrone (mcg)	50.0	350.0	250.0
Estradiol (mcg)	36.0	380.0	250.0

Therapeutic Review

Hormone replacement therapy (HRT) is all about balance and individualized treatment dosages. Needs change over time, and ongoing reevaluation is beneficial through relationship-centered care.

Laboratory

- The levels of all three estrogens (along with progesterone, testosterone, dehydroepiandrosterone [DHEA], cortisol, and thyroid hormones) must be measured before the patient is prescribed HRT, and regularly thereafter, to help maintain the patient on the optimal amount of each hormone.

BOX 35-5e. Symptoms of Increased Testosterone Production

- Anxiety
- Depression
- Changes in memory
- Fatigue
- Hypoglycemia
- Salt and sugar cravings
- Agitation
- Anger
- Facial hair or hirsutism
- Acne
- Increase in insulin resistance
- Decreased high-density lipoprotein
- Irregular menstrual periods
- Infertility
- Weight gain (apple body shape)
- Fluid retention
- Mood swings
- Hair loss
- Poor prognosis in patients with breast cancer
- Increased risk of breast cancer

Ways to lower testosterone in a woman:

- Saw palmetto
- Metformin
- Spironolactone

Data from Hanaway P. Hormone essentials: personalizing diagnosis and treatment. Presented at Module I: Anti-Aging and Regenerative Fellowship, Las Vegas, NV, December 10-12, 2007; and Bland J, ed. *Functional Medicine Approaches to Endocrine Disturbances of Aging.* Gig Harbor, WA: Institute for Functional Medicine, 2001:71.

Lifestyle

- Many positive lifestyle behaviors can be protective by increasing 2-hydroxyestrone levels.
  - Regular moderate exercise. 
  - Weight loss is encouraged if the patient is overweight. This is one of the most important goals in balancing hormones in overweight women. 

Nutrition

- Cold water fish twice weekly 
- Cruciferous vegetables including broccoli, cabbage, Brussels sprouts, kale, and cauliflower 

Botanicals

- Kudzu (rich in isoflavones): 100 mg daily 
- Turmeric extract: 500 to 1000 mg two to three times a day 

Supplements

- If homocysteine is elevated, suspect poor methylation. Supplement with the following: vitamin B_6, 50 mg daily; vitamin B_{12}, 1000 mcg weekly; and folic acid, 800 mcg daily to increase 2-hydroxyestrone levels. 
- Fish oil with eicosapentaenoic acid and docosahexaenoic acid: 1000 mg daily 
- Zinc if deficient: 15 to 30 mg daily (needed for testosterone metabolism) 
- Indole-3-carbinol 300 mg daily or diindolylmethane (DIM) 225 mg daily 

Mind-Body Therapy

- Chronic stress and anxiety are foundational elements in hormone imbalance because the perception of stress has a direct effect on the hypothalamic-pituitary axis (see Chapter 93, Relaxation Techniques). 

Pharmaceuticals (Hormones)

A practitioner usually begins by prescribing 20% estradiol (E_2) and 80% estriol (E_3). Then the percentages of E_2 and E_3 are adjusted according to repeated laboratory testing. The combination of E_2 and E_3 together is called biest and is a prescription that a compounding pharmacist can formulate. Any percentage of these two estrogens can be used because the dosage is individualized. Start low and go slow.

Progesterone

- For premenstrual syndrome 
  - Consider progesterone alone cyclically.
  - Oral administration of sustained-release capsules (compounded) or micronized progesterone (Prometrium; comes in 100- and 200-mg formulations), at 25 to 400 mg (most common, 50 to 200 mg) given cyclically from days 12 to 24 of the menstrual cycle
  - Topical administration, at 5 to 50 mg applied daily on days 14 to 25 of the cycle
- For perimenopause 
  - Oral administration and topical application with doses same as for premenstrual syndrome. The patient should use this cyclically alone or combined with estrogen.
  - Use the lowest possible dose of progesterone in patients with obesity or metabolic syndrome.
- For postmenopausal or surgical menopause status 
  - Oral sustained-release capsules (dose at bedtime because of sedation) 50 to 200 mg or topical compounded cream, at 20 to 50 mg daily. Patients may also use 100 mg of Prometrium at bedtime if this dose is needed (lowest dose available is 100 mg).
  - Treatment may be continuous or stopped for 5 days a month.

Estrogen

- For perimenopause 
  - Bi-estrogen (80% E_3, 20% E_2). Compound 2 mg E_3 with 0.5 mg E_2 per gram and start at 0.25 mg cream topically daily or twice daily, if progesterone alone does not control symptoms.
- For postmenopausal status and surgical menopause 
  - Bi-estrogen (50% E_3, 50% E_2). Compound 1 mg E_3 with 1 mg E_2 per gram and start 0.25 mg cream topically daily or twice daily. Patients may use it continuously or stop 5 days a month.

Testosterone

- For postmenopause 
  - Topical compounded cream, at 0.25 to 2.0 mg once daily
- For surgical menopause 
  - Topical compounded cream, at 0.25 to 2.0 mg daily

Converting Administration Routes

- Approximate ratio for transdermal to sublingual to oral
  - For progesterone, estrogen, and DHEA: transdermal 1 to sublingual 2 to oral 4 to 5
  - For testosterone: transdermal 1 to sublingual 2 to oral 5 to 6

Continued

Other Considerations

- After hormones are prescribed, the patient should have hormone levels checked again in 90 days and then every 6 to 12 months.
- The evidence/harm rating for hormones is a 2. If the recommendation were equine estrogen with progestin, as used in the Women's Health Initiative study, the rating would be a 3 because of the increased risk of myocardial infarction, stroke, deep vein thrombosis, and breast cancer.
- As with any therapy, hormones should be matched to the unique needs of the patient to provide the most benefit with the least amount of harm.

KEY WEB RESOURCES

International Academy of Compounding Pharmacists: http://www.iacprx.org.	This Web site includes a directory of compounding pharmacists in the United States.
Professional Compounding Centers of America: http://www.pccarx.com.	This site also includes a directory of compounding pharmacists in the United States.
Laboratories (see Appendix in This Text for a Complete List)	
Genova Diagnostic Laboratory: www.genovadiagnostics.com.	This laboratory performs salivary and 24-hour urine hormone testing, as well as estrogen metabolism testing.
Metametrix Clinical Laboratory: www.metametrix.com.	This laboratory conducts estrogen metabolism testing.
NeuroScience, Inc.: www.neurorelief.com.	This laboratory performs salivary testing of hormones.
ZRT Laboratory: www.zrtlab.com.	This laboratory also performs salivary testing of hormones.

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Chapter 36

Polycystic Ovarian Syndrome

Melinda Ring, MD

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder, affecting 10% of women of reproductive age, yet it is frequently overlooked.[1,2] PCOS affects young women with oligo-ovulation (which leads to oligomenorrhea in more than 75% of affected patients), infertility, acne, and hirsutism. It also has notable metabolic sequelae, including an elevated risk of diabetes and cardiovascular disease, and attention to these factors is important.[3] The heterogeneous nature of the condition and the diversity of presentations led to a symptom-based approach to treatment, because PCOS manifests differently, depending on many interacting factors including environmental exposures, genetics, and lifestyle (Fig. 36-1). This chapter discusses the pathophysiology and integrative approach to treatment of women with PCOS.

Pathophysiology

When PCOS was first described (as Stein-Leventhal syndrome) in the 1930s, the presence of cysts in the ovaries was believed to be a defining factor in the origin of the syndrome.[4] Since then, research has shown that, in fact, the cysts are only one potential expression of what begins as a disorder in the endocrine system. On pelvic ultrasound, 90% of women with biochemical features of PCOS will have characteristic changes; however, 20% to 30% of women without the hormonal issues of PCOS will have similar ultrasound features.[5] Our current understanding, albeit incomplete, is that PCOS phenotypic expression results from primary hormone imbalances. The three prevalent theories for the pathogenesis of PCOS are as follows:

1. Hypothalamic-pituitary dysfunction results in gonadotropin-releasing hormone and luteinizing hormone dysfunction, which then has downstream effects on ovarian hormone production.
2. A primary ovarian defect (with or without an adrenal defect) in steroidogenesis results in hyperandrogenism.
3. A metabolic disorder characterized by peripheral insulin resistance exerts adverse effects on the hypothalamus, pituitary, ovaries, and, possibly, adrenal gland.

Variables including genetic factors and lifestyle choices contribute to the wide range of manifested symptoms and make the diagnosis challenging unless the clinician is attuned to the potential problem.

Criteria for PCOS have been debated among leading organizations since 1990. The differences reflect the controversy over the origin of the syndrome, as well as its heterogeneous manifestations (Table 36-1).[6–8] The diagnostic criteria have unifying trends, however. All require the presence of at least one of the stigmata of ovarian disease: a history of anovulation or the finding of classic polycystic ovaries on ultrasound. All three schemata are consistent in the inclusion of hyperandrogenism, through either clinical expression (hirsutism or acne) or laboratory confirmation. Finally, all guidelines also require exclusion of hormonal disorders that may mimic PCOS. Although insulin resistance has been noted consistently among women with PCOS, it is not included in any of the diagnostic criteria.

Based on current data, evaluation for PCOS should include a search for both primary markers and secondary dysfunctions. History and physical examination focus on symptoms and signs such as oligomenorrhea, acne, hirsutism, and central obesity, as well as searching for manifestations of other confounding diseases. Laboratory tests should include androgen levels (dehydroepiandrosterone [DHEA] sulfate and total and free testosterone measured by equilibrium dialysis) and tests to rule out alternative diagnoses as warranted (e.g., congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, 21-hydroxylase–deficient nonclassic adrenal hyperplasia, androgenic or anabolic drug use or abuse, syndromes of severe insulin resistance, thyroid dysfunction, or hyperprolactinemia). Laboratory testing for antimüllerian hormone is a newer diagnostic tool, not yet widely available, that holds promise as a confirmatory test. A search for evidence of metabolic syndrome and cardiovascular risk should also be performed (e.g., insulin resistance measurement by oral glucose tolerance test including glucose and insulin levels and measurement of lipids and inflammatory

FIGURE 36-1
Proposed relationships leading to phenotypic expression of polycystic ovarian syndrome.

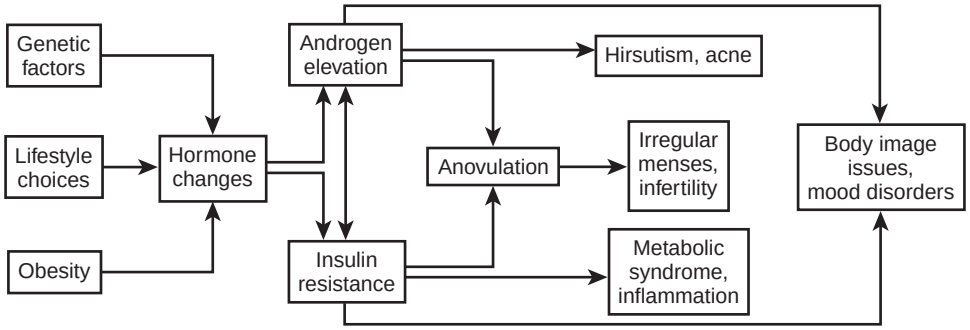

TABLE 36-1. Differing Criteria for Polycystic Ovarian Syndrome Among Organizations

ORGANIZATION	CRITERIA	OVARIAN DYSFUNCTION	OVARIAN MORPHOLOGY	HYPERANDROGENISM
National Institutes of Health (1990)[6]	Both of the following and exclusion of related disorders	Oligo-ovulation (less than 6 menses per year)		Clinical or biochemical (not specified)
Rotterdam Group (2003)[7]	Any two of three of the following and exclusion of related disorders	Oligo-anovulation (nonspecified)	Polycystic ovaries (> 12 follicles 2 to 9 mm, or ovarian volume > 10 mL)	Clinical or biochemical (free testosterone or free testosterone index)
Androgen Excess Society (2006)[8]	Hyperandrogenism as critical, with addition of at least one ovarian marker and exclusion of related disorders	Oligo-anovulation and/or polycystic ovaries	Oligo-anovulation and/or polycystic ovaries	Clinical or biochemical (free testosterone)

markers such as C-reactive protein and fibrinogen). Pelvic ultrasound can also support the diagnosis.

A thorough clinical assessment is critical both to confirm the diagnosis and to identify risk factors for long-term health maintenance. This information helps the clinician prioritize integrative approaches when creating a management plan by elucidating the primary metabolic targets. The plan should take into equal consideration each woman's unique concerns such as weight management, acne, hair loss, or infertility.

Integrative Therapy

A holistic approach to PCOS addresses not just the patient's immediate symptoms and risk management, but also the impact of the syndrome on her mental state and sense of self.

Lifestyle

Weight Management

Weight management plays a central role in the expression of symptoms and long-term consequences in women with PCOS. Fifty percent to 70% of women with PCOS are obese and should be informed that even 5% to 10% weight loss of body mass is associated with significant improvement in clinical metabolic and hormonal markers.[9–11] Guiding women in this arena can be challenging because insulin resistance may inherently make weight loss more difficult, and women are often frustrated by repeated failed attempts to lose weight. Current evidence suggests that the approaches described in the next sections may be most successful.

Physical Activity

Exercise is an important lifestyle approach in PCOS, with diverse benefits such as improved insulin sensitivity and preservation of lean body mass. A 2010 systematic review of exercise therapy in PCOS identified eight studies (five randomized controlled and three cohort) involving moderate intensity physical activity (aerobic and/or resistance) for 12 to 24 weeks.[12] The most consistent improvements included improved ovulation, reduced insulin resistance (9% to 30%), and weight loss (4.5% to 10%). The optimal exercise regimen for PCOS has yet to be defined, so current theories regarding interval training and full-body exercise should be used (see Chapter 88: Writing an Exercise Prescription).

A study published in *Human Reproduction* compared the effects of exercise versus a low-calorie diet in 40 women with PCOS.[13] The exercise group had higher ovulation rates,

better insulin sensitivity, and greater reduction in waist measurements despite less absolute weight loss.

Nutrition

Macronutrients

Although caloric restriction is clearly needed for weight loss, to date only a few small studies have examined the impact of macronutrient composition in PCOS. Several studies ranging from 1 to 6 months that compared a high-protein and low-carbohydrate diet with a high-carbohydrate and low-protein diet showed no significant difference in terms of weight loss, improvements in circulating androgens, glucose metabolism, and leptin.[14,15] Conversely, two pilot studies showed that low-carbohydrate diets were associated with improved depression scores and self-esteem ratings, as well as lower fasting insulin levels and lower rates of acute insulin response to glucose.[16,17] None of these studies took into account the glycemic index of the carbohydrates or the source of protein (animal versus plant based), which may be important factors in insulin resistance and hormone regulation. In 2010, the first study examining impact of glycemic index in overweight and obese premenopausal women with PCOS ($N = 96$) randomized these women to either an ad libitum low–glycemic index diet or a macronutrient-matched healthy diet and followed the women for 12 months or until they achieved a 7% weight loss. The attrition rate was high in both groups (49%). Among the women who completed the study, those on the low–glycemic index diet showed greater improvements in insulin resistance ($P = .03$), menstrual cyclicity (95% compared with 63%; $P = .03$), and serum fibrinogen concentrations ($P < .05$). At this point, no firm recommendations can be given about macronutrient content, although trends suggest that women may do best on a low-carbohydrate diet with inclusion of low–glycemic index, high-fiber carbohydrates (see Chapter 85: The Glycemic Index/Load).

Soy

Soy intake in PCOS is a controversial topic. Soy is a plant food that is also a complete protein, meaning that it has all the required amino acids. It is also low in fat and contains essential fatty acids, numerous vitamins, minerals, and fiber. Soy foods include soy milk and cheese, tofu, tempeh, miso, soy sauce, and edamame. Soy contains phytoestrogens, which led to the debate of its benefits versus risks in PCOS.

Currently, very few studies have actually looked at PCOS and soy intake. One study showed favorable results for PCOS in improving cholesterol.[18] Twelve obese women with PCOS who had high insulin and high cholesterol levels consumed 36 g of soy each day for 6 months. The results showed favorable improvement in reducing low-density lipoprotein cholesterol. The investigators noted no effect on weight loss, hormones, or menstrual cycle in this study. Conversely, many animal studies showed that soy intake can negatively affect fertility. A review of seven soy intervention studies done on women using 32 to 200 mg/day of isoflavones showed increased menstrual cycle length.[19] Current evidence does not imply that soy prevents ovulation, but soy may delay it.

More studies need to be conducted on soy consumption in polycystic ovarian syndrome (PCOS). Women with PCOS who struggle with infertility, consume few calories, or eat a poor diet may want to avoid or limit soy products. Otherwise, a moderate to low intake of soy (once a day or several times a week) can be part of a healthy diet for women with PCOS.

Omega-3 Fatty Acids

Inflammation has been identified in patients with PCOS, whether as a consequence or a contributing factor remains unclear.[20,21] In comparison with control subjects, patients with PCOS have decreased fibrinolytic activity, higher levels of plasminogen activator inhibitor-1, and increased C-reactive protein levels (in both obese and nonobese women), all of which are markers for inflammation.[20,21] Attention to reduction of cardiovascular risk should probably be more aggressive in those women with PCOS who have increased C-reactive protein levels. Including omega-3 fatty acids will help combat the inflammatory component of PCOS, as well as support cardiovascular health (see Chapter 86, The Antiinflammatory Diet). The lignans in flaxseeds may provide additional benefit through support of estrogen elimination.

Supplements

Inositol Family

Investigations into the cause of insulin resistance in PCOS led some researchers to investigate whether derangements in insulin signal transduction could be overcome by oral administration of D-*chiro*-inositol (DCI), a mediator of insulin action that forms naturally in the human body from the metabolism of pinitol and myoinositol (commonly known as inositol) in the diet. In several early studies, evidence favored a benefit of this supplement in improved insulin sensitivity, triglyceride and testosterone levels, as well as improved blood pressure, ovulation, and weight loss.[5,22,23] Forty-four obese women with PCOS were randomly assigned to receive placebo or DCI (1200 mg once a day) for 8 weeks. Supplementation with DCI resulted in an improvement in insulin resistance ($P = .07$), a 55% reduction in the mean serum free testosterone concentration ($P = .006$), and an increase from 27% to 86% in ovulation compared with placebo ($P < .001$). The more readily commercially available D-pinitol (D-*chiro* (+)-*O*-methyl inositol) was shown to raise DCI serum levels; however, results of clinical end points such as impact on insulin sensitivity were mixed.[24,25] In an important study of this nutrient in diabetic patients, 600 mg of pinitol twice per day for 3 months lowered blood glucose levels by 19.3%, lowered average glucose levels by 12.4%, and significantly improved insulin resistance.[24] In another study, 25 women received inositol for 6 months. Twenty-two of the 25 (88%) patients had a single spontaneous menstrual cycle during treatment, of whom 18 (72%) maintained normal ovulatory activity. Ten pregnancies (40% of patients) occurred.

Dosage

DCI: 600 mg daily if less than 60 kg (130 lb) or 1200 mg daily if heavier; pinitol: 600 mg twice daily

Precautions
No interactions with herbs and supplements are known. There is concern that high consumption of inositol might exacerbate bipolar disorder.

Chromium
Chromium is an essential trace mineral that enhances the action of insulin. Although supplementing with chromium has been shown in studies to improve the blood glucose control in type 2 diabetes mellitus, little research has focused specifically on the PCOS population.[26] A pilot study of six women with PCOS concluded that 1000 mcg per day of chromium for as little as 2 months improved insulin sensitivity by an average of 38% (significant) and decreased baseline insulin by 22% (not statistically significant).[27]

Dosage
Chromium picolinate: 600 to 1000 mcg in divided doses daily. Picolinate, a byproduct of the amino acid tryptophan, is combined to support absorption of chromium. Dietary sources include Brewer's yeast, liver, mushrooms, wheat germ, oysters, and some fresh fruits.

Precautions
The daily adequate intake for women ranges from 20 to 45 mcg, depending on age. Laboratory animals have tolerated 350 times this dose without adverse effects, although a question of possible mutagenicity exists with prolonged use. In humans, short-term use of chromium at 1000 mcg daily is safe; these doses are not recommended in pregnancy or renal insufficiency. Prolonged use should be avoided due to concerns about adverse effects.

Vitamin D
Vitamin D plays a role in insulin resistance and egg follicle maturation and development. In a small trial of 13 women with PCOS and vitamin D deficiency, normal menstrual cycles resumed within 2 months in 7 of the 9 women who had irregular menstrual cycles after vitamin D repletion with calcium therapy.[28] Two women even established pregnancies. The authors of the study suggested that abnormalities in calcium balance may be responsible, in part, for the arrested follicular development in women with PCOS and may contribute to the pathogenesis. Vitamin D also plays a key role in glucose regulation, notably in decreasing insulin resistance.[29,30] Low levels of vitamin D have been negatively correlated with the incidence of type 1 and type 2 diabetes.

Dosage
Vitamin D_3: 2000 units daily. Higher doses may be prescribed based on serum 25-OH vitamin D levels. Overweight individuals have a greater risk of vitamin D deficiency because, as a fat-soluble vitamin, vitamin D may not be as bioavailable in high amounts of fat tissue.

Precautions
Vitamin D is well tolerated. Gastrointestinal side effects are most common.

N-Acetylcysteine
Many studies of *N*-acetylcysteine (NAC) have shown benefit in diabetes and several showing benefit in PCOS. NAC has multiple actions, including increasing the antioxidant glutathione, lowering inflammatory markers such as tumor necrosis factor-alpha, and improving insulin sensitivity.[31,32] A study in clomiphene-resistant patients showed improved ovulatory rates (49.3% versus 1.3%) and pregnancy rates (21% versus 0%).[33]

Dosage
Give 1200 to 1800 mg/day in divided doses.

Precautions
NAC is well tolerated, with occasional reports of nausea.

Botanicals

Cinnamomum Cassia
Cinnamomum cassia (not *Cinnamomum zeyanicum* or *Cinnamomum verum*) has been studied in vitro and in humans for lowering glucose levels in diabetes.[34–36] A pilot study published in the July 2007 issue of *Fertility and Sterility* showed that ¼ to ½ teaspoon of cinnamon powder reduced insulin resistance in 15 women with PCOS.

Dosage
The dose is 1 to 6 g powdered cinnamon (¼ to 1 teaspoon) or 200 to 300 mg cassia extract.

Precautions
Cinnamon is well tolerated. Gastrointestinal side effects are most common.

Licorice
Licorice root and glycyrrhetinic acid have antiandrogen effects that may support goals in PCOS. Licorice root as part of a traditional Chinese medicine formula has also been associated with reduced serum testosterone and ovulation induction in women with PCOS.[37,38] Licorice additionally is synergistic with spironolactone; its impacts on potassium loss, hypertension, and fluid retention counteract the opposing actions of spironolactone. Thirty-two hirsute women with PCOS were given 100 mg of spironolactone per day; half also received 3.5 g/day of a licorice root extract standardized to 7.6% glycyrrhetinic acid for 2 months.[39] Licorice use was associated with amelioration of orthostatic symptoms, polyuria, and systolic blood pressure drops, especially during the first 2 weeks of treatment.

Dosage
Glycyrrhiza glabra: 500 mg standardized to 6% to 15% glycyrrhizin (approximately 3.0 to 8.0 g of crude plant material).

Precautions
At lower doses or normal consumption levels, few adverse reactions are evident. A no-observed effects level has been proposed as purified glycyrrhizin, 2 mg/kg/day, and the acceptable daily intake for glycyrrhizin is suggested at 0.2 mg/kg/day. Toxicity from excessive licorice ingestion is well established, with hypokalemia, hypertension, and fluid retention. Licorice is contraindicated in pregnancy.

Chaste Tree Berry (Vitex Agnus-castus)
Vitex is one of the most popular botanicals for PCOS, although data from well-done studies are not available. *Vitex* is believed to shift the estrogen-progesterone balance

in favor of progesterone through increased luteinizing hormone and mild inhibition of follicle-stimulating hormone secretion. *Vitex* also reduces prolactin secretion, which when elevated may inhibit fertility. A small study involving women with fertility disorders examined pregnancy rates from a chaste berry–containing herbal blend versus placebo twice daily for 3 months.[40] Women with secondary amenorrhea or luteal insufficiency in the active treatment group achieved pregnancy twice as often as in the group receiving placebo. However, the total number of patients conceiving was small (15 women).

Two other publications explored the benefits of a *Vitex*-containing blend on progesterone level, basal body temperature, menstrual cycle length, pregnancy rate, and side effect profile.[41,42] The designs were double-blind placebo-controlled trials of a proprietary nutritional supplement containing chaste berry, green tea, L-arginine, and vitamins and minerals. The treatment group (n = 53) demonstrated increased mean midluteal progesterone, especially among women with very low pretreatment levels. Cycle length and luteal basal body temperatures improved significantly. After 3 months, 14 women in the treatment group were pregnant (26%) compared with 4 of the 40 women in the placebo group (10%; P = .01). These studies are difficult to extrapolate given the proprietary nature of the supplements, although the trends toward improvement with no side effects warrant further consideration. Several small studies in the German literature also reported a benefit of *Vitex* for acne, with self-reports of improvement of up to 70%.[43]

Dosage

Vitex products are available in many different dosage forms, including fresh and dried berries, capsules containing powdered chaste berries, and liquid preparations such as extracts and tinctures. The German Commission E recommends a daily intake of 30 to 40 mg of dried herb. *Vitex* should be standardized to 0.5% agnuside and 0.6% aucubin per dose.

Precautions

Animal and human studies suggest that *Vitex* may interfere with oral contraceptives and hormone therapy. Based on in vitro data, *Vitex* may also interact with dopamine agonists (e.g., bromocriptine, levodopa). Use during pregnancy is not recommended.

Other Herbs: Saw Palmetto and Green Tea

Herbalists recommend several other herbs for PCOS based on biochemical activity. Minimal research has been done to verify benefits or identify appropriate doses, however.

Saw Palmetto

Elevated 5-alpha-reductase activity has been demonstrated in women with PCOS.[44] Saw palmetto inhibits 5-alpha-reductase and thereby reduces the conversion of testosterone to dihydrotestosterone, the more potent form. Although saw palmetto has the potential for benefit in reducing acne, excess facial and body hair, and androgenic hair loss, no research has been done in women, and saw palmetto has potential interactions with drugs such as oral contraceptive pills (OCPs). Saw palmetto should not be recommended at present.

Green Tea *(Camellia sinensis)*

Green tea extracts have been proposed as a natural remedy for PCOS based on several pathways. Polyphenols may reduce inflammation and insulin resistance, stimulate thermogenesis, and increase production of sex hormone–binding globulin, thus leading to reduced free testosterone. However, a study from Asia of high-concentration polyphenol extracts for 3 months did not find improvements in laboratory or clinical measures.[45] At this point, green tea extract should not be recommended, although drinking 3 cups of organic green tea daily is a healthy option.

Complementary Healing Approaches

Acupuncture

Acupuncture has the potential to influence PCOS through its effects on the sympathetic nervous system, the endocrine system, and the neuroendocrine system.[46,47] In a 2009 study, one group of women with PCOS was treated for 4 months with electroacupuncture, another group of women was given heart rate monitors and told to exercise three times a week, and a third, control group was educated about the importance of exercise and a healthy diet but received no instructions. The investigators found that the women who received acupuncture or who exercised had decreased sympathetic activity. The women who received electroacupuncture treatments also had more regular menstrual cycles, reduced testosterone levels, and reduced waist circumference. Experimental observations in animal and clinical data suggest that acupuncture exerts beneficial effects on insulin resistance and ovulation. Although research studies are limited, acupuncture as an adjunctive therapy may be considered in many women for the direct impact not only on PCOS parameters, but also on associated mood disorders and stress.

Mind-Body Therapy

Women with PCOS have a significantly increased prevalence of depression and anxiety.[48–50] Mood disorders may be directly related to biochemical imbalances (androgens, insulin resistance), and they may also be exacerbated by stress related to body image issues and infertility. Addressing concerns through mind-body approaches, self-care, and cognitive-behavioral therapy should be encouraged for all women.

Pharmaceuticals

Medication decisions should be based on a woman's predominant symptoms and goals. Major classes include insulin sensitizers, weight loss medications, and hormone modulators.

Insulin Sensitizers

Metformin improves insulin resistance and hyperandrogenism.[51] It is also associated with regulation of menstruation and ovulation and may benefit up to 79% of women attempting to conceive. Metformin is considered weight neutral, as opposed to many other medications used for glucose regulation.

Dosage

Start with 500 mg daily for 1 week; titrate to 500 mg twice daily in week 2 and as needed thereafter. The maximum daily dose is 2.5 g in two or three divided doses.

Precautions
Side effects are gastrointestinal and include nausea and diarrhea. Metformin should be avoided if creatinine clearance is less than 30 mL/minute. *Thiazolidinediones* are less thoroughly studied in PCOS compared with metformin. This class of medications is associated with weight gain, thus making it an unattractive choice for many women struggling with PCOS. Studies of troglitazone (now off the market because of hepatotoxicity), pioglitazone, and rosiglitazone demonstrated improvements in insulin sensitivity, hyperandrogenemia, and ovulatory rates. Given the potential for adverse effects, this class of medications is best reserved for patients with established diabetes mellitus.

Weight Loss Medications
Orlistat, given with an energy-restricted diet, was shown to improve insulin resistance, as well as lower free testosterone markers, in obese women in some but not all studies.[52–54] The trials were short term (3 to 6 months), and orlistat needs further investigation to determine its utility in patients with PCOS.

Dosage
A dose of 120 mg, three times daily before meals, was used for 3 to 6 months in the studies.

Precautions
Orlistat may cause fat-soluble vitamin deficiency and greasy stools.

Hormone Modulators
Oral Contraceptives
Oral contraceptive pills (OCPs) are first-line options for androgen excess issues such as hirsutism and acne, in accord with the 2008 Endocrine Society Clinical Practice Guidelines. OCPs reduce luteinizing hormone secretion and thus ovarian androgen secretion; additional reductions in free androgen concentration occur through increased levels of sex hormone–binding globulin.[55] OCPs provide additional benefit by protecting against endometrial hyperplasia in amenorrheic women with excess estrogen exposure.

Dosage
Appropriate choices include OCP preparations containing 30 to 35 mcg of ethinyl estradiol combined with a progestin with minimal androgenicity, such as norethindrone, norgestimate, desogestrel, or drospirenone.

Precautions
Risks and side effects of OCPs are similar to those for women without PCOS. The concern also exists that OCPs may increase some cardiovascular risk factors such as inflammatory markers and insulin resistance. Absence of pregnancy should be documented before OCPs are begun. If the woman has had no menstrual period for 6 or more weeks, withdrawal bleeding should be induced by administration of 5 to 10 mg of medroxyprogesterone acetate daily for 10 days before initiation of OCP treatment (to minimize breakthrough bleeding when starting the pill).

Although oral contraceptive (OCP) use helps many women overcome the troublesome symptoms of polycystic ovarian syndrome (PCOS), these drugs have been associated with higher risk of cardiovascular disease in the general population.[56,57] The risk of cardiovascular disease is associated with increased age, smoking, and hypertension. Additional concerns include a negative impact on inflammatory markers and diabetes risk. Studies are needed in the PCOS population to assess the long-term benefit-to-risk ratio of using OCPs. For now, increased awareness and attention to regular follow-up of metabolic and cardiovascular markers are critical in any woman taking OCPs.

Progestins
Progestins are appropriate for women who need endometrial protection but who are not interested in or appropriate for OCPs. Cyclic progestins promote withdrawal bleeding and prevent endometrial hyperplasia.

Dosage
Synthetic progestin: medroxyprogesterone acetate: 10 mg orally daily for 7 to 10 days every 1 to 2 months. Bio-identical progestin: micronized progesterone: 400 mg orally daily for 10 days every 1 to 2 months. Bio-identical progesterone cream has not been used in research studies, and whether the creams can provide consistent levels sufficient for uterine protection is unclear.

Precautions
Sedation or confusion may occur.

Antiandrogens
Antiandrogens, which block androgen binding to receptor, are often used off label for hirsutism.[58] Most commonly prescribed is spironolactone. Flutamide is another option, although it is associated with more side effects.

Dosage
Spironolactone: 50 to 200 mg/day; flutamide: 250 mg two to three times a day

Precautions
Contraception is essential, because if pregnancy occurs, an antiandrogen such as spironolactone could be teratogenic; discontinuation 3 months before conception is recommended. If spironolactone alone is used, endometrial protection may be needed.

Clomiphene Citrate
Clomiphene citrate is an antiestrogen and an effective option to stimulate ovulation induction for women with PCOS. Approximately 80% of women with PCOS ovulate in response to clomiphene citrate, and approximately 50% conceive.

Dosage
The strategy is to use the lowest dose of clomiphene possible to initiate ovulation, starting with 50 mg/day, for 5 days (usually days 5 to 9). If no follicle development occurs with this dose, the dose or duration of treatment can be increased.

Statins

Statins are an area of debate in the literature regarding their cardiovascular and endocrine benefit in women with PCOS. An initial study was very promising: 40 patients with PCOS were randomly assigned to atorvastatin at 20 mg daily or placebo.[59] After 12 weeks, the researchers reported an absolute reduction in free androgen index (−32.7%) and total testosterone (−24.6%) and increased sex hormone–binding globulin (+13.7%) in the atorvastatin group, but none in the placebo group. Patients in the atorvastatin group had lower serum insulin levels and homeostasis model of insulin resistance (HOMA-IR) compared with increases in the placebo group. Conversely, a study published in 2010, in which 20 patients with PCOS who had low-density lipoprotein levels higher than 100 mg/dL took atorvastatin at 40 mg/day or placebo for 6 weeks of treatment, showed reduced androgen levels, biomarkers of inflammation, and blood pressure.[60] However, atorvastatin worsened hyperinsulinemia and failed to improve endothelial function in women with PCOS. Until the full picture is defined, reserving statin use for women only for treatment of hyperlipidemia and not as an attempt to treat hyperandrogenemia or insulin resistance seems prudent.

Dosage

Doses are prescribed per usual recommendations for hyperlipidemia.

Precautions

Statins are considered possibly teratogenic in pregnancy. The usual concerns regarding liver and muscle issues apply.

Surgery

When severe symptoms are not controlled with the therapies described earlier and a patient has morbid obesity, bariatric surgery may be considered. Results of two small studies on the effects of bariatric surgery have been published.[61] A retrospective study evaluated 30 women with PCOS who underwent laparoscopic Roux-en-Y gastric bypass. Postoperative benefits included resolution of menstrual irregularity (100%), improvement in hirsutism (75%), resolution of type 2 diabetes, and ability to cease medications for hypertension (78%) and hyperlipidemia (92%). These results were confirmed in a prospective study evaluating 17 women with PCOS.

Surgery may also be performed for ovulation induction in the management of clomiphene citrate–resistant anovulatory women with PCOS. Various types of ovarian surgery are employed (e.g., wedge resection, electrocautery, laser vaporization, multiple ovarian biopsies), and all procedures result in an altered endocrine profile after the procedure. One plausible mechanism postoperatively is that the rapidly reduced secretion of all ovarian hormones restores feedback to the hypothalamus and pituitary and results in appropriate gonadotrophin secretion. These surgical procedures provide an option, albeit one used less often now, when natural and pharmaceutical approaches are not successful in anovulatory patients with PCOS.

Prevention Prescription

- Maintain appropriate weight and a regular aerobic exercise routine.
- Avoid excessive amounts of saturated fat such as those found in red meat, fried foods, and dairy.
- Replace vegetable oils with olive or canola oil for cooking.
- Consume omega-3–rich fats found in cold-water fish, nuts, greens, and ground flaxseed.
- Encourage soy-based foods such as soy milk, edamame, tempeh, miso, soy nuts, and nongenetically modified tofu. Try to eat 1 to 2 oz a day.
- Avoid dietary supplements or environmental exposures that may increase circulating hormone levels such as pesticides, herbicides, and bovine growth hormone–rich dairy products.
- Avoid supplements or drugs that include dehydroepiandrosterone, androstenedione, testosterone, and human growth hormone.

Therapeutic Review

A1

Lifestyle approaches are first-line recommendations for PCOS, both in conventional and integrative medicine approaches. Many women with PCOS do well with attention to diet, exercise, supplements, and acupuncture. Some women need medications to achieve needed improvements when metabolic derangements are greater.

Lifestyle

- Remove exacerbating factors. Minimize exposure to hormone-disrupting chemicals.

Nutrition

- Promote weight loss to achieve an ideal body weight. Start with achievable goals and provide adequate support.
- Eat 1 to 2 servings of soy-rich foods daily. Each 1-oz serving (approximately the size of the palm of the hand) provides approximately 25 mg. B1
- Encourage a low-carbohydrate diet that takes into account the glycemic index of foods. B1
- Encourage foods rich in omega-3 fatty acids (e.g., salmon, nuts, or ground flaxseeds). B1

Continued

Physical Activity

- Recommend moderate exertion 30 to 60 minutes daily. A1

Supplements

- Vitamin D_3: 2000 units daily (dose based on serum 25-OH vitamin D level) B1
- Chromium picolinate:1000 mcg daily B2
- D-*chiro*-inositol/pinitol: 600 mg once or twice per day B2

Botanicals

- *Cinnamomum cassia:* ¼ to 1 teaspoon B1
- Licorice root in conjunction with spironolactone for amelioration of side effects and complementary action B2
- Chaste tree berry (*Vitex*): 60 drops of tincture or 175 mg of extract, standardized to 0.6% agnusides C2

Complementary Therapies

- Acupuncture may reduce sympathetic nervous system tone and improve menstruation. It has additional benefits for stress reduction and mood. A1
- Mind-body therapies can help women cope with stress, depression, and anxiety related to PCOS. A1

Pharmaceuticals

- Insulin sensitizers include metformin, at 500 to 1000 mg twice daily. A2
- If the patient is unable to achieve satisfactory weight loss, consider support with orlistat. A2
- Medications such as clomiphene may be prescribed in consultation with a reproductive endocrinologist for ovulation induction. A2
- Antiestrogens for hirsutism include spironolactone, at 50 to 200 mg/day, or flutamide, at 250 mg two to three times a day. A2
- Oral contraceptive pills are prescribed for amenorrhea, hyperandrogenism, and uterine protection. A2

Surgical Therapy

- If the patient has morbid obesity with significant comorbidities despite the foregoing measures, consider referral for bariatric surgery. A3
- Ovarian surgery may be indicated for infertility. A3

KEY WEB RESOURCES

American Association of Clinical Endocrinologists: www.aace.com.	This Web site contains a position statement on metabolic and cardiovascular consequences of PCOS, as well as practice management forms for new and follow-up visits for patients with PCOS.
Womenshealth.gov: www.womenshealth.gov/faq/polycystic-ovary-syndrome.cfm.	This Web site, from the U.S. Department of Health and Human Services Office on Women's Health, provides patient education materials on PCOS.
American Society for Reproductive Medicine: www.asrm.org.	This Web site describes medical and surgical options for PCOS.

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Chapter 37

Osteoporosis

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Osteoporosis is defined as a generalized skeletal disorder characterized by compromised bone strength, which predisposes individuals to an increased risk of fracture. It is a significant cause of pain, disability, and death throughout the world. That treatment strategies are limited and imperfect heightens the importance of preventive strategies. Integrative medicine emphasizes the use of lifelong exercise habits and an antiinflammatory diet to prevent the development of osteoporosis.

Pathophysiology and Epidemiology

The incidence of osteoporotic fractures varies widely across populations. The Chinese have relatively low rates, whereas in Iceland rates are high.[1] More than 10 million people in the United States have osteoporosis, and more than 2 million osteoporotic fractures occur each year.[2] Women are at higher risk than men and account for approximately 75% of all cases. However, men are at greater risk of dying of a hip fracture should they sustain one (20.7% versus 7.5%.).[3]

To assess bone health, the World Health Organization (WHO) uses only the dual x-ray absorptiometry (DEXA) scan, which measures bone density but not quality. By this criterion, approximately 7% of postmenopausal women 50 years old or older have osteoporosis, and 40% have osteopenia. The costs to the U.S. health care system are significant, totaling more than $16 billion annually. As the population ages, the costs related to osteoporosis prevention and treatment are expected to continue to climb.[4]

Osteoporosis is a multifactorial disease arising from genetic, hormonal, metabolic, mechanical, and immunologic factors (Fig. 37-1). Our bones provide the support structure for our bodies, protect vital organs, and play a central role in mineral and acid-base balance. The two main types of bone cells are osteoblasts (which synthesize the organic bone matrix and its calcification) and osteoclasts (which resorb bone to allow for metabolic requirements and for repair and remodeling).

Bone mass reaches its peak at approximately 30 years of age and begins to decline after age 40 years. Repair and renewal of bone continue throughout adult life, however, with approximately 15% of bone mass turning over each year. Bone is dynamic, constantly responding to a range of hormonal, metabolic, neurologic, and mechanical signals. Bone mineral density (BMD) is a function of bone gained during growth and lost during aging.

Bone loss begins in both men and women in the fourth decade. Women lose an average of 35% of their cortical bone and 50% of their trabecular bone. Because men reach higher peak bone mass, have a larger cortical thickness, and have better preservation of bone microstructure, they are half as likely as women to experience a fracture. Women typically lose 0.5 to 0.9% of bone density per year during the perimenopause, 1% to 3 % during the menopausal years, and 1% per year into old age.[3]

Screening and Diagnosis

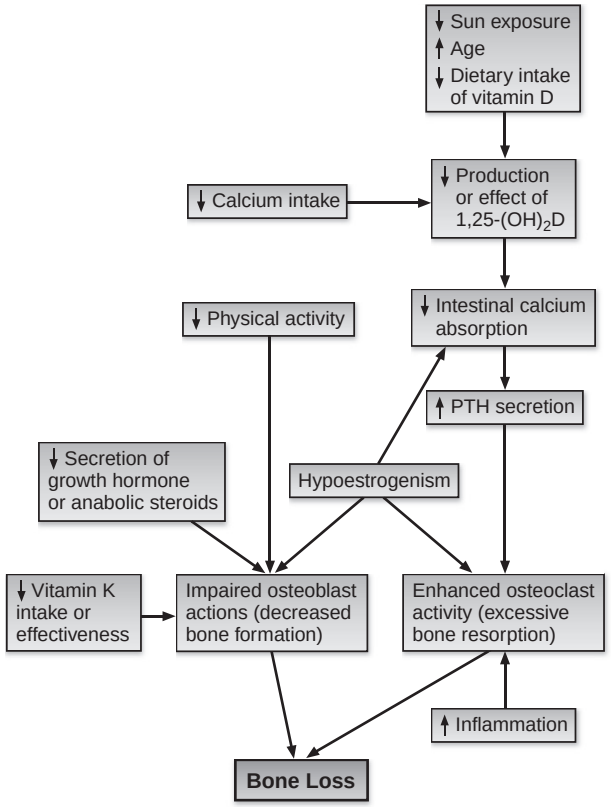
Assessing Bone Strength

Bone strength is determined by bone quality as well as by bone mass. Bone quality is influenced by bone microarchitecture and the composition of the bone matrix and mineral.[5] No established way exists to assess bone quality in a clinical practice setting. Bone mass or BMD is most commonly assessed using a DEXA scan.

Osteoporosis is defined as a BMD more than 2.5 standard deviations (SD) below the mean for young adults. Osteopenia is defined as a BMD 1 to 2.5 SD below the young adult mean.

The usefulness of screening for fracture risk with DEXA has been questioned. Some studies did not show BMD measurement to be helpful in predicting nonvertebral fracture risk.[6] Other studies showed a strong correlation between low femoral neck BMD and risk of hip fracture.[7] In addition, evidence indicates a significant inverse relationship between BMD and vertebral fracture risk.[8] Nonetheless, a wide overlap exists between the bone densities of women who will eventually suffer a fracture and those who will not.[9]

FIGURE 37-1
Pathophysiology of osteoporosis. 1,25-$(OH)_2D$, 1,25-dihydroxyvitamin D (vitamin D component that aids calcium absorption); PTH, parathyroid hormone.



Measuring biochemical markers of bone turnover combined with BMD may provide a more accurate prediction of future fracture risk.[10] Other known risk factors for osteoporotic fracture should be assessed as well.

The North American Menopause Society (NAMS) recommends that BMD be measured in all women 65 years old or older, in younger postmenopausal women with one or more risk factors, and in all women with medical conditions associated with an increased risk of osteoporosis.[11]

Risk Factors for Osteoporotic Fracture

The focus of osteoporosis screening programs is to reduce the risk of fracture. In addition to bone density, many other factors influence fracture risk. The Women's Health Initiative (WHI) investigated whether an algorithm could be created that would predict the 5-year risk of hip fracture among the 93,676 postmenopausal women who participated in the observational component. Eleven factors were found to be predictive: age (number of years older than 50), self-reported health, weight, height, race or ethnicity, self-reported physical activity, fracture at 55 years old or older, parental hip fracture, smoking status, corticosteroid use, and treated diabetes.[12]

Other factors that increase the risk of a fracture include nutritional deficiencies, high alcohol intake, excessive caffeine consumption, premature menopause, malabsorption disorders, autoimmune disease, small body frame, white /Caucasian or Asian descent, impaired vision, dizziness or balance problems, fainting or loss of consciousness, physical frailty, vitamin D deficiency, and use of medications, including corticosteroids, aromatase inhibitors, anticonvulsants, sedatives, anticholinergics, antihypertensives, heparin, cyclosporine, and medroxyprogesterone acetate.

Role of Inflammation

Chronic inflammation is implicated in the process of aging,[13,14] and it plays a role in the development of a wide range of chronic diseases, including cardiovascular disease, Alzheimer disease, diabetes, and cancer.[15,16] Growing evidence indicates that osteoporosis is also, in part, a result of chronic low-grade inflammation.[17–21] Women with chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease are known to be at increased risk of developing osteoporosis.[22] However, elevated levels of high-sensitivity C-reactive protein (hsCRP) are associated with lower BMD in healthy women, as well as in women with inflammatory conditions.[19]

Proinflammatory cytokines such as interleukin-6 (IL-6), IL-1, and tumor necrosis factor-alpha (TNF-alpha) promote accelerated bone loss by activation of osteoclasts, inhibition of collagen production in osteoblasts, and enhanced breakdown of the extracellular matrix.[16] Furthermore, suppression of proinflammatory cytokines appears to support the growth of new bone. For instance, TNF-alpha inhibitors such as Etanercept have been found to improve BMD in patients with spondyloarthropathy.[23]

Additionally, diets rich in fruits, vegetables[24] and omega-3 fatty acids[25] have been found to decrease the risk of developing osteoporosis. Fruit and vegetable consumption is associated with both increased peak bone mass and improved bone health in older populations.[26–29] The bone-building effects of fruits and vegetables may result from several factors: antiinflammatory and antioxidant properties; alkalinizing effects; the nutrients, such as potassium, vitamin K, and vitamin C, that they provide; and the presence of other unknown compounds and synergistic effects. For all these reasons, an anti-inflammatory diet is recommended as the foundation of an integrative bone health plan.

Integrative Therapy

Nutrition for Bone Health

Calcium

Calcium is an essential nutrient for building and maintaining healthy bones; 99% of calcium in the body is in bone, and 38% of bone matrix consists of calcium. Surprisingly, however, high calcium intakes do not ensure strong bones, and low calcium intakes do not necessarily lead to weaker bones.[2,30] Calcium is absorbed in the small intestine by a transcellular transport mechanism that requires adequate vitamin D. Calcium may also be absorbed by passive diffusion when calcium intakes are high. Calcium excretion increases as dietary protein[31] and sodium intakes rise.[32] Vegetarians excrete less calcium in their urine than do omnivores.[33]

Calcium absorption can be improved and excess excretion can be decreased by the following: maintaining a 25(OH)D concentration higher than 34 ng/mL (85 nmol/L),[34] avoiding

TABLE 37-1. Dietary Reference Intakes for Calcium and Vitamin D

	CALCIUM			VITAMIN D		
Life Stage Group	*Estimated Average Requirement (mg/day)*	*Recommended Dietary Allowance (mg/day)*	*Upper Level Intake (mg/day)*	*Estimated Average Requirement (mg/day)*	*Recommended Dietary Allowance (Units/Day)*	*Upper Level Intake (Units/Day)*
Infants 0–6 mo	*	*	1,000	†	†	1,000
Infants 6–12 mo	*	*	1,500	†	†	1,500
1–3 yr	500	700	2,500	400	600	2,500
4–8 yr	800	1,000	25,000	400	600	3,000
9–13 yr	1,100	1,300	3,000	400	600	4,000
14–18 yr	1,100	1,300	3,000	400	600	4,000
19–30 yr	800	1,000	2,500	400	600	4,000
31–50 yr	800	1,000	2,500	400	600	4,000
51–70 yr (M)	800	1,000	2,000	400	600	4,000
51–70 yr (F)	1,000	1,200	2,000	400	600	4,000
Older than 70 yr	1,000	1,200	2,000	400	800	4,000
14–18 yr, pregnant or lactating	1,100	1,300	3,000	400	600	4,000
19–50 yr, pregnant or lactating	800	1,000	2,500	400	600	4,000

From Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press, 2011.
*For infants, adequate intake is 200 mg/day for 0 to 6 monthsof age and 260 mg/day for 6 to 12 monthsof age.
†For infants, adequate intake is 400 mg/day for 0 to 6 monthsof age and 400 mg/day for 6 to 12 monthsof age.

excess animal protein, increasing consumption of fruits and vegetables, limiting dietary sodium to less than 2400 mg/day,[35] avoiding excess caffeine,[36] eating fewer highly refined carbohydrates,[37] and having an adequate intake of essential fatty acids.[38]

In the United States, the Institute of Medicine (IOM) issued a 2010 update of the dietary reference intakes (DRIs) for calcium and vitamin D (Table 37-1).

A *Lancet* meta-analysis published in 2007 reviewed 29 randomized trials with more than 63,000 patients and found good evidence that the use of calcium, alone or in combination with vitamin D, prevented osteoporosis in women and men 50 years old and older.[39] The meta-analysis also showed a 12% reduction in the risk of fractures, with treatment more effective at higher doses of calcium (higher than 1200 mg) and vitamin D (higher than 800 units). Calcium sources in the diet extend significantly beyond dairy products (Tables 37-2 and 37-3). An estimate of calcium intake from all dietary sources should be made before supplements are added.

In postmenopausal women with low calcium intakes, the addition of 500 mg per day of calcium citrate has been found to significantly reduce bone loss in the femur, radius, and spine.[40] Milk consumption[41] and higher calcium intakes alone may not favorably affect fracture risk, however.[42] Accordingly, calcium supplementation should be part of a broader strategy that includes adequate vitamin D and other bone-building foods and nutrients.

TABLE 37-2. Dairy Calcium Sources

FOOD	AMOUNT (oz)	CALCIUM (mg)
Milk	8	300
Yogurt	8	275–325
Hard cheeses high in calcium (cheddar, Swiss, Edam, Monterey Jack, Provolone, Parmesan, Romano, part-skim mozzarella)	1	200–300
Soft cheeses low in calcium (Brie, Neufchatel)	1	20–50

TABLE 37-3. Nondairy Calcium Sources

FOOD	AMOUNT	CALCIUM (mg)
White beans	1 oz cooked	161
Spinach	½ cup	122
Turnip greens	½ cup	99
Soybeans	½ cup cooked	90
Broccoli	1 cup cooked or fresh	90
Bok choy	½ cup cooked or fresh	80
Almonds	1 oz dry-roasted	80
Salmon	3 oz, canned with bones	180
Dried figs	10	269

A 2010 meta-analysis in *BMJ* (the *British Medical Journal*) suggested increased cardiovascular events in women taking calcium. The studies, conducted in patients with osteopenia, were not controlled for risk factors for heart disease, however. In addition, when calcium was administered with vitamin D (as is recommended), it did not lead to any increased risk.[43]

Large tablets may be difficult to swallow and may not fully disintegrate in the stomach. Some people tolerate calcium supplements better in the form of powders, capsules, and liquids. Calcium supplementation should not exceed 500 mg at any one time, to maximize absorption. Avoid taking calcium supplements along with psyllium or with foods high in oxalic acid (e.g., spinach) or phytic acid (e.g., wheat bran). Chewable calcium supplements are well tolerated by children.

Calcium carbonate is best taken with meals and is less expensive than calcium citrate. Calcium carbonate provides 40% elemental calcium. Calcium citrate is well absorbed with or without meals,[44] and it is the best form for older adults with reduced stomach acid. Calcium citrate provides 21% elemental calcium. Calcium from dolomite, oyster shell, or coral is not recommended.

Acid-Base Issues

The skeleton plays a key role in acid-base homeostasis.[45] Eating animal protein generates acids that are excreted in the urine. High intakes of animal protein can lead to significant calcium resorption from bones to buffer the acids.[4,46] Urinary losses of calcium rise in proportion to net renal acid secretion. In contrast, fruits and vegetables generate bicarbonate, which can buffer the acidifying effects of animal protein, alkalinize the urine, and significantly lower urinary calcium excretion.[4] A study by Buclin et al[46] revealed that acid-forming diets increased calcium excretion by 74% when compared with base-forming diets.

In bone, minute downward shifts in the local pH can stimulate osteoclast activity and impair the activity of osteoblasts.[47] The typical Western diet tends to produce chronic low-grade metabolic acidosis that is harmful to bone health.[48–50] Diets with less animal protein and increased amounts of fruits and vegetables are therefore recommended.

Muhlbauer described 25 plant foods as bone resorption inhibitory food items (BRIFI). These include garlic, rosemary, Italian parsley, sage, thyme, parsley, dill, onion, arugula, prune, fennel, orange, leek, yellow boletus, wild garlic, field agaric, red cabbage, celeriac, red wine, and lettuce.[51] In addition to effects on acid-base balance, the benefits of plant foods also appear to be related to the pharmacologically active compounds they contain. Certain specific monoterpenes,[52] flavonoids, and phenols[53] may be responsible for the observed beneficial effects on bone.

Vitamin D

Vitamin D is essential for calcium absorption and for bone health. The hormonally active form of vitamin D, 1,25(OH)D, induces active transport of calcium across the intestinal mucosa. Vitamin D also stimulates the absorption of phosphate and magnesium ions and acts synergistically with vitamin K to stimulate bone mineralization directly.

Vitamin D deficiency and insufficiency are widespread throughout North America.[54–56] Breast-fed infants, women, older adults, obese persons, and people with darker skin tones are at higher risk of deficiency. An international epidemiologic study found that 64% of postmenopausal women seeking medical care for osteoporosis had inadequate vitamin D concentrations (less than 30 ng/mL).[57] Supplementation with vitamin D at doses of 700 to 800 units/day has been shown to reduce fracture risk in older adults.[58,59] Vitamin D also reduces the risk of falls[60–62] and improves lower extremity function[63] in older adults.

Current recommended intakes of vitamin D are considered too low by many researchers.[64,65] All patients should be screened at least once for vitamin D deficiency with a measurement of their serum 25(OH)D concentration. Although in 2010 the IOM revised the vitamin D deficiency level to 20 ng/mL, data support higher levels for bone health. For example, a 2005 meta-analysis found that optimum fracture prevention was reached at a level of 40 ng/mL (100 nmol/L).[59] Each incremental increase in 25(OH)D is associated with an increase in BMD.[66–68]

Vitamin D can be obtained through sunlight exposure, from a limited number of foods, or from supplements. Sunlight exposures of 10 to 15 minutes, without sun block, at the appropriate latitude and season, can be a good source of endogenously produced vitamin D. A few foods are naturally rich in vitamin D: fatty ocean fish such as salmon, sardines, and black cod, as well as sun-exposed mushrooms. Fortified foods include some brands of orange juice, fortified milk, and some yogurts. Vitamin D supplementation is an inexpensive and reliable way to ensure an optimum serum concentration of 40 ng/mL (100 nmol/L). For most adults older than age 65, a supplement of at least 700 units/day is needed to achieve this serum concentration.[69,70] Vitamin D_3 (cholecalciferol) is the preferred form to use,[71] and it should be taken with meals.

Essential Fatty Acids

Both omega-6 and omega-3 polyunsaturated fatty acids are essential nutrients. They are incorporated into cell membranes, where they influence membrane characteristics and become precursors for eicosanoids such as prostaglandins, leukotrienes,

and thromboxanes. An ideal ratio between omega-6 and omega-3 fatty acids is thought to be 1:1 to 2:1.[72] However, Western diets tend to be relatively high in omega-6 fats and low in omega-3 fatty acids, and typical ratios are approximately 10:1 (omega-6 to omega-3).[73] These fats perform opposing roles in the body, and the balance between them plays a significant role in regulating the inflammatory response.

Omega-3 fatty acids are known to have antiinflammatory effects and act to suppress production of IL-1-beta, TNF-alpha, and IL-6.[74,75] Certain omega-6 fatty acids, such as gamma-linolenic acid (GLA) are also known to possess antiinflammatory effects. In contrast, the omega-6 fatty acid linoleic acid (LA) tends to have proinflammatory effects and leads to increased production of IL-1, TNF, and IL-6 cytokines.

The intake and ratio of essential fatty acids in the diet appear to play important roles in bone health. In animal studies, fish oils rich in omega-3 fatty acids have been found to attenuate bone loss associated with estrogen withdrawal.[76] Animal studies have also shown that the omega-3 fatty acid eicosapentaenoic acid (EPA) enhances calcium absorption, reduces calcium excretion, and increases calcium deposition in bone.[77]

Limited human studies of omega-3 supplementation for osteoporosis prevention or treatment have been conducted. One small study found that supplementation with calcium, EPA, and GLA resulted in a decrease in bone turnover and an increase in lumbar and femoral bone density in older women.[77] In the Rancho Bernardo study, higher ratios of omega-6 to omega-3 fatty acids were associated with lower BMD in the hip for all women studied and with lower BMD in the spine for women not taking hormone replacement therapy (HRT).[78] Overall, omega-3 fatty acids appear to enhance calcium absorption, reduce calcium excretion, and improve mineralization of bone matrix and bone strength.[38]

Protein

Protein is required for bone formation, and adequate protein intake, particularly in the premenopausal years, is essential.[79] However, high levels of animal protein in the diet are associated with increased fracture rates and accelerated bone mineral loss.[80–82] In the Nurses' Health Study, protein intakes higher than 95 g/day were associated with significantly higher forearm fracture rates than were protein intakes lower than 68 g/day.[81] In another study, lowering protein intakes to current recommended dietary allowance (RDA) guidelines (0.8 g/kg) resulted in significant reductions in urinary calcium excretion and in markers of bone resorption.[83] Several studies also showed that an increased ratio of vegetable to animal protein was protective against fractures.[84–86] To support bone health, an adequate but not excessive intake of protein is recommended. Some protein-rich vegetarian foods such as tofu and edamame should be included.

Vitamin K

The two naturally occurring classes of vitamin K are phylloquinone (K_1), which is synthesized by plants, and menaquinone (K_2), which is synthesized by bacteria. Both forms are useful in the prevention and therapy of osteoporosis. Vitamin K plays a key role in carboxylating osteocalcin and other bone proteins.[87] As mentioned, vitamins K and D act synergistically to stimulate bone mineralization.[88,89]

Epidemiologic studies consistently show a link between higher vitamin K status and reduction of fracture risk. Booth et al[90] reviewed data from the Framingham Heart Study and found that elderly men and women in the highest quartile of dietary vitamin K had a relative risk for hip fracture of 0.35. Women in the Nurse's Health Study who consumed one or more servings of lettuce per day (a source of vitamin K_1) had a relative risk of 0.55 for hip fracture.[91] Patients with osteoporotic fractures of the spine and femoral neck were found to be markedly deficient in vitamin K_1 and in the MK-7 and MK-8 forms of vitamin K_2.[92] Other studies have shown similar findings.[93] Most vitamin K intervention studies also showed a reduction in BMD loss and improved bone biomarkers.[94]

The Vitamin K Supplementation in Postmenopausal Women with Osteopenia (ECKO) trial was a 2-year randomized controlled trial of 440 postmenopausal women with osteopenia. The women were treated with 5 mg of vitamin K_1 daily. No significant difference in changes in BMD was noted between the two groups. Although fewer women in the vitamin K group had clinical fractures (9 versus 20, $P = .04$), the study was not sufficiently powered to measure fractures.[95]

Subclinical vitamin K deficiency is common, and typical dietary intakes are lower than the levels associated with decreased fracture risk.[96] The current DRI for adult women is 90 mcg, but amounts of 450 mcg/day or higher may be needed for optimum bone health.[87] The best food sources of vitamin K_1 are green leafy vegetables such as lettuce, collards, spinach, and kale, as well as other vegetables rich in chlorophyll, such as broccoli. Other plant sources include vegetable oils, nuts, and fruits. Animal foods such as chicken, soft cheeses, and butter contain relatively small amounts of vitamin K_2. Natto, a fermented soybean food, is a very rich source of vitamin K_2. Vitamin K is fat soluble, and foods rich in vitamin K should be eaten with some healthy fat, such as olive oil. Patients taking anticoagulants should aim for a consistent intake of vitamin K–rich foods.

Vitamin K supplementation does not have an overcoagulation effect, and it has an excellent safety profile. In 2001, the IOM showed no evidence of toxicity with vitamin K supplementation, and in Japan, vitamin K_2 is prescribed at doses of 45 to 90 mg (1000 times the RDA) without side effects. Vitamin K supplements should not be used by patients taking anticoagulants.

Magnesium

Epidemiologic studies have linked higher magnesium intakes with increased BMD.[11,12] Some intervention trials of magnesium supplementation have also shown an increase in BMD, as well as reduced fracture rates.[97,98] In the WHI trial, however, participants in the highest quintile of magnesium intake had the highest rate of wrist and lower arm fractures.[99]

Therefore, the data on the relationship between magnesium intake and bone remain inconclusive. The average magnesium intake for U.S. women is 228 mg/day, whereas the DRI for magnesium is 320 mg/day, so insufficient intakes are common. Magnesium deficiency may impair osteoblast function and induce bone resorption by osteoclasts.[100] Magnesium is also required for the conversion of vitamin D to 1,25-dihydroxycholecalciferol (calcitriol).[101] Good sources of magnesium include nuts and seeds, soybeans, dark green leafy vegetables, and dairy products.

Trace Minerals

Several trace minerals including zinc, copper, boron, and manganese act as cofactors in specific enzymes related to bone metabolism. Serum concentrations of zinc and copper have been found to be lower in osteoporotic women than in controls.[102] A varied, whole food diet in addition to a good-quality multivitamin/mineral supplement should ensure an adequate supply of these nutrients.

Vitamin C

Vitamin C (ascorbic acid) is a required nutrient for collagen formation. Although vitamin C deficiency is often unrecognized, it is relatively common in the United States; 18% of adults consume less than 30 mg/day.[103] Vitamin C, along with calcium intakes of 500 mg/day or more, appears to support an increase in BMD.[104]

Soy

Studies of soy's effects on bone have shown mixed results.[105] Unfortunately, as outlined in a 2006 meta-analysis, these studies have many flaws. Of the 11 randomized controlled trials, no two studies used identical products; they studied isoflavones rather than soy as a whole food; some studies used very low doses of isoflavones, whereas others did not specify the amounts; and most trials lasted for only 6 to 12 months, too short to detect effect on BMD.[106]

An exception to these poorly designed trials is the Shanghai Women's Health Study. This study, which examined food frequency questionnaires of 75,000 Chinese women 40 to 70 years old, found a relative risk of fracture of 0.63 in the highest quintile of soy protein intake (13 g/day or more).[107] In fact, a significant reduction in fracture risk was seen beginning in the second quintile, at soy protein intakes of 5 g/day (21 mg/day of isoflavones). This study examined the intake of traditionally eaten whole soy foods, such as tofu and fresh soybeans, rather than isolated isoflavones. This is also one of the few studies of soy to look at the key end point of fracture risk, as opposed to BMD or markers of bone turnover.

Soy appears to have certain beneficial effects on bone: stimulating production of osteoprotegerin by osteoblasts, suppressing activation of osteoclasts, and increasing production of insulin-like growth factor-I.[108,109] On the whole, the evidence from in vitro, animal, and human studies supports a beneficial effect of soy on bone health.[110,111] Based on the available evidence, one to two servings/day of whole soy foods can be recommended.

Substances That May Be Harmful to Bone Health

Sodium

Average sodium intakes in the United States (3500 mg/day) exceed the recommended intake of less than 2400 mg/day, and high-salt diets are known to increase urinary calcium excretion.[12] The Dietary Approaches to Stop Hypertension and Sodium Reduction (DASH II) diet, which included 9.5 servings of fruits and vegetables per day, low-fat dairy products, whole grains, and reduced meat and sodium intake, resulted in decreased calcium losses and reduced bone turnover.[112] However, the bone benefits of DASH II diet appear to be related to its overall effects rather than specifically to the reduction in sodium. Increasing calcium and potassium intakes can substantially offset the urinary losses of calcium caused by high sodium intakes.[32] Because there are cardiovascular benefits to moderating sodium intake and because many diets do not contain sufficient calcium, patients should be advised to stay within the recommended sodium intake of less than 2400 mg/day.

Caffeine

Excessive caffeine intake is associated with a modest increase in the risk of osteoporotic fracture.[36] The increased risk appears to occur in women who consume more than 300 mg of caffeine/day or approximately 4 cups of coffee, and who also have low calcium intake. Excessive caffeine intake should be avoided.

Phosphorus

Phosphorus is required to form hydroxyapatite, a key component of bone. The RDA is 700 mg; however, typical North American diets contain amounts ranging from 1000 to 1600 mg per day. Furthermore, additives in processed foods such as hot dogs and processed cheese can add as much as 1000 mg/day of additional phosphorus to the diet. Total phosphorus intake may be underestimated because phosphorus from food additives is often not included in food composition tables.[113] Excessive intake of phosphorus may be harmful to bone health; it has been shown to depress serum calcium levels, increase secretion of parathyroid hormone, decrease markers of bone formation, and increase markers of bone absorption.[114] The Brazilian Osteoporosis Study found that a higher intake of phosphorus was associated with an increased risk of fragility fractures in women older than 40 years.[115] Although human studies are few, preventing excessive phosphorus intake by reducing intake of processed foods and by avoiding excess animal protein in the diet seems to be a prudent approach.

Vitamin A

Vitamin A (retinol) intakes of more than 3000 mcg/day are associated with a significantly increased risk of hip fracture.[116] This increased risk exists for retinol intake from foods and from supplements.[117] Although not all studies support these findings, consumers should choose supplements that contain less than 2000 mcg of retinol, or preferably, products that contain only beta-carotene or mixed carotenoids.

Smoking

Cigarette smoking is a known risk factor for osteoporosis, but the underlying mechanisms for this association are not fully understood. The effect of smoking on fracture risk is not closely linked to BMD, and it may be related to lower body mass, earlier age of menopause, estrogen-lowering effects, impaired calcium absorption, or increased production of free radicals.[118] In the Nurses' Health Study, smokers had a relative risk of 1.2 for hip fracture, and this figure rose to 1.4 for those who smoked 25 or more cigarettes/day.[119] A meta-analysis involving more than 59,000 men and women found that smokers had a relative risk of 1.13 for any fracture and a relative risk of 1.6 for hip fractures.[120] Clearly, for many reasons, people should be encouraged not to begin smoking. Current smokers who quit will obtain benefits to their bone health after a period of 10 years.[119]

Alcohol

Animal studies showed that chronic heavy alcohol consumption, especially during adolescence and young adulthood, can significantly damage bone health.[121] In contrast, low or moderate consumption of alcohol in adulthood appears to have protective effects on bone.[122] Moderate alcohol consumption has recognized cardiovascular benefits,[123] but it can also increase the risk of breast cancer in women,[124] and it has other potentially detrimental effects on health.[125] Men may benefit from a daily alcoholic beverage; women should be advised to have fewer than seven alcoholic drinks per week.

Botanicals

Numerous in vitro and animal studies and a smaller number of human trials have examined the potential of herbal medicines to enhance bone health.[53] A study of Shen Gu (Mixture for Nourishing Kidney and Strengthening Bone) in 96 osteoporotic patients found significant beneficial effects on bone as compared with controls.[126] The Ayurvedic herbal-mineral preparation Reosto, which contains a mixture of botanicals and organic calcium, was studied in a randomized double-blind placebo-controlled trial. BMD increased significantly in the treatment group versus controls over the study period of 12 months.[127] A 12-week study involving 62 postmenopausal women found that black cohosh *(Actaea racemosa)* increased concentrations of bone-specific alkaline phosphatase (a metabolic marker for bone formation) and stimulated osteoblast activity.[128] *Dioscorea spongiosa,*[129,130] *Astragalus membranaceus,*[131] walnut extract (*Juglans regia* L.),[132] and curcumin, a compound found in turmeric root *(Curcuma longa),*[133] have also shown osteoprotective effects in laboratory and animal studies. Further research is needed to assess the role of botanical medicines in supporting bone health.

Tea (Camellia sinensis)

Tea has antiinflammatory effects, cardiovascular benefits, and cancer protective properties.[134,135] Several studies have linked tea consumption to modest increases in BMD.[135,136]

Mind-Body Connection

Chronic stress, through activation of the sympathetic nervous system, tends to exert catabolic effects on the body that result in the breakdown of energy stores and body tissues. In animal studies, both chronic stressors and the administration of glucocorticoids were shown to stimulate bone resorption.[137,138] Major depression[139,140] and anorexia nervosa[141] are both associated with elevation of serum cortisol levels and with increased bone loss. Increased sympathetic nervous system activity stimulates resorption of bone by osteoclasts and inhibits bone formation by osteoblasts.[142]

Bone remodeling appears to be influenced by input from the central nervous system, as well as by previously recognized local factors and hormonal signals.[143] Stress reduction, using mind-body practices such as meditation, self-hypnosis, guided imagery, breath work, or biofeedback, is highly recommended as part of an integrative plan to support bone health and overall well-being.

Exercise

In addition to high-quality nutrition, exercise is the other major factor needed to build and maintain strong bones. Bone is dynamic tissue that responds to the physiologic and biomechanical signals it receives. Both general physical activity and mechanical loading contribute to building peak bone mass, beginning in the prepubertal years.[144,145]

Bone density at all skeletal sites is strongly correlated with muscle mass, and muscle mass is strongly linked to physical activity.[146] Muscle mass generally increases until approximately the age of 30 years and begins to decline after 50 years of age. Muscle strength losses tend to be most striking after the age of 70 years. Investigators have proved, however, that regular exercise at any age, even in very old persons, can result in increased muscle strength, balance, and functional capacity.[147,148]

Exercise training programs in premenopausal and postmenopausal women have been shown to prevent or reverse bone loss consistently in both the lumbar spine and the femoral neck.[149] The Bone Estrogen Strength Training (BEST) Study found that postmenopausal women who received 800 mg/day of calcium citrate, along with a structured exercise program, increased their muscle mass by 11% to 21% and increased their BMD by approximately 2%.[150] Even women with established osteoporosis can improve their bone mass with a low-impact exercise program.[151] Fracture risk can also be decreased with exercise programs. Walking for at least 4 hours per week has been found to decrease hip fracture risk by 41%.[152] Another study of postmenopausal women found a reduced risk of vertebral fractures after a 2-year program of back-strengthening exercises.[153]

In the Senior Fitness and Prevention (SEFIP) study, 246 women who were older than 65 years old were randomized to an 18-month exercise program or a wellness program. Participants in the exercise program showed an increase in BMD at the spine of 1.77% (controls increased 0.033%) and at the femoral neck of 1.01% (controls decreased 1.05%). Fewer falls occurred in the exercise group (1.0 per person compared with 1.66 in the control group). In addition, health care costs were lowered in the exercise group (€2225 versus €2780 in controls).[154]

Recommended physical activities include walking, gentle and vigorous aerobic exercise, jumping, running, weight training, and racquet sports. Ideally, people should aim for 30 to 45 minutes of exercise, five or more times per week. Weight training is best done on alternate days. Tai chi is highly recommended to reduce the number of falls in older adults.[155–157]

Considerations in Younger Women

Ideally, every young woman should reach her own highest possible peak bone mass by age 30 to 35 years. Peak bone mass is influenced by genetic factors, as well as by diet and physical activity during childhood, adolescence, and young adulthood. Young women should be counseled about the importance of a healthy diet, adequate calcium and vitamin D, and regular weight-bearing exercise. Maintaining an ideal body weight and engaging in regular physical activity may be the most important modifiable factors in the development of optimum bone mass.[158]

Young women who use depot medroxyprogesterone acetate (DMPA) for contraception are at risk for bone loss. Women 18 to 21 years old who use DMPA have been found to lose bone at a rate of 1.5% per year during a time when control groups gained bone at an average rate of 2% per year.[159] BMD tends

to recover after discontinuation of DMPA.[160] Smoking, heavy alcohol consumption, anorexia nervosa,[141] late-onset menarche, amenorrhea,[161] primary ovarian failure, and autoimmune diseases[162] are other risk factors that may prevent young women from achieving their optimum peak bone mass.

Some bone loss normally accompanies pregnancy and lactation and is then usually recovered after infants are weaned.[163] Epidemiologic studies show that multiple pregnancies and periods of lactation are not associated with lower bone mass or increased fracture risk.[164]

Pharmaceuticals

Osteoporosis is best approached with a lifelong, comprehensive prevention program. Women of all ages should be aware of the diet and lifestyle choices that support bone health. Ongoing strategies should include optimum diet, appropriate supplementation, regular physical activity, and fall prevention. Secondary causes of osteoporosis should be corrected when possible.

In addition, pharmacologic therapy for prevention or treatment of osteoporosis may be recommended. Guidelines for initiating therapy vary among different organizations. The NAMS guidelines recommend treatment in all postmenopausal women with prior vertebral or hip fracture or with hip or spine T-scores lower than −2.5 and in postmenopausal women with T-scores between −2.0 and −2.5 and with one or more additional risk factors.[165] Some women may wish to begin an extensive bone-building program and continue to monitor their bone density before making a decision to begin medication.

The number needed to treat (NNT) and, when available, the number needed to harm (NNH) are useful communication tools for discussing the benefit of any medication used for prevention. These numbers are especially useful in osteoporosis in which the NNT tends to be quite high, thus making the decision much less clear and more closely related to a patient's values. (Some patients like to do everything possible to prevent a possible problem, whereas others prefer to take as few medications as possible.)

Role of Estrogen

As estrogen levels fall in the years following menopause, bone loss accelerates. The primary action of estrogen on bone is to inhibit the osteoclast by increasing the amount of osteoprotegerin produced by osteoblasts.[166] Estrogen also has antiinflammatory effects and suppresses the production of bone-resorbing cytokines.[167–169] Consequently, at the time of menopause, the concentration of inflammatory cytokines that can induce osteoclastogenesis rises.[170,171]

Postmenopausal HRT has beneficial effects on bone, reduces the risk of colon cancer, and can alleviate hot flashes and vaginal dryness. Conversely, women who use HRT have an increased risk of cardiovascular disease, stroke, thromboembolic events, and breast cancer.[172] In the WHI trial, women receiving hormone therapy with conjugated equine estrogen, alone or with medroxyprogesterone acetate, had increased BMD and lower fracture rates. However, the study investigators concluded: "When considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit, even in women considered to be at high risk of fracture."[173] Some leading health organizations recommend against the use of HRT for the prevention of chronic disease.[174] Thus, treatment with HRT should be individualized, based on a careful exploration of the risks and benefits for each woman.

Bisphosphonates

Antiresorptive therapies reduce fracture risk by inhibiting the activity of osteoclasts and reducing bone turnover, thus increasing bone mass. High bone turnover is particularly relevant in the pathogenesis of vertebral fractures.[39] Bisphosphonates are indicated for both prevention and treatment of postmenopausal osteoporosis. The most common side effects are dyspepsia, nausea, and abdominal pain. Osteonecrosis of the jaw is a serious, rare event associated with bisphosphonate use (most often when bisphosphonates are prescribed intravenously as a component of cancer treatment). Some concern also exists that bisphosphonates may impair microdamage repair and thus increase the brittleness of bone.[175,176]

Alendronate has been shown to increase BMD and to reduce the incidence of fractures of the spine and hip in women with osteoporosis.[177] Esophagitis may occur with alendronate. The usual dose range is 35 to 70 mg once weekly. Risedronate also increases BMD and reduces vertebral and some nonvertebral fracture rates.[178] The usual dose is 35 mg once weekly. Ibandronate has indications and side effects similar to those of the two other bisphosphonates discussed. Ibandronate may be given as a once-per-month dose of 150 mg.[179] Of the three oral forms, alendronate has the lowest 3-year NNT to prevent vertebral fractures (NNT = 15) (Tables 37-4 and 37-5).[165,180]

TABLE 37-4. Vertebral Fracture Prevention Studies

MEDICATION	DOSE	3-YEAR NNT TO PREVENT VERTEBRAL FRACTURE	TRIAL
Alendronate (Fosamax)	5 mg/day for 2 yr then 10 mg/day	15/34	FIT
Ibandronate (Boniva)	2.5 mg/day or 20 mg eod for 12 doses every 3 months	21	BONE
Risedronate (Actonel)	2.5 or 5 mg/day	20	VERTA-NA
Zoledronic acid (Reclast)	5 mg IV every yr	14	HORIZON
Raloxifene (Evista)	60 or 120 mg/day	29	MORE
Strontium ranelate	2 g/day	9	SOTI
Teriparatide (Forteo)	20 mcg sq/day	12	—

BONE, oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe; eod, every other day; FIT, Fracture Intervention Trial; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; IV, intravenously; MORE, Multiple Outcomes of Raloxifene Evaluation; NNT, number needed to treat; SOTI, Spinal Osteoporosis Therapeutic Intervention; VERTA-NA, Vertebral Efficacy with Risedronate Therapy—North America.

TABLE 37-5. Hip Fracture Prevention Studies

MEDICATION	DOSE	NNT TO PREVENT A HIP FRACTURE	TRIAL
Alendronate	5 mg/day for 2 yr then 10 mg/day	91	FIT
Risedronate	2.5 or 5 mg/day	91	HIP
Zoledronic acid	5 mg IV/yr	91	HORIZON
Strontium ranelate	2 g/day	48	TROPOS

FIT, Fracture Intervention Trial; HIP, Hip Intervention Program; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; IV, intravenously; NNT, number needed to treat; TROPOS, Treatment of Peripheral Osteoporosis.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators act as estrogen agonists on bone and lipid metabolism while also having antagonist actions on breast and endometrial tissue. Raloxifene has been shown to be effective at reducing postmenopausal bone loss and at decreasing the risk of vertebral fractures.[181] The 3-year NNT to prevent vertebral fractures is 29. Raloxifene also significantly reduces the risk of breast cancer and improves lipid profiles.[182] The usual dose is 60 mg/day. Side effects include deep vein thrombosis and pulmonary embolism.

Calcitonin

Calcitonin is produced by thyroid C cells and acts to inhibit bone resorption by inhibiting osteoclast activity. Calcitonin from salmon may be used to treat osteoporosis in women who have been postmenopausal for at least 5 years. Calcitonin is effective in reducing the pain associated with acute compression fractures of the vertebrae,[183] and it may reduce the incidence of vertebral fractures. It is normally given as a daily intranasal spray of 200 units. Side effects are usually minor and include flushing, nausea, and diarrhea.

Teriparatide

Teriparatide (PTH 1-34) is a medication that includes a sequence of 34 amino acids contained in parathyroid hormone. Teriparatide has anabolic effects on bone and stimulates osteoblast cell proliferation. This agent is useful in reducing the incidence of new vertebral and nonvertebral fractures in postmenopausal women.[179,184,185] The 3-year NNT to prevent vertebral fractures is 12. Teriparatide is given as a once-daily subcutaneous injection (20 mcg) for a period of up to 2 years. This therapy may be followed by an antiresorptive agent. Side effects include nausea and headaches.

Strontium

Strontium ranelate is a promising medication that is currently used in Europe for the treatment of postmenopausal osteoporosis. Several studies found it to be an effective agent in reducing vertebral and nonvertebral fracture risk in both younger postmenopausal women and very old adults.[186,187] The 3-year NNT to prevent vertebral fractures is 9, the lowest of all currently available therapies. Strontium ranelate acts both to stimulate bone formation and to reduce bone resorption. Adverse effects include nausea and diarrhea.[188]

Pharmaceuticals to Avoid

Many pharmaceuticals can negatively affect bone density. In May 2010, the U.S. Food and Drug Administration added a warning label to proton pump inhibitors and stated that these drugs were associated with possible increased risk of fractures of the hip, wrist, and spine.

Conclusion

Osteoporosis is a costly and potentially disabling condition affecting millions of people. An integrative approach encompassing diet, exercise, supplements, and mind-body therapies, as well as pharmaceutical medications when indicated, is recommended to prevent and treat this disorder. The good news is that essentially the same strategies that help people build healthy bones will also protect them against heart disease, diabetes, depression, and a host of other chronic conditions.

Prevention Prescription

Recommendations to build and maintain healthy bones:

- An antiinflammatory diet that includes an abundance of deeply colored fruits and vegetables, healthy fats, whole grains, and antiinflammatory herbs, teas, and spices
- Elemental calcium intake from diet in addition to supplements adding up to at least 800 mg per day
- A serum 25-OH vitamin D concentration in the range of 40 ng/mL (100 nmol/L)
- A balanced ratio of omega-6 to omega-3 fatty acids
- Adequate but not excessive protein (0.8 g/kg), including some vegetarian protein sources
- One to two servings per day of whole soy foods
- A good-quality multivitamin and mineral supplement
- Physical activity for 30 to 45 minutes most days of the week that includes weight-bearing, aerobic, and weight-lifting exercise
- A daily mind-body practice
- Avoidance of smoking, excess alcohol intake, excess caffeine consumption, and vitamin A (retinol) in amounts greater than 2000 mcg/day
- Reduction of the risk of falls and, if possible, avoidance of prescribing medications that harm bone or increase the risk of falls
- Pharmaceutical therapies that are individualized, with risk and benefits explored with each patient

Therapeutic Review

Osteoporosis is a costly and potentially disabling condition affecting millions of people. An integrative approach encompassing diet, exercise, supplements, and mind-body therapies, as well as pharmaceutical medications when indicated, is recommended to prevent and treat this disorder. The good news is that essentially the same strategies that help people build healthy bones will also protect them against heart disease, diabetes, depression, and a host of other chronic conditions.

Laboratory Evaluation

- 25-Hydroxy vitamin D level with a goal near 40 ng/mL
- Dual x-ray absorptiometry bone scan
- Consider highly sensitive C-reactive protein, thyroid-stimulating hormone, calcium, and alkaline phosphatase.
- To assess metabolic markers of bone turnover, consider urine levels of *N*-telopeptides or deoxypyridinium.

Lifestyle

- Avoid first-hand and second-hand smoke exposure. A1

Exercise

- 30 to 45 minutes/day of aerobic, weight-bearing, and weight-lifting exercise (Patients with osteoporosis should consult with a health professional to plan an appropriate, safe exercise program.) B1

Nutrition

- Limit
  - Sodium B1
  - Caffeine B1
  - Phosphorus (including phosphoric acid in soda) B1
- Encourage
  - Antiinflammatory diet C1
  - Calcium-rich diet (see Table 37-2) C1
  - Adequate protein intake from plant sources more than from animal sources; one to two servings a day of whole soy foods B1
  - Vitamin K_1–rich foods. These include any green plant with chlorophyll such as green leafy vegetables such as lettuce, collards, spinach, kale, and broccoli. Other plant sources include vegetable oils, nuts, and fruits. Animal foods that include vitamin K_2 include chicken, soft cheeses, and butter. Natto, a fermented soybean food, is a very rich source of vitamin K_2. B1
  - Tea *(Camellia sinensis),* 2 cups a day C1

Supplements

- Vitamin D: 1000 to 2000 units/day B1
- Calcium citrate or carbonate as required so that total daily intake from diet, in addition to supplements, is at least 800 mg/day B1
- Multivitamin and multimineral: Minerals should include zinc, copper, magnesium, boron, and manganese. C1

Mind-Body Therapy

- Meditation, self-hypnosis, guided imagery, biofeedback, and breath work B1

Pharmaceuticals

- Consider a bisphosphonate in patients with a previous osteoporotic fracture, or a T-score between 2.0 and −2.5 and one or more additional risk factors. B2
- Consider a selective estrogen receptor blocker such as raloxifene, at 60 mg daily, in patients also at risk for breast cancer. B2
- Consider calcitonin in postmenopausal women. This can also reduce pain associated with vertebral compression fracture. The dose is one spray (200 units) in alternate nostrils daily. B2

KEY WEB RESOURCES

Bayer HealthCare BEST strength training videos: http://cals.arizona.edu/cpan/	This is the Web site for University of Arizona Center for Physical Activity and Nutrition. Detailed information is available on the Bone Estrogen Strength Training study, and a training guide book and continuing education course is available.
Foundation of Osteoporosis Research and Education 10-Year Fracture Risk Calculator (FORE Fracture Risk Calculator): http://riskcalculator.fore.org	This easy-to-use fracture risk calculator requires that you enter a BMD score, age, height, and weight, in addition to some other basic lifestyle information.
National Osteoporosis Foundation: http://www.nof.org	This Web site provides detailed information for health care professionals and patients about osteoporosis prevention and treatment.

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Chapter 38

An Integrative Approach to Obesity

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Overview: The Danger and the Crisis

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Pathophysiology

Definition of Overweight and Obesity

In 2004, obesity was reclassified by Medicare as a chronic disease. Obesity is characterized by an excess of body fat and is most often defined by the body mass index (BMI), a mathematical formula that correlates well with excess weight at the population level. The BMI is measured by taking weight in kilograms, divided by height in meters squared (kg/m^2). Worldwide, adults with a BMI of 25 to 30 are categorized as overweight, whereas obesity is classified according to stages or grades (Table 38-1). Grade III obesity was formerly known as morbid obesity, but the term was appropriately changed for several reasons: morbidity may not occur at a BMI higher than 40 but certainly can be found at BMIs lower than that. BMI can sometimes be inaccurate because it does not distinguish between fat and muscle, nor does it predict body fat distribution. On a population level, however, BMI does seem to track trends in adiposity as opposed to muscularity, and those individuals with large muscle mass with resulting high BMIs are easily distinguishable from those with large amounts of adipose tissue.

In a clinical setting, the most valuable measurement strategy for classifying weight other than the BMI is waist circumference. The presence of extreme abdominal fat has been shown to be an independent risk factor for diabetes, high blood pressure, and cardiovascular disease. [6] Waist circumference is obtained by placing a measuring tape in a horizontal plane around the waist at the level of the umbilicus and the superior iliac crests.

Risk of obesity and associated diseases is increased if waist circumference is greater than 40 inches in male patients and more than 35 inches in female patients.

In children, the term obesity is generally not used because of the potential prejudicial issues that may ensue when a child is labeled with such a title. As a result, overweight in children is defined conservatively as being at or higher than the 95th percentile of age- and sex-adjusted weight. At risk for overweight falls under the classification of those children who are at the 85th to 94.9th percentile. Increasing concern about the potentially high numbers of overweight children not classified correctly has prompted an ongoing initiative to revise the definition.

Obesity-Related Health Risk and Morbidity

The disease risk profile based on BMI and waist circumference is described in Table 38-2. Evidence shows that obesity is a proinflammatory state that increases the risk of several chronic diseases, including hypertension, dyslipidemia, diabetes, cardiovascular disease, asthma, sleep apnea, osteoarthritis, and several cancers.[7] Excess weight may also promote gallstone formation, fatty liver, gastroesophageal reflux, menstrual abnormalities, infertility, stress incontinence, gout, carpal tunnel syndrome, and low back pain.[8–12] Obese adults have more annual admissions to hospitals, more outpatient visits, higher prescription drug costs, and worse health-related quality of life than do adults of normal weight.[13]

The United States stands at the center of a global obesity epidemic in both adults and children. According to data from the World Health Organization (WHO), 1.6 billion adults worldwide were overweight in 2005. At least 400 million adults were obese, and 20 million children younger than 5 years of age were overweight. The WHO predicts that 2.3 billion adults will be overweight and 700 million will be obese by the year 2015.[1] On U.S. soil, overweight and obesity affect 65% to 80% of adults and a rising proportion of children, with the prevalence of obesity increasing year by year. Evidence suggests that the more extreme degrees of obesity are rapidly increasing over time compared with overweight.[2]

The trends in childhood obesity are similar to those in adults. The U.S. Centers for Disease Control and Prevention reported a tripling of obesity rates since 1990. Despite the limitations in defining obesity (or overweight) in children to avoid the potentially stigmatizing label that comes with it, data continue to show that weight in children is accelerating at an alarming rate. Overweight in some minorities is estimated to be as high as 50%.[3,4] Studies suggest that obesity is also occurring in infants and toddlers, and that waist circumference has been rising along with childhood body mass index (BMI), perhaps at an even greater rate.[5] This finding is deeply worrisome because central adiposity points toward an increased risk of insulin resistance, metabolic syndrome (hypertension, dyslipidemia, and type 2 diabetes), and its eventual transition to cardiovascular disease. The health implications of an increasing, uncontrollable rise in childhood overweight and obesity predict a corresponding rise in the chronic health risks that accompany them.

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Pathogenesis

The challenge with understanding the etiology of obesity is that obesity is the result of a relatively straightforward series of outcomes achieved by a set of complex and dynamic interactions. Obesity is a direct result of long-term mismatches in energy balance, with daily intake of energy greater than daily output. This condition puts people in a state of positive energy balance, and the longer they are there, the more weight they will gain. The complexity lies in how that energy balance is maintained.

Calories encompass the value of energy that determines this state of balance. We eat food, and various metabolic processes in our bodies break it down into energy. The relationship between energy and matter is under the control of the laws of physics, specifically the first law of thermodynamics, proved by Sir Isaac Newton, which states that all energy in the universe is conserved. In relation to food, when more energy is taken in by the body relative to the energy consumed, the surplus is ultimately converted into matter. This works well in a vacuum, but it may not be easily translated into the real world. Although energy intake is relatively determined by food and drink, with each having a particular caloric value, the nature of that matter can vary. Thus, calories may not be equal and can translate into differing amounts of energy burned by the body over a fixed period of time. Although a pound of lead and a pound of feathers may drop in a vacuum at the same speed, when a similar experiment is conducted outside, air resistance causes the lead to drop like a stone and the feathers to float to the earth at a leisurely pace. Calories operate in a similar fashion. The calories you eat are absorbed at different rates and have different amounts of fiber, carbohydrates, protein, and fat, along with other chemicals and nutrients that may translate into different metabolic signals that affect the energy equation.[23] Consequently, if it is true that calories are not equal, calorie type may influence energy balance as much as amount. A study from the Harvard School of Public Health confirmed this to be true; overweight patients fed 300 more calories per day actually lost more weight than did their counterparts who were eating food of different composition.[24]

Whereas we are beginning to discover the inherent complexity on the left side of the energy equation (calories in), measuring energy output has always been a much more intricate calculation because of the number of variables that determine the consumption of calories. Energy output is expressed as the sum of various processes, including resting energy expenditure, basal metabolic rate, physical activity, rates of growth, and thermogenesis. Studies have confirmed that macronutrient distribution, endocrine factors, and diverse genetic predispositions may contribute important mitigating influences at any given level of calorie consumption.[2]

Although the pathogenesis of obesity involves a set of complex multifactorial details to explain a relatively simple

TABLE 38-1. Adult Classification of Overweight

CLASSIFICATION	BODY MASS INDEX (kg/m²)
Underweight	18.5
Normal weight	18.5–24.9
Overweight/preobese	25.0–29.9
Obese	
Class I	30.0–34.9
Class II	35.0–39.9
Class III	40.0 or higher

Adapted from the National Heart, Lung and Blood Institute, National Institutes of Health. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* NIH publication no. 00–4084. Bethesda, MD: U.S. Department of Health and Human Services, 2000.

TABLE 38-2. Classification of Overweight and Obesity and Associated Disease Risk

CLASSIFICATION*	BMI (kg/m²)	OBESITY STAGE	*Disease Risk (Relative to Normal Weight and Waist Circumference)†*	
			WAIST CIRCUMFERENCE	WAIST CIRCUMFERENCE
			Men: up to 40 in. (up to 102 cm); women: up to 35 in. (up to 88 cm)	Men: more than 40 in.; women: more than 35 in.
Underweight	Lower than 18.5	—	—	—
Normal	18.5 to 24.9	—	—	—
Overweight	25.0 to 29.9	—	Increased	High
Obese	30.0 to 34.9	I	High	Very high
	35.0 to 39.9	II	Very high	Very high
Extremely obese	40.0 or higher	III	Extremely high	Extremely high

Adapted from World Health Organization. *Preventing and Managing the Global Epidemic of Obesity.* Report of the World Health Organization Consultation of Obesity. Geneva: World Health Organization; 1997.
BMI, body mass index.
*For persons 20 years old and older.
†Disease risk for type 2 diabetes mellitus, hypertension, and cardiovascular disease. Increased waist circumference can be a marker for increased disease risk, even in persons of normal weight.

The impact of obesity on children demonstrates the dire seriousness of this epidemic. Since 1990, because of childhood obesity, type 2 diabetes has been transformed from a disease that once affected adults in midlife to a pediatric epidemic affecting children as young as 6 years old.[14] At current rates of incline, the projection is that rates of type 2 diabetes in children will soon be higher than rates of type 1 diabetes. Obesity in children produces a risk profile similar to that of adults, thus raising the risk of several conditions, including hypertension, dyslipidemia, gallstones, and sleep apnea, as well as increasingly elevated levels of androgens, promoting orthopedic abnormalities (e.g., slipped capital epiphyses), and increasing intracranial pressure.[15–20] In women, adolescent obesity is associated with completion of fewer years of education, higher rates of poverty, and lower rates of marriage and household income, whereas in men, adolescent obesity is associated with increased all-cause mortality, as well as mortality from cardiovascular disease and colon cancer.[21, 22]

condition, what should not be forgotten is that human physiology is much the same as it has always been. The increase in obesity prevalence in the past few decades cannot be explained by changes in the human gene pool, but rather by environmental changes that have not been seen previously in our collective history. An environment that promotes excess food intake of poor quality and discourages physical activity will most surely produce obesity in a species that has adapted itself to survive by responding to caloric scarcity within the confines of a world that demands a significant level of energy expenditure.[13]

Integrative Assessment

People living in the United States average 2.7 office visits to a physician per person per year, and 60% of these visits occur within a primary care setting. Patients regard physicians as a primary resource for preventive health information and recommendations. Moreover, when physicians counsel patients to make a change in their lifestyle, they are more likely to make an attempt.[25] Ideally, assessment and treatment of obesity should be done within the setting of a multidisciplinary team designed to manage medical, nutritional, emotional, and exertional components of the desired lifestyle intervention—in this case, weight loss. This ideal setting is often unavailable or unrealistic, however, and in a primary care setting, an obesity management strategy can still be implemented successfully with simple interventions by a single practitioner. Initial goals should focus on modest weight loss of 5% to 10% of total body weight over a 12- to 16-week period of time. Such weight loss has been shown in studies to improve blood glucose control in obese patients with type 2 diabetes.[26] Modest weight loss has also been found to prevent the progression of diabetes and cardiovascular disease in those obese individuals with impaired glucose tolerance and insulin resistance.[27] Improvements can be seen in most obesity-related conditions, from lipid disorders and hypertension to joint pain, muscle weakness, and lung function, after such a modest 5% to 10% reduction in total weight.

An integrative assessment of obesity should include a thorough medical history and physical examination with anthropomorphic measurements, weight history, nutritional and dietary history, assessment of current and past physical activity, diagnostic laboratory evaluation, electrocardiogram (if considering weight loss medications), and screening for current levels of motivation, emotional status, availability of support systems, and potential barriers to treatment.

A medical history should inquire about the presence of obesity-related conditions in the individual or family: asthma and sleep apnea, coronary artery disease with or without dyslipidemias, diabetes, hypertension, thrombophlebitis and cellulitis, chronic pain, muscle and joint disorders, impingement syndromes, menstrual abnormalities, infertility, and stress incontinence, along with obesity-related cancers of the esophagus, colon, rectum, and pancreas and hormonally related cancers such as breast, ovarian, endometrial, and prostate. Metabolic syndrome should be identified because it is often a marker for insulin resistance, which ultimately leads to type 2 diabetes (Table 38-3). Current medical history, physical examination, and laboratory information allow an accurate diagnosis of metabolic syndrome. Abdominal obesity and hypertriglyceridemia may be particularly early markers of the syndrome and represent a readily detectable indicator of diabetes risk.[28]

TABLE 38-3. Clinical Identification of Metabolic Syndrome

RISK FACTOR	DEFINING LEVEL
Abdominal adiposity	Waist circumference
Men	102 cm (40 inches)
Women	88 cm (35 inches)
Triglycerides	150 mg/dL
HDL cholesterol	
Men	40 mg/dL
Women	50 mg/dL
Blood pressure	130/85 mm Hg or higher
Fasting blood glucose level	110 mg/dL or higher

Adapted from National Heart, Lung and Blood Institute, National Institutes of Health.
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): *National Cholesterol Education Program*. Bethesda, MD: National Institutes of Health; 2004.
HDL, high-density lipoprotein.

Current medications should be assessed for their potential promotion of weight gain. Psychiatric medications are notorious for contributing to weight gain and include antipsychotics, some antidepressants, and antiseizure medications. Other commonly used drugs that promote weight gain include long-acting steroid medications, some oral contraceptives, certain diabetic medications, and drugs for the treatment of blood pressure. Weight-neutral alternatives are available and should be attempted if weight loss is a priority (Table 38-4).

Weight history should assess the progression of weight gain over time to illustrate the use of any previous weight loss strategies such as special diets, exercise programs, meal replacements, nutritional supplements, medications, or surgical procedures. The practitioner should understand how much weight was lost and over what period of time, what was the period of weight maintenance, and what promoting factors caused weight regain, if any. "Yo-yo" dieting, consisting of repetitive patterns of weight loss followed by weight regain, may provide information about previous successful strategies, as well as recurrent negative behavioral patterns.

Laboratory testing is an important adjunct to information obtained from a patient's history, and patients should be screened for obesity-related conditions such as hypothyroidism, liver disease, metabolic syndrome, dyslipidemia, glucose intolerance, insulin resistance, diabetes, and, if suspected, polycystic ovarian syndrome (PCOS) and Cushing syndrome. Because obesity is a proinflammatory condition, the prudent approach may be to assess inflammatory markers such as high-sensitive C-reactive protein. Serum 25-(OH) vitamin D levels should be obtained in light of research demonstrating the trend toward significant vitamin D deficiency and decreased bioavailability of vitamin D in the obese population.[29] Vitamin D deficiency is associated with muscle weakness, fatigue, and pain in bones, joints, and muscles, among other things. Normalizing vitamin D status in the obese population should be a priority.

TABLE 38-4. Medications Associated With Weight Gain

DRUG CLASS	MEDICATIONS THAT MAY PROMOTE WEIGHT GAIN	ALTERNATIVE DRUGS THAT MAY BE WEIGHT NEUTRAL OR PROMOTE WEIGHT LOSS
Psychiatric/ Neurologic		
Antipsychotics	Olanzapine, clozapine, risperidone	Ziprasidone, quetiapine
Antidepressants	SSRIs, tricyclics, lithium	Bupropion, nefazodone
Antiepileptics	Valproate, gabapentin, carbamazepine	Topiramate, lamotrigine, zonisamide
Diabetes Agents	Insulin Sulfonylureas Thiazolidinediones	Metformin, exenatide* Acarbose, miglitol
Steroid Hormones	Hormonal contraceptives Corticosteroids Progestational steroids	Barrier methods NSAIDs
Miscellaneous Agents	Antihistamines	Decongestants, inhalers
	Alpha-antagonists, beta blockers	ACE inhibitors, calcium channel blockers

Adapted from the North American Association for the Study of Obesity, Obesity Research, Stanford University Libraries, Stanford, CA. ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs; SSRIs, selective serotonin reuptake inhibitors. *Incretin mimetic.

Laboratory tests to consider in the evaluation of obesity include fasting blood sugar (100 to 125 indicates prediabetes); triglycerides (high in metabolic syndrome), high-density lipoprotein (low in vitamin D deficiency); 25-hydroxyvitamin D; thyroid-stimulating hormone (hypothyroidism); cortisol, 8 AM spot or 24-hour urine (Cushing disease); high-sensitive C-reactive protein (inflammation); and aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase (steatohepatitis).

Nutritional assessments and evaluations of physical activity can be done concurrently by other members of the weight loss team (dietitians and exercise specialists) or with simple diagnostic tools and lines of questioning. Dietary recall over the course of 1 to 2 days can provide an idea of food intake, eating patterns, and quality of choices. This approach is limited by the tendency of most people to underreport intake of food, as well as uncertainty about identifying a representative day or so in an individual's typical routine. Various software programs and online tools are available for performing nutrient analyses of dietary records and for calculating calories, macronutrient and micronutrient profiles, fiber, essential fats, and sources of each. This information can be useful to provide to clients who are undergoing nutritional counseling.

Further inquiry is often necessary to obtain more details from food records that are often vague and nonspecific. Even when reports of food intake are underreported or somewhat inaccurate, however, viewing the amount of calories one consumes over a 24-hour period can often be surprising and revelatory to the individual who is unaware of portion sizes and the nutritional content of food. Providing patients with a visual illustration of this can be valuable.

Ultimately, for an intervention to be successful, it must closely match the individual's readiness to change. Commitment to such behavioral change is maximized when goals are self-selected and fit with personal lifestyle and values. Gaining clarity on these values is obtained through interactions that allow the practitioner to understand and appreciate the world of the client. Such techniques as motivational interviewing and the Pressure System model (PSM) can provide primary providers with the kinds of counseling tools they need to improve the likelihood that their patients will implement the suggested strategies[30] (see Chapter 99, Motivational Interviewing).


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Interventions must match readiness to change. Commitment to behavioral change is maximized when goals are self-selected and fit with personal lifestyle and values. Patient ambivalence is universal and should be recognized and acknowledged. Doing so will encourage the patient to argue for instead of against change.

Integrative Therapy

In general, the primary clinical intervention for weight management involves lifestyle modification. This includes attention to levels of activity, nutrition, stress management, sleep, sexual activity, relationships, and motivation. Lifestyle modification should be part of any program addressing excess weight, regardless of BMI. More aggressive approaches that include weight loss medications, low-calorie diets with or without liquid meal replacements, and various methods of fasting require a BMI of 30 or higher without comorbidities or of 27 or higher with the presence of one or more comorbid conditions (see Table 38-4). These strategies require frequent monitoring and, if implemented for longer than 3 months, should be administered by a medical professional trained in supervised weight loss strategies (i.e., a physician certified by the American Board of Bariatric Medicine). For patients who have given serious attempts to their weight loss without appropriate long-term results, surgical interventions should be evaluated as a viable option.

Physical examination should evaluate and define weight relative to BMI. Body fat percentage can be determined in an office setting with skin calipers or bioelectric impedance analysis. Body fat distribution should be assessed with special attention to abdominal adiposity. Waist circumference is the best measure for this: it is determined by placing a measuring tape in a horizontal plane around the waist at the level of the umbilicus and superior iliac crests. Measuring neck circumference may give clues in patients with potential sleep apnea (neck size larger than 17 inches), whereas obtaining measurements of chest, arm, thigh, and calf circumference can provide baseline dimensions to compare against as weight loss ensues.

Other physical signs may confirm the presence of obesity-related conditions or point the physician toward other diagnostic tests for validation. Thinning hair, periorbital edema, absent hair on the lateral aspect of the eyebrows, loose skin under the chin and arms, brittle nails, and cold hands and feet may signify an underactive thyroid. Carotid bruits, decreased pulses, or cardiac abnormalities, such as the presence of an enlarged heart or murmurs, can indicate cardiovascular disease. Signs of elevated cortisol, such as abdominal striae, fat storage in the back that produces a "hump-like" abnormality, thinning hair, round face with a double chin, swollen hands or feet, and atrophy in the proximal muscles of the legs, can all prompt an evaluation for Cushing syndrome or at least an assessment of life stressors. Hepatomegaly and ascites can raise suspicions of liver damage. Facial hair, acne, and baldness in the presence of weight gain and infertility can prompt an evaluation for polycystic ovarian syndrome. Immobility, tenderness, swelling, and joint deformities can point to arthritis, whereas numbness in a stocking-glove distribution raises concerns about diabetic neuropathy.

Therapeutic Counseling

Once the assessment has been made and initial treatment goals have been established, a regular visit schedule should be proposed and agreed on by the management team and patient. The more contact patients have with practitioners, the longer they will remain in a program, and the greater potential they have to achieve and maintain their weight loss goals. Frequent visits with physicians and ancillary staff (dietitians, exercise physiologists or trainers, counselors) are recommended and promote greater compliance, as do group support programs.[31–34] Behavioral and nutritional counseling can be done by physicians or dietitians and coded for using Current Procedural Terminology (CPT) codes for individuals (97802) or groups (97804). A minimum of one visit per month is encouraged, and weekly or twice-monthly visits are recommended. Programs offering combination visits with a physician followed by ancillary practitioners can allow for efficient delivery of information in a multidisciplinary fashion without having to extend doctor visits. Obese individuals with eating disorders or who have comorbid psychological conditions such as depression or anxiety should be provided with the opportunity for psychotherapy and other counseling by licensed mental health professionals.

Nutrition

Diet and its role in weight loss have been studied abundantly over the decades, with evidence to support restriction of calorie-containing macronutrients (carbohydrates, fats, and proteins) as an effective means of achieving weight loss.[35] However, further research suggests that macronutrient-restricted diets may be no better than overall calorie-restricted diets for achieving long-term results.[36–38] Moreover, dietary adherence, rather than type of diet, predicts the greatest success regarding weight lost over time.[39] These three points suggest that personal preference is an important consideration when tailoring individualized dietary interventions for successful weight loss. Assessment tools such as 24-hour dietary recall and food frequency questionnaires are important methods for identifying personal preference as a means of recommending dietary approaches to reduce calorie intake.

Popular Diets and Common Weight Loss Programs

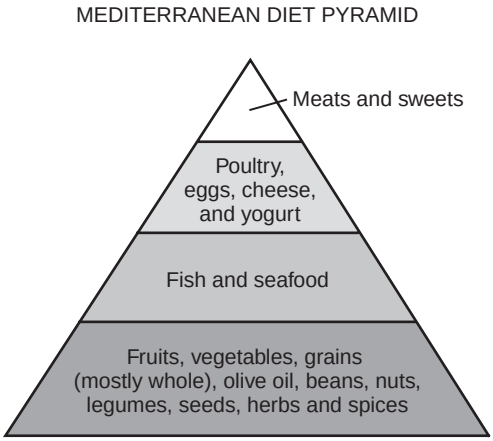
Many people seek out recommendations from popular diets and common weight loss programs, most of which have minimal evidence or formal studies to show their effectiveness. However, evidence studying the efficacy of four popular diets (Atkins, Zone, Weight Watchers, and Ornish) for weight loss showed modest reduction in body weight. The study showed that increased adherence was associated with greater weight loss and cardiac risk factor reduction for each diet group.[40] This finding further supports individualized dietary interventions based on personal preference as an important factor in recommending therapy.

Although questions remain about long-term effects and mechanisms, data suggest that a low-carbohydrate, high-protein, high-fat diet may be considered a feasible alternative recommendation for weight loss.[41] Three popular examples are the Atkins diet, the South Beach diet, and the Zone diet. The Atkins diet focuses on eliminating the majority of carbohydrate sources with no modification of fat or protein calories. The South Beach diet offers a 2-week elimination of all carbohydrates followed by the addition of low-glycemic sources in moderate amounts. The Zone diet encourages physical activity, exercise, and hydration and limits carbohydrates. Another popular diet that achieves weight loss by what is most likely calorie restriction is the Ornish diet, mainly a very low-fat vegetarian plan that combines dietary approaches with group support, stress reduction, and moderate exercise. Research from Stanford University in California studied the Atkins, Zone, LEARN (Lifestyle, Exercise, Attitudes, Relationships, Nutrition), and Ornish diets, by specifically looking at macronutrient quality, and concluded that weight loss diets focusing on macronutrient composition should attend to the overall quality of the diet, including the adequacy of micronutrient intakes. Concerning calorie-restricted diets, those providing moderately low carbohydrate amounts and containing nutrient-dense foods may have a micronutrient advantage.[41]

Each year, millions of U.S. residents enroll in commercial and self-help weight loss programs. Health care providers and their patients know little about the clinical utility of these programs because of the absence of systematic reviews. The University of Pennsylvania in Philadelphia performed an evaluation of major commercial weight loss programs in the United States (eDiets.com, Health Management Resources, Take Off Pounds Sensibly, Optifast, and Weight Watchers). The outcome of the systematic review showed that use of the major commercial and self-help weight loss programs involved in the trial, with the exception of Weight Watchers, is suboptimal.[42] The study noted limitations related to lack of control for high attrition rates. The investigators also reported that many of the programs were associated with high costs and a high probability that participants will regain 50% or more of lost weight in 1 to 2 years. This study further supports the need for controlled trials to assess the efficacy and cost effectiveness of commercial weight loss interventions. Additional commercial programs that lack research but continue to gain popularity are Jenny Craig and LA Weight Loss. These programs, like Weight Watchers, provide weight loss services including prepackaged food, planned menus, and psychological support. Limitations are cost, sales promotions that encourage on-the-spot commitment to prepaid contracts, and the cost of food and additional vitamins.

In February 2011, the Department of Geriatrics and Metabolic Diseases in Naples, Italy, evaluated the effect of Mediterranean diets on body weight in randomized controlled trials using a meta-analysis. This research found that the Mediterranean diet could be a useful tool to reduce body weight, especially when it is calorie restricted, associated with physical activity, and followed for more than 6 months. The Mediterranean diet was not found to promote weight gain, a finding that removes the objection to its relatively high fat content.[43] This research further supports evidence suggesting that macronutrient-restricted diets may be no better than overall calorie-restricted diets in achieving long-term weight loss. Key components of the Mediterranean diet emphasize exercise, primarily plant-based foods (fruits, vegetables, whole grains, legumes, and nuts), olive oil and canola oil, two or more servings of fish and seafood weekly, and limitations

FIGURE 38-1
Mediterranean diet pyramid. (From Oldways Preservation and Exchange Trust. <www.oldwayspt.org;> 2009 Accessed 04.08.11.)



Food groups	Guidance
Meats and sweets	Less often
Poultry, eggs, cheese and yogurt	Moderate portions, daily to weekly
Fish and seafood	Often, at least two times a week
Fruits, vegetables, grains (mostly whole), olive oil, beans, nuts, legumes, seeds, herbs and spices	Base every meal on these foods

on red meat (Fig. 38-1). The diet also recognizes the importance of enjoying meals with family and friends.

The antiinflammatory diet designed by Andrew Weil, MD, based on principles found in the Mediterranean diet, is not intended as a weight loss program, although people have found they have lost weight while adhering to it. General dietary recommendations include eating as much whole, fresh, and unprocessed food as possible (fruits, vegetables, whole and cracked grains, beans and legumes, nuts, avocados, and seeds), with an emphasis on variety of these foods. The diet also limits consumption of processed foods, "fast foods," and foods high in saturated fat sources. The elimination or significant limitation of these foods is most likely an important factor contributing to weight reduction. The diet is based on a 2000 calorie per day plan that provides adequate vitamins, minerals, essential fatty acids, dietary fiber, and protective phytonutrients. At this point, no research has been conducted to study the effects on weight loss associated with the Weil antiinflammatory diet (see Chapter 86, The Antiinflammatory Diet).

Ultimately, dietary restriction as a management strategy for weight reduction can often be used as a sole intervention. Evidence suggests, however, that its use in combination with other strategies such as exercise, behavioral therapy, surgery, and pharmacologic treatments may increase overall success.

The best nutritional plan for weight loss is the one to which the patient will adhere.

Exercise

When consulting with someone who is interested in using exercise as a weight management tool, assessment is essential to setting attainable goals and creating an action plan. For sedentary individuals who are starting an exercise program, the initial goal is simply to start moving. Creating a habit of exercise or movement that emphasizes enjoyment and adherence is an important first step. During this phase, the intensity of exercise is not of paramount importance, but adherence to a modest volume of movement is. Even with modest amounts of movement, one can experience favorable functional changes in strength and endurance that can be a positive and encouraging first step. After a pattern of regular movement has been established and exercise tolerance has improved, the notion of increasing the frequency, duration, and intensity of activity becomes more realistic. Improvements to the thermoregulatory, muscular, and cardiovascular systems of the body operate synergistically to make higher intensities and longer durations more easily tolerated. Ratings of perceived exertion, pedometers, and heart rate monitors are all tools that can be used when making the transition to this next phase of exercise. Although this more detailed phase of exercise prescription is not absolutely needed for managing obesity, it can be very helpful. Exercise has only mild effects on resting metabolic rate, but exercise of sufficient intensity can alter aerobic capacity and improve an individual's capacity to burn calories. Given that most exercise bouts are limited to the 20- to 60-minute window, the productivity of an exercise session can be key to success.

Aerobic capacity or Vo_2max refers to the number of liters of oxygen that can be consumed per minute at maximal aerobic workloads. This workload has been traditionally expressed in terms of metabolic equivalents (METs) or in terms of milliliters of oxygen consumed per minute per kilogram (mL O_2/min/kg). The more oxygen someone can consume per minute or the more METs they can produce per minute, the more calories they can burn. For example, two people seem identical on the surface. Both women are 55 years old, are 5 foot 4 inches tall (165 cm), and weigh 165 pounds (75 kg). Subject number 1 can produce 12.8 METs (45 mL O_2/min/kg) during a treadmill test, whereas subject number 2 can produce 8 METs (28 mL O_2/min/kg) during her treadmill test. Both women achieve maximal heart rates of 165 beats per minute at the end of the tests. Translated into exercise (30 minutes on a treadmill) at a comfortable heart rate for both women (127 beats per minute), the differences are substantial. Subject 1 will burn approximately 13.0 calories per minute for 30 minutes and 390 calories during the 30-minute exercise bout. Subject 2 will burn approximately 8 calories per minute and 240 calories for the 30 minutes. Having a very clear picture of what your clients' abilities are—even determining their aerobic capacity—before creating an exercise prescription is a powerful tool for anyone facilitating weight loss.

During a period of weight loss, clients will inevitably have some losses in lean mass, as well as losses in fat mass. Given

the protein-sparing effects induced by resistance training, the addition of resistive muscular work makes sense. Full body exercise routines that engage as many muscles as possible not only save time but also can have beneficial effects on the hormonal response to resistance training.[44] A twice-weekly regimen is sufficient to produce these results.

Supplements

Omega-3 Fatty Acids

Omega-3 fatty acids have been shown in various studies to have significant positive effects on cardiovascular health.[45] They are an integral part of an antiinflammatory diet, as well as having an indication for the treatment of elevated triglycerides.[46] Omega-3 fatty acids should be considered in the obese patient with cardiovascular comorbidities because clinical studies show that disease risk decreases as the ratio of omega-3 to omega-6 in the diet increases.[47] Supplements are available in prescription form as omega-3-acid ethyl esters under the trade name Lovaza.

Dosage

For improvement of cardiac disease risk, the recommended dose is 1 to 3 g daily, and the ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) should be greater than 1. For the treatment of high triglyceride levels, the recommended dose is higher, at 2 to 4 g of combined EPA and DHA.

Precautions

Individuals with allergies to fish or shellfish should use caution when taking fish oil. Omega-3 fatty acids have antiplatelet and antithrombin effects, which may cause bruising or may interact with additional blood thinning agents. However, bleeding effects of fish oils taken alone have not been shown to be clinically significant even in large doses.[46] Side effects include a fishy aftertaste and mild gastrointestinal upset.

Vitamin D

Overweight individuals tend to have lower blood levels of vitamin D because excess adipose tissue absorbs and stores this fat-soluble vitamin. In addition, unlike normal-weight individuals who turn over fat tissue, those with relatively immovable fat stores cannot liberate the vitamin D they have. As a general rule, obese individuals are less active outdoors and are exposed to less ultraviolet radiation, a situation that compounds their vitamin D deficiency. Studies have validated that obese individuals tend to have significantly low levels of vitamin D, with symptoms of muscle weakness, muscle aches, bone pains, and fatigue, all of which are potential manifestations of vitamin D deficiency.[48] Additional research has validated the lower comparative bioavailability of vitamin D in obese individuals; they need more of it compared with nonobese subjects.[29] Higher levels of calcium in the presence of adequate serum vitamin D levels has been shown to inhibit fatty acid synthase, an enzyme that converts calories into fat, whereas diets low in calcium increase the enzyme by as much as fivefold.[49]

Dosage

First, the clinician should determine the patient's serum 25-hydroxyvitamin D level in the blood. Recommended adequate blood levels of vitamin D are between 40 and 60 ng/mL.[50] Supplementation should be adequate to correct deficiencies if present. Obese individuals may need two to three times more vitamin D daily than those of normal weight, somewhere between 3000 and 6000 units daily, without posing any risk of toxicity.[49]

Precautions

Gastrointestinal effects of larger doses of vitamin D have been reported. Some suggestion exists that this effect may result from the gelatin capsule of prescription formulations and not the preparation itself. These symptoms may be remedied by opening the capsule and ingesting the liquid form. Vitamin D toxicity is often difficult to diagnose. This condition depends on blood levels of calcium (usually above 10.4 mg/dL) and occurs when 25-hydroxyvitamin D levels are usually higher than 200 ng/mL. Hyperphosphatemia and hypercalcemia that occur in vitamin D toxicity can cause constipation, confusion, depression, increased thirst, urination, and electrocardiographic changes, with ultimate calcification of organs and tissues leading to damage and organ failure.[49]

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a polyunsaturated fatty acid in the omega-6 category found naturally in beef and whole-fat dairy products. CLA supplements have been widely promoted as being beneficial for weight loss in some individuals. CLA has been shown to be an effective supplement for reducing fat mass in animal models, but results in humans have been inconsistent. One meta-analysis found that CLA produces a modest loss in body fat in humans.[51]

Dosage

Modest weight loss (between 1.1 and 2.6 kg) in human studies was achieved at a dose of 3.2 g daily.

Precautions

Although no serious adverse effects have been related to the use of CLA, this substance has been linked to slight increases in inflammatory markers, including C-reactive protein and white blood cell counts. This finding contradicts research in animal models, which suggested that CLA is more of an anti-inflammatory substance. CLA was also reported to be linked to an increased risk of insulin resistance in certain individuals, as well as greater gastrointestinal upset.[51]

Green Tea and Green Tea Extract

Animal studies suggested a fat-burning, weight loss, and cholesterol-lowering effect of green tea extracts. This effect seems to be synergistically improved with the addition of exercise. A small Asian study validated significant reductions in body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area after 12 weeks of consuming one bottle of tea with 690 mg catechin antioxidants per day.[52] Another Japanese study found that green tea contains ingredients besides caffeine that stimulate thermogenesis and burn fat.[53]

Dosage

Studies found that fat-burning results occurred with tea containing 690 mg of catechins daily. Depending on the brand, the recommended dose consists of 2 to 3 cups of green tea per day (for a total of 240 to 320 mg polyphenols) or 100 to 750 mg per day of standardized green tea extract. Caffeine-free products are available.

Precautions

One cup of green tea typically contains approximately 50 mg of caffeine as compared with 90 to 150 mg of caffeine for a percolated cup of coffee. People with heart problems, kidney disorders, stomach ulcers, anxiety, and sleep disorders should not take green tea. When considering green tea, pregnant and breast-feeding women should consult their obstetricians.

People who drink excessive amounts of caffeine for prolonged periods may experience irritability, insomnia, heart palpitations, and dizziness. Caffeine overdose can cause nausea, vomiting, diarrhea, headaches, and loss of appetite.

Mind-Body Therapy

Mind-body therapies such as mindfulness and mindful eating programs, meditation, hypnosis, and biofeedback are popular strategies used to facilitate weight loss plans with a specific target on emotional eating patterns. Stress reduction and improved emotional regulation can potentially allow individuals to make better food choices, feel fuller faster, and recognize abnormal eating habits. By accessing the parasympathetic nervous system more often, the balance of stress hormones, including epinephrine and cortisol, can be shifted in a positive direction. Studies have confirmed that stress-induced cortisol secretion is linked to abdominal obesity, endocrine abnormalities such as increased insulin, metabolic derangements in blood lipids, and hemodynamic changes in blood vessels.[54] Decreasing cortisol levels can aid in a positive strategy to address weight gain proactively.

Unfortunately, the available literature on these therapies in the obese population is relatively scarce. Preliminary studies showed mindfulness meditation to reduce episodes of binge eating and nighttime eating disorder.[55] Some studies looking at the role of biofeedback techniques and hypnosis in weight loss showed a mildly positive effect.[56] At present, recommending these strategies to the right individuals who are open to them seems prudent as an adjunct to an ongoing lifestyle management program.

Pharmaceuticals

Pharmacologic treatment may be considered an adjunct to lifestyle modification in those patients who have not lost at least 1.1 lb (0.5 kg) per week after 3 to 6 months of implementing their lifestyle program.[57] These medications are appropriate for patients with a BMI 30 or higher or 27 or higher in the presence of comorbid conditions. At present, two classes of drugs are used for weight control: (1) drugs that suppress appetite and augment thermogenesis (phentermine) and (2) drugs that prevent the absorption of fat through the gastrointestinal tract (orlistat). The withdrawal of sibutramine by Abbott Laboratories from both the U.S. and European markets because of an increased risk of stroke and heart attacks raised concern about the long-term effects of stimulant medications and prompted petitioning for higher standards of review for weight loss medications.[58] When considering drug therapy, the clinician should conduct a careful review of medical history, drug interactions, and potential side effects before prescribing weight loss medications. Evaluation of a recent electrocardiogram is recommended to assess a patient's cardiac health before administering medications with known stimulant effects, and aggressive regular monitoring (1- to 2-week visits) should be done during initial treatment to assess vital signs and tolerance to therapy. Longer-term therapy should also prompt regular medical supervision with at least monthly visits.

Phentermine

Phentermine (Adipex-P) is a norepinephrine reuptake inhibitor with schedule IV identification (debated in some medical circles) that has been approved by the U.S. Food and Drug Administration (FDA) for short-term use (12 weeks) since 1959. Phentermine is the most commonly prescribed weight loss medication to date, probably because of its low cost, its long history of use, and, contrary to popular belief, its low addictive potential. To illustrate this point, the *Drug Abuse Warning Report (DAWN),* published in 2006 by the Substance Abuse and Mental Health Services Administration of the U.S. Department of Health and Human Services, showed that anorectics such as phentermine had among the lowest drug misuse or abuse rates per 100,000 emergency room visits, even lower than ibuprofen.[59] Unfortunately, many of the current guidelines for prescribing phentermine reflect recommendations that are more than 50 years old, rather than current evidence of efficacy and safety.[60] Because it has a molecular structure similar to that of amphetamine, phentermine was originally labeled a schedule IV drug; however, over many decades of clinical use, phentermine has proved to have little to no addictive value, and no abuse or withdrawal syndromes are associated with its use.[59] Continuous use beyond 12 weeks is a common off-label use pattern in bariatric medicine and has validation in the international literature.[61] Putting time limits on medication use for the treatment of a chronic illness such as obesity seems inappropriate when (and only when) the risk of taking the medication is less than the risk of leaving the illness untreated. Weight loss during drug therapy should perhaps not be considered an indication to stop treatment any more than a positive outcome would be for the treatment of other chronic diseases. For this to happen, however, the long-term safety of agents must be assessed and documented in the literature.[62] The literature suggests the effectiveness of phentermine in helping patients lose weight and maintain that loss for at least a year, if not longer.[63]

Dosage

Phentermine is often prescribed in doses of 15 to 37.5 mg once daily, typically in midmorning. It is sometimes prescribed in half doses given early in the morning then at midmorning, to extend its effects toward evening, when individuals tend to have higher calorie intake.

Precautions

Side effects include insomnia, dry mouth, palpitations, hypertension, and constipation.

Contrary to popular belief, phentermine has a low addiction potential.

Orlistat

Orlistat (Xenical) works by inhibiting lipases in the gastrointestinal tract such that fat absorption is partially blocked. It is FDA approved for up to 2 years of continuous use, and it has been shown to be effective for significant and sustainable weight loss, as well as for improving lipid levels, enhancing glucose metabolism, and lowering blood pressure.[64] The discontinuation rate is relatively high because of gastrointestinal side effects related to fat malabsorption and roughly equates to 33% in various studies.[65] In one study, lifestyle intervention and orlistat treatment for 4 years delayed the development of type 2 diabetes in obese subjects by 37%, a finding perhaps suggested to result in part from the weight loss achieved.[66] Orlistat is now available in half strength (60 mg per dose) over the counter under the brand name Alli.

Dosage

Orlistat is prescribed in doses of 120 mg taken three times daily with meals, and the dose can be omitted when patients ingest a low-fat meal. Starting orlistat once daily with the fattiest meal (usually dinner) and then advancing the dose to three times daily as needed can help lessen the intensity and frequency of side effects.

Precautions

Common adverse effects include bloating, flatulence, and fatty or oily stools. Oily spotting, increased fecal urgency or incontinence, and abdominal pain can also be experienced, especially when patients are noncompliant with a low-fat diet. Use of fiber supplements, especially psyllium, can be helpful in reducing side effects. Patients should also take a daily multivitamin, independently of orlistat, to compensate for the potential decreased absorption of fat-soluble vitamins (A, D, E, and K).

Off-Label Use of Medications for Weight Loss

Physicians commonly prescribe a wide variety of drugs for other indications. An estimate suggests that 21% of all prescriptions are issued for off-label use.[67] Physicians certified in the treatment of obesity often use phentermine on a long-term basis, as has been validated by studies demonstrating safety in patients after more than 10 years of continuous phentermine use.[62]

Additionally, three drugs with other indications besides weight loss are being investigated: bupropion, topiramate, and metformin. Bupropion (Wellbutrin) is a norepinephrine and dopamine reuptake inhibitor that is approved for the treatment of depression and was shown to have a dose-dependent weight loss effect in a double-blind placebo-controlled study. In this study, 83% of patients achieved weight loss of more than 5% of initial body weight when they took 400 mg/day of sustained-release bupropion as compared with 59% of subjects taking 300 mg/day and 46% treated with placebo.[68] Topiramate (Topamax) is an antiepileptic drug that has shown positive weight loss effects during clinical trials in smaller doses than achieved for seizure control.[69] Metformin (Glucophage) is indicated for the treatment of type 2 diabetes, but it has also been used off-label for the treatment of insulin resistance syndromes, especially PCOS. Studies have suggested a mild weight loss effect in abdominally obese women with PCOS.[70] Metformin has also been shown to promote weight loss in morbidly obese children and in men with normoglycemic hyperinsulinemia.[71]

Surgery

Bariatric surgery is well established as the most effective treatment for obesity; however, it is indicated only for the management of severe obesity with or without comorbidities, when other therapies have been tried without long-term success.[72] Surgical interventions are currently indicated for patients with a BMI of 40 or higher or 35 or higher with comorbid conditions and reduced quality of life (i.e., hypertension, sleep apnea, diabetes). Typically, reimbursement for surgical procedures will be granted only after at least a 6-month trial of medically supervised weight loss.

Bariatric surgery rapidly evolved with the advent of laparoscopic approaches in the mid-1990s. Currently, most bariatric surgery is initially attempted in laparoscopic fashion. Surgical weight loss falls into the category of restrictive procedures, malabsorptive procedures, or a combination of the two. Strictly malabsorptive procedures such as jejunoileal bypass and duodenal switch are seldom performed. Purely restrictive procedures include the vertical banded gastroplasty (rarely done these days), adjustable gastric banding, and vertical sleeve gastrectomy (an emerging procedure). The Roux-en-Y gastric bypass, involving restriction of stomach size along with bypassing a large part of the stomach and duodenum, is an example of a combined restrictive and malabsorptive procedure. It is still the most popular procedure; however, restrictive techniques are beginning to emerge as competitive procedures that are less invasive and have fewer side effects.

A Cochrane Review compared different surgical procedures, all of which were found to be more effective in promoting weight loss than were nonsurgical methods.[73] Roux-en-Y gastric bypass was more effective than laparoscopic adjustable gastric banding and just as effective as vertical sleeve gastrectomy. Weight loss of up to 33% has been maintained after gastric bypass surgery for up to 10 years, and loss of 50% or more of excess weight is achieved with either of the procedures, again an outcome superior to that of nonsurgical approaches.[73] In addition, resolution of comorbidities is often common. Meta-analyses demonstrated complete resolution of type 2 diabetes in 31% to 77% of patients who underwent laparoscopic banding and in 72% to 100% of patients who had Roux-en-Y bypass.[74] Similar resolution of blood pressure abnormalities has been verified. A Swedish study demonstrated a substantially reduced 10-year mortality rate with bariatric surgery as compared with nonsurgical treatment of obesity.[75]

Bariatric surgery is typically safe, with surgical mortality approaching as low as 0.1% to 0.3%, whereas postoperative complications occur in 4% to 10%.[76,77] Emerging evidence indicates that bariatric surgery may be beneficial for patients with BMIs lower than 35 and comorbidities; however, it is still too early to recommend surgery to those individuals.[78]

Individuals considering bariatric surgery require thorough preparation for the effects of such a procedure on their long-term lifestyle. This preparation should be facilitated by a multidisciplinary team of surgical and nonsurgical practitioners. Coordination of treatment has been cited as one of the most important advances in the care of patients undergoing these surgical procedures.[79] Postoperative challenges include malabsorptive nutritional

deficiencies, dumping syndrome that involves profuse diarrhea and stomach pain after overeating refined carbohydrates in patients who underwent bypass procedures, changing dietary patterns to accommodate effects of the procedure, and the physical and emotional changes that occur when experiencing large amounts of weight loss. Regular close monitoring by nutritionists is necessary to provide assistance with safe and efficacious dietary advancement along with guidance of supplement needs for those individuals exhibiting vitamin and mineral deficiencies, a potential problem for all patients after bypass procedures. Preoperatively, all patients need psychological evaluation to assess whether they are appropriately motivated, likely to be compliant in their long-term program, and prepared to accept the changes that often occur with dramatic reductions in weight. Regular access to behavioral experts is essential for patients as they lose weight. Often, maladaptive patterns of eating are a defense mechanism used by patients to deal with elevated levels of emotional stress. When those options are eliminated by a surgical process, the potential for other patterns of behavior to emerge is evident. Having a management strategy to support patients through these psychological adaptations and providing them with proactive alternatives to stress response other than with food can create life-changing opportunities. Support groups are often used as adjuncts to individual behavioral therapies and can be helpful in long-term weight management after surgery.

Therapies to Consider

The clinical literature contains few substantiated claims to document the effectiveness and safety of over-the-counter weight loss aids.[80,81] Even so, use of supplements for weight loss is a popular practice. As of 2004, more than 50 individual dietary supplements and more than 125 commercial combination products were available for weight loss.[81] In 2002, retail sales of weight loss supplements were estimated to be more than $1.3 billion.[82] The literature also points out that some individuals use over-the-counter aids while continuing to take their prescription weight loss drugs.[83] This situation emphasizes the need for practical navigation by medical practitioners as they monitor and counsel their patients about the use of anorectic supplements. The well-publicized toxicity of ephedra highlights the potential dangers of relying on such supplements and botanicals as a sole weight loss strategy [84] Given the widespread use of these agents, clinicians who treat obesity should be familiar with the risk-to-benefit profile of common products, to counsel patients about their use or avoidance more accurately. Table 38-5 summarizes the evidence for efficacy and safety of common weight loss supplements.

TABLE 38-5. Evidence Summary and Clinical Advice for Common Individual Weight Loss Supplements

	Evidence Summary		
SUPPLEMENT	**PRODUCT EFFICACY**	**PRODUCT SAFETY**	**CLINICAL ADVICE**
Apple cider vinegar	U[a]	U	Counsel and caution
Cascara	U[a]	U	Counsel and caution[b]
Chitosan	A	P	Discourage
Chromium	U[c]	U	Counsel and caution
Conjugated linoleic acid	U[c]	U	Counsel and caution
Dandelion	U[a]	U	Discourage[b]
Ephedra alkaloid-caffeine combinations[d]	P	A	Discourage
Ginseng	U[a]	U	Counsel and caution
Glucomannan	U[e]	P	Counsel and caution
Green tea	U[a]	P[f]	Counsel and caution
Guar gum	A	P	Discourage[g]
Guggul	U[a]	U	Counsel and caution
Hydroxycitric acid	U[h]	U	Counsel and caution
Laminaria	U	U	Counsel and caution
L-Carnitine	U[a]	P	Counsel and caution
Licorice	U[a]	U	Counsel and caution
Psyllium	U[a]	P	Counsel and caution

Continued

TABLE 38-5. Evidence Summary and Clinical Advice for Common Individual Weight Loss Supplements—cont'd

SUPPLEMENT	*Evidence Summary* PRODUCT EFFICACY	PRODUCT SAFETY	CLINICAL ADVICE
Pyruvate	U[e]	U	Counsel and caution
St. John's wort	U[a]	U	Counsel and caution
Vitamin B_5	U[a]	P	Counsel and caution

Adapted from Saper R, Phillips R, Eisenberg D. Common dietary supplements for weight loss. *Am Fam Physician.* 2004;70:1731–1738.
A, absent; P, present; U, uncertain.
Note: If strong evidence indicates the presence of efficacy and safety, then the suggested clinical advice to provide the patient is to recommend the supplement actively. None of the weight loss supplements meet these criteria. If strong evidence indicates the absence of efficacy or safety, then the suggested clinical advice is to discourage use of the supplement actively. If the evidence does not meet the criteria to recommend or discourage (i.e., evidence for efficacy or safety is uncertain with no strong evidence against efficacy or safety), then the suggested clinical advice is to counsel and caution the patient on the available scientific information.
[a]No or few human weight loss trials.
[b]Given the inadvisability of using conventional diuretics or laxatives for the purpose of weight loss, it is reasonable to discourage these agents if they are used by the patient only for losing weight. If overweight patients are using these supplements for other indications (e.g., hypertension, constipation), to counsel and caution may be reasonable.
[c]Most or all trials do not show weight loss, but the small number of trials and subjects precludes definitive efficacy conclusions.
[d]Also includes country mallow, bitter orange, guarana, and mate.
[e]Most or all trials demonstrate weight loss, but the small number of trials and subjects precludes definitive conclusions.
[f]If taken in appropriate doses (the equivalent of less than 5 cups of green tea daily).
[g]"Discourage" refers to the use of guar gum as an antiobesity agent only. Guar gum and other fiber agents may have a role, however, in obese patients for the treatment of comorbidities such as diabetes, glucose intolerance, or hyperlipidemia.
[h]Efficacy data are contradictory.

Prevention Prescription

- The basis for prevention of weight gain is learning how to follow an antiinflammatory diet that emphasizes vegetables and fruits from all parts of the color spectrum, whole grains, fish and other sources of omega-3 fatty acids, vegetable protein more than animal sources, monounsaturated fats, and low-fat dairy. To make this a long-term lifestyle change, fruits, vegetables, and high-fiber grains must be used to displace high-calorie processed foods of poor nutritional content (see Chapter 86, The Antiinflammatory Diet).
- Fostering a healthy relationship with food and becoming aware of reactive, habitual patterns of eating are vital to preventing weight gain. Learning techniques of mindful eating can facilitate this process.
- Physical activity may play a role in the prevention of weight gain[85]; 30 minutes/day, 5 to 7 days/week of any physical activity should be encouraged (see Chapter 88, Writing an Exercise Prescription).

Therapeutic Review

All patients should undergo the following assessments. Appropriate therapy can then be determined.

Medical History

- Assess for comorbid diseases and concomitant medications that induce weight gain.

Nutrition History

- Determine previous weight loss attempts and use 24-hour recall and food frequency questionnaires.
- Rule out clinically significant eating disorders (anorexia and bulimia nervosa, binge-eating disorder, nighttime eating syndrome).

Anthropometric Measurements

- Weight, height, BMI, waist circumference, body composition, blood pressure, heart rate

Laboratory Tests

- Complete blood count, metabolic profile, fasting lipids, thyroid-stimulating hormone, liver function tests, fasting serum glucose and insulin, hemoglobin A1c (if diabetic), high-sensitive C-reactive protein, 25-(OH) vitamin D
- Electrocardiogram, unless recent one (within 6 to 12 months) is available for review

General Evaluation

- Assess for motivation, importance, and confidence for weight loss, barriers to change, and realistic weight loss goals.
- Assess exercise history, sleep patterns, relevant stressors, and social support.

Therapeutic Options

- BMI 25 or higher
  - Promote a balanced hypocaloric diet and physical activity, and provide behavioral modification counseling.
  - Reduce caloric intake from baseline by 500 to 1000 cal/day to yield a 1- to 2-lb weight loss per week. A1
  - Encourage purposeful activity for at least 60 minutes daily 6 to 7 days of the week. Total time may be broken into short bouts of 10 to 15 minutes each during the initial adoption of an exercise program only. A1
  - Stress management techniques include mind-body therapies such as meditation, biofeedback, or hypnosis. B1
  - Ensure adequate sleep and treatment of any concomitant sleep disorders. B1
  - Suggest interactive individual or group support sessions for nutrition education and behavioral modification. C1
  - Refer to a dietitian, mental health professional, or exercise specialist as needed. C1
- BMI 30 or higher or 27 or higher with comorbid conditions
  - Full liquid fast, protein-sparing modified fast, and pharmacotherapy with dietary intervention are suitable for this BMI level. A2
  - Orlistat, 120 mg orally three times daily, is the first option. This medication is localized to the gut and can be used in combination with phentermine. A2
  - Phentermine can be taken alone (15 to 37.5 mg daily) or in combination with orlistat (approved for 3-month use by the Food and Drug Administration). A2
  - Suggest omega-3 fatty acids, at 2 to 4 g/daily. A2
  - Treat vitamin D deficiency appropriately to achieve serum 25-(OH) vitamin D levels between 40 and 60 ng/mL. A2
  - Other dietary supplements should be used, if at all, on an individualized basis determined by risk-to-benefit ratio and by evaluating the efficacy and safety of each product or combination. B2
- BMI 40 or higher or 35 of higher with comorbid conditions
  - Weight loss surgery, if other treatment modalities are ineffective, is suitable for this BMI level. C3

KEY WEB RESOURCES

Procedures for Collecting 24-Hour Food Recalls: http://www.csrees.usda.gov/nea/food/efnep/ers/documentation/24hour-recall.pdf.	This useful handbook from the U.S. Department of Agriculture describes the procedures for conducting a 24-hour diet recall, which is an in-depth interview that collects detailed information on all foods and beverages consumed by a participant during the previous 24 hours. These recalls are best administered "unannounced" (not scheduled on a specific day) so that participants cannot change their eating habits based on anticipation of the interview.
NutritionQuest assessment and analysis services: http://www.nutritionquest.com/assessment.	This company is a leader in the field of diet and physical activity assessment, and their Web site is the official source of the Block Food Frequency Questionnaire and other dietary and physical activity questionnaires developed under the guidance of Dr. Gladys Block. Block Assessment Tools are designed and tested for usability and have a long history of validation in various demographic subpopulations. These tools are available in both paper and electronic format.
Basal metabolic rate calculator: http://www.calculator.org/calculate-online/health-fitness/basal-metabolic-rate.aspx.	This tool calculates how many calories your body requires each day.
Mayo Clinic calorie calculator: http://www.mayoclinic.com/health/calorie-calculator/NU00598.	This calculator includes individual activity in the calculation.
FitDay.com: http://www.fitday.com/.	This Web site allows you to track your nutrition and fitness goals online.
The Center for Mindful Eating: http://www.tcme.org/.	This organization helps people learn how to use eating as a mindful process that brings awareness to what we are eating, thus leading to healthier food choices and reduced calorie consumption.

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References are available online at expertconsult.com.

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Chapter 39

Dyslipidemias

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Pathophysiology

Dyslipidemias, including lipoprotein overproduction or deficiencies, are a common clinical problem. Approximately 25% to 30% of adults in the United States have total cholesterol levels of 240 mg/dL or higher, and more than half of all U.S. residents have a total cholesterol level that exceeds 200 mg/dL.[1] The number of patients with dyslipidemias and cardiovascular disease (CVD) is expected to increase because of an aging U.S. population and an increasing incidence of diabetes and obesity. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines recommend that all adults 20 years old and older have a baseline fasting lipoprotein profile followed by appropriate management if lipid levels are abnormal, or repeat testing approximately every 5 years if lipid values are normal. The current recommendation is that high-risk children be screened starting at the age of 10 years, although universal screening is being considered by the National Institutes of Health. All adults and high-risk children (those with diabetes, obesity, or a family history of premature CVD or dyslipidemia) should have a complete lipid evaluation. Although routine screening of all children remains controversial, children or adolescents who have parents, grandparents, or siblings with premature atherosclerosis or dyslipidemias can be considered for lipid screening.[2,3]

Many clinical prevention trials have demonstrated that cholesterol treatment leads to prevention of atherosclerosis, stabilization of atherosclerotic plaque, improved function of arteries, regression of existing plaques, and reduction of cardiovascular events and total mortality.[4,5] High-risk patients benefit most from cholesterol treatment. High-risk patients include those with the following:

- CVD or noncoronary atherosclerosis
- Genetic dyslipidemias
- Diabetes mellitus
- Multiple risk factors, including lipoprotein abnormalities[1]

The NCEP ATP III guidelines recommend evaluation for underlying atherosclerosis and comprehensive risk assessment for all patients before determining lipoprotein goals, by using history, physical examination, and overall risk assessment. Consideration is given to other methods of screening (stress tests or imaging of blood vessels) if the patient has symptoms or is considered high-risk (greater than a 20% 10-year risk of coronary heart disease [CHD]). Low-density lipoprotein cholesterol (LDL-C) treatment goals are risk stratified using 10-year risk estimates from NCEP ATP III guidelines. Clinicians can estimate CHD risk with risk calculators for desktop or handheld computers available at the NCEP Web site (see Key Web Resources).

Table 39-1 outlines the ATP III classification of LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). HDL-C and LDL-C continue to be important risk factors in adults older than 65 years of age.[1] Clinicians should consider each older adult for dyslipidemia treatment individually, based on the patient's motivation, prognosis, comorbidities, and potential improvement in quality of life. Table 39-2 outlines classifications of lipids for children and adolescents.

Measuring Cholesterol and Lipoprotein Levels

Note that total cholesterol and HDL-C levels are not influenced by fasting and can be measured at any time of day. Lipoprotein profiles must be done after a 12- to 14-hour fast because TG measurements are variable in the nonfasting state. When total cholesterol, TG, and HDL-C are measured, and serum TG levels are less than 400 mg/dL, LDL-C can be estimated using this formula:

$$\text{LDL-C} = \text{Total cholesterol} - (\text{HDL-C} + \text{TG}/5)$$

Dividing the clinical TG levels by 5 provides an estimate of very-low-density lipoprotein cholesterol (VLDL-C). However, the LDL-C calculations are not accurate if the TG level exceeds 400 mg/dL.[1]

TABLE 39-1. Adult Treatment Panel III Classification of Total, Low-Density Lipoprotein, and High-Density Lipoprotein Cholesterol and Triglycerides

CHOLESTEROL AND TRIGLYCERIDES (mg/dL)	DESCRIPTOR
Total cholesterol	
Less than 200	Desirable
200–239	Borderline high
Greater than 240	High
LDL-C*	
Less than 100	Optimal
100–129	Near optimal/higher than optimal
130–159	Borderline high
160–189	High
Greater than 190	Very high
HDL-C	
Less than 40	Low
Greater than 60	High
Triglycerides	
Less than 150	Normal
150–199	Borderline high
200–500	High
Greater than 500	Very high

Data from National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106:3143–3421.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Primary target of therapy.

A lipoprotein profile is usually sufficient to develop a clinical classification and treatment approach for dyslipidemias. When the TG level is more than 400 mg/dL, however, lipoprotein phenotyping to determine the specific biochemical abnormality may be useful to direct treatment. In addition, newer technology and research have found that the LDL particle number is a better predictor of CVD risk than the LDL-C level (or the total amount of cholesterol available in LDL particles).[6,7] Research shows that small LDL (type B) particles are easily oxidized, thus leading to greater penetration of the arterial wall and resulting in the development of atherosclerosis. Small LDL particles are common when TG levels exceed 80 to 100 mg/dL.[6] Special testing is needed to determine whether a patient has small LDL or the less atherogenic large LDL particles. This determination is most accurate with nuclear magnetic resonance testing, which is emerging as a more sensitive and predictive test for cholesterol risk. More research is under way regarding the best use of this test and the assessment of LDL particles.[6]

Factors That Can Affect Cholesterol Measurements

Certain patient-related factors, including the following, can influence cholesterol measures and should be considered when interpreting test results[1]:

- Acute or chronic illness (e.g., heart attack, viral illness, bacterial infection)
- Recent general surgery
- Pregnancy or lactation
- Poor nutritional status or ongoing significant weight loss
- Nonfasting state (affects TG levels, not HDL-C or total cholesterol)
- Improper fingerstick technique ("milking the finger")
- Day-to-day or seasonal variation

TABLE 39-2. Classifications of Lipid and Lipoprotein Concentrations for Children and Adolescents*

	ACCEPTABLE (mg/dL)	BORDERLINE (mg/dL)	HIGH RISK (mg/dL)
Total cholesterol	Less than 170	170–199	200 or greater
LDL-C	Less than 110	110–129	130 or greater
TG			
0–9 yr	Less than 75	75–99	100 or greater
10–19 yr	Less than 90	90–129	130 or greater
HDL-C	Greater than 45	40–45	Less than 40

(LDL-C), high-density lipoprotein cholesterol (HDL-C), and non–HDL-C by 38.6; for triglyceride (TG), divide by 88.6. Data from National Institutes of Health. *Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents*. http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Accessed 18.1.12.
*To convert mg/dL to SI units, divide the results for total cholesterol, low-density lipoprotein cholesterol

Secondary Causes of Dyslipidemias

Before conducting extensive testing or making treatment decisions, clinicians must evaluate patients to rule out the following potential secondary causes of dyslipidemias:

- Poorly controlled diabetes mellitus
- Obesity and metabolic syndrome
- Medications (steroids, including estrogen, progesterone, prednisone, anabolic steroids, beta blockers, or *cis*-retinoic acid)
- Obstructive liver disease
- Nephrotic syndrome
- Multiple myeloma
- Hypothyroidism
- Excess dietary alcohol, saturated fat, carbohydrate, or caloric intake

A directed medical history, nutrition history, thyroid-stimulating hormone assay, and fasting blood chemistry survey (including glucose, liver enzymes, and creatinine) can rule out most of the common secondary causes. Treating the secondary cause usually markedly improves or normalizes abnormal cholesterol levels.

Dyslipidemia Classifications

Table 39-3 presents a practical system for classifying dyslipidemias based on clinical, genetic, and biochemical parameters. This approach uses results from the lipoprotein profile and is compatible with the more complex Fredrickson-Levy system.

High Low-Density Lipoprotein Cholesterol Levels

Elevated LDL, with normal TG, is considered either primary or familial hypercholesterolemia, a relatively common disorder caused by defects in the LDL receptor gene. Familial hypercholesterolemia is expressed during childhood and is autosomal dominant, with selective elevation of LDL, usually higher than 180 mg/dL in adults or higher than 170 to 200 mg/dL in children. Most adult patients with isolated LDL-C elevations greater than 180 mg/dL have familial hypercholesterolemia and are considered to have primary hypercholesterolemia, which is probably attributable to multiple causes, including nutrition, obesity, and behavioral and genetic factors.

High Triglyceride Levels

High TG levels (higher than 500 mg/dL) result from elevations of chylomicrons, intermediate-density lipoproteins, or VLDLs. Fasting TG levels higher than 1000 mg/dL can result from either genetics or a combination of genetics and a secondary cause, such as alcohol abuse, poorly controlled diabetes, estrogens, obesity, renal disease, or steroid use. Because patients with a TG level higher than 1000 mg/dL have a high risk of developing pancreatitis, this is the priority of treatment.

Low High-Density Lipoprotein Cholesterol Levels

HDL-C is an independent risk factor and is the most powerful predictor of premature CHD.[1] Low HDL-C (less than 40 mg/dL, TG less than 150 mg/dL) is associated with genetic factors, male sex, smoking, obesity, and a sedentary lifestyle. Familial hypoalphalipoproteinemia (low HDL-C), a syndrome found in 7% to 10% of patients with CHD who are younger than

TABLE 39-3. Dyslipidemia Classifications

Lipoprotein Levels (mg/dL)				
LDL-C	**HDL-C**	**TG**	**CLASSIFICATION**	**GENETIC DISORDER**
Greater than 130	Greater than 40	Less than 150	High LDL-C	Familial hypercholesterolemia (LDL-C greater than 200 mg/dL)
				Primary hypercholesterolemia (LDL-C 130–199 mg/dL)
NA	NA	Greater than 500*	High triglycerides	Lipoprotein lipase deficiency
				Apoprotein C III deficiency
				Familial hypertriglyceridemia
Less than 130	Less than 40	Less than 150	Low HDL-C	Hypoalphalipoproteinemia
				Tangier disease
				Fish-eye disease
Greater than 130	Less than 40	Greater than 150	Combined dyslipidemia	Familial combined hyperlipidemia
				Familial dysbetalipoproteinemia

NA, not applicable.
*Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol measurements are not accurate when triglyceride (TG) is higher than 400 mg/dL. Ideally, weight loss is accomplished through a modest, consistent reduction in calorie intake (approximately 500 cal/day) and an increase in physical activity (at least 150 minutes/week of moderate physical activity).

60 years of age, is characterized by an HDL-C level lower than 40 mg/dL, normal TG, and autosomal dominant inheritance. Other genetic forms of low HDL-C exist, but they are far less common. Medications, including beta blockers (nonsympathomimetic), retinoids, progestins, and anabolic steroids, can significantly lower HDL-C. Weight loss, lowering TG, exercise (if HDL-C exceeds 30 mg/dL), smoking cessation, and some medications (niacin, fibrates) can raise HDL-C levels.

Combined Dyslipidemia

Combined dyslipidemia is common and important; it is frequently found in patients who survive myocardial infarction or who undergo coronary revascularization. Combined dyslipidemias include abnormalities of several lipoproteins, usually elevated LDL-C and TG, with low HDL-C. Moderately elevated TG (TG 150 to 499 mg/dL) is usually associated with small atherogenic LDL particles, low HDL-C, and altered HDL effectiveness.[1,6]

Metabolic syndrome is a common, high-risk syndrome that resembles combined dyslipidemia and includes multiple risk factors related to abnormal metabolism caused by the central deposition of body fat and secondary insulin resistance resulting in hyperinsulinemia. This situation causes glucose intolerance or type 2 diabetes and hypertension, in addition to combined dyslipidemia, all of which are considered important CVD risk factors (see Chapter 31, Insulin Resistance and the Metabolic Syndrome).

In addition to the metabolic syndrome, other causes of combined dyslipidemias include the following:

- Lack of physical activity
- Hypothyroidism
- Diabetes mellitus
- Alcohol abuse
- Nephrotic syndrome
- Use of glucocorticoids

Integrative Therapy

Lifestyle: Weight Management

Overweight and obesity increase the risk of CVD in part because of negative effects on lipid levels, by increasing LDL-C and TG and decreasing HDL-C. Although separating the effects of weight loss from the effects of the diet changes made to achieve the weight loss is difficult, a modest 10% weight loss leads to reductions of approximately 15% for total cholesterol and 20% for TG. HDL-C levels may be reduced during active weight loss but are often increased after weight has stabilized at a lower level.[8] Weight loss also reduces risk by increasing LDL particle size.[8]

Exercise training trials have demonstrated 3% to 10% increases in HDL-C and modest reductions in LDL-C (1% to 5%) and TG (4% to 15%) levels, with greater improvements in lipid levels if weight loss occurs.[9,10] In addition to lipid and overall cardiovascular benefits, regular exercise is important for effective long-term weight management because it increases calorie expenditure, maintains or increases muscle mass, and helps maintain metabolic rate.

Although many popular diet books suggest that specific diet patterns or food choices are more effective for weight loss, body weight depends primarily on energy balance. If calories consumed are greater than calories expended, weight gain will occur; conversely, if calories consumed are less than those expended, weight loss will occur. Higher-protein diets may lead to better control of appetite and lower calorie intake, but they are often lower in cardioprotective foods such as whole grains, fruits, and some vegetables.[11] An evaluation of several popular diets revealed that the degree of adherence to the diet plan, rather than the plan itself, predicted weight loss.[12]

Generally, an intake of 1800 to 2000 calories/day for men and 1500 to 1800 calories/day for women represents the recommended 500 calories/day energy deficit, although these numbers vary with body size and activity level. Calorie reduction can be accomplished by counting calories (i.e., keeping a list of food intake and tallying calories to stay within the prescribed limit), but an emphasis on portion control and adjustments in meal composition also lead to weight loss. Reducing portions of calorie-dense foods (meats, starchy foods, salad dressings, spreads, sweet drinks, desserts, and snack foods) by approximately one fourth to one third while increasing quantities of foods of lower calorie density (vegetables, fruits) can be effective. The plate method helps control calories by emphasizing meal composition and encouraging patients to visualize their meal on a plate. One quarter of the plate should be dedicated to a protein food and another quarter to a starchy food (grains, potato, corn, peas), whereas the remaining half of the plate is dedicated to nonstarchy vegetables (anything other than potatoes, corn, or peas).[13]

Nutrition

Recommendations for lifestyle changes to improve serum lipids are based on a vast body of epidemiologic investigations, metabolic studies, and clinical trial evidence. Diet trials have demonstrated significant reduction in heart disease risk and improvement in lipid values with a variety of dietary approaches.[14,15] Diet guidelines published by the American Heart Association (AHA) and the NCEP are based on a review of currently available evidence and are generally regarded as the standard of treatment.[1,16] Ongoing and future research will add to our understanding of the complex effects of lifestyle on serum lipids and heart disease risk.

The NCEP ATP III defines lifestyle modification as the critical first step in the management of dyslipidemia.[1] Table 39-4 lists levels of LDL-C at which lifestyle change should be initiated based on a patient's risk. In most situations, a trial of nutrition and exercise changes should be recommended for at least 3 to 4 months before supplements, botanicals, or pharmaceuticals are considered. Effective lifestyle modifications vary depending on the type of dyslipidemia and may include weight management, exercise, smoking cessation, changes in specific dietary components (saturated fat, carbohydrate, fiber, alcohol, and soy), and the addition of supplements or botanicals (Table 39-5).

Macronutrient Distribution

Extensive research has demonstrated that the proportion of fat, carbohydrate, and protein in the diet affects serum lipids. Very-low-fat diets (10% to 20% of calories) often lead to a reduction in LDL-C, primarily because of the smaller

TABLE 39-4. Low-Density Lipoprotein Cholesterol Goals and Cut Points for Initiating Lifestyle Changes or Medical Therapy: National Cholesterol Education Program Adult Treatment Panel III Guidelines

PATIENT RISK GROUP	LDL-C GOAL (mg/dL)	LDL-C LEVEL (mg/dL) AT WHICH TO START LIFESTYLE CHANGES	LDL-C LEVEL (mg/dL) AT WHICH TO CONSIDER STARTING MEDICAL THERAPY
CHD or CHD risk equivalent (10-yr risk less than 20%)*	Less than 100 (less than 70 optional)	Greater than 100	Greater than 100
2 or more risk factors (10-yr risk 10%–20%)	Less than 130	Greater than 130	Greater than 130 (10-yr risk 10%–20%) Greater than 160 (10-yr risk < 10%)
0–1 risk factor†	Less than 160	Greater than 160	Greater than 160 (160–189: medical therapy optional)

Data from Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
*A coronary heart disease (CHD) risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD. Evidence now supports the use of low-density lipoprotein cholesterol (LDL-C)–lowering medications in this category even if LDL-C levels are less than 100 mg/dL; statin clinical trials demonstrated risk reduction at any LDL-C level for patients with CHD. Medications that primarily modify triglycerides and high-density lipoprotein (e.g., nicotinic acid or fibrate or fish oil) are indicated when those values are abnormal.
†Almost all people with zero to one risk factor have a 10-year risk lower than 10%; thus, 10-year risk assessment in people with zero to one risk factor is not necessary.

TABLE 39-5. Nutrition Priorities for Different Lipid Abnormalities

LIPID ABNORMALITY	NUTRITION PRIORITY
LDL-C elevation	Limit saturated fat to 7% of calories and cholesterol to 200 mg/day
	Avoid trans fats
	Increase dietary fiber, especially soluble fiber
	Weight management
	Consider psyllium and plant sterol or stanol supplements
TG elevation 150–500 mg/dL	Weight management and exercise
	Limit sugars, sweet drinks, and alcohol
	Moderate total carbohydrate intake (up to 60% of calories)
	Moderate unsaturated fat intake
TG elevation >500 mg/dL	Limit total fat intake to 10%–15% of calories
	Avoid alcohol
	Weight management and exercise
Low HDL-C	Weight management and exercise
	Moderate unsaturated fat, moderate carbohydrate (avoid very low-fat diets)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

amounts of saturated fat in the diet. However, the higher carbohydrate content (65% to 75% of calories) found in these diets may increase TG, as well as reduce HDL-C and LDL particle size, thus making a very-low-fat diet inappropriate for patients with elevated TG or low HDL. Moderate-fat diets (30% to 40%) result in a lower carbohydrate intake (40% to 55%), which can help reduce TG and maintain or increase HDL-C.[17] Diets higher in fat do not increase LDL-C as long as saturated fat is controlled, but because fat is calorie dense, these diets can make weight loss more of a challenge. The Therapeutic Lifestyle Change (TLC) diet from the NCEP ATP III recommends a moderate-fat, moderate-carbohydrate diet with 25% to 35% of the calories as fat, 15% to 20% as protein, and 45% to 60% as carbohydrate.[1]

Type of Fat

Based on the number of double bonds in the fatty acid chain, fats in food can be classified as saturated or unsaturated. Trans fat, a term describing the fatty acid structure resulting from partial hydrogenation, is technically a monounsaturated fat (MUF), but it has negative effects on CVD risk. Saturated fats raise LDL-C and HDL-C levels, whereas trans fats raise LDL-C, reduce HDL-C, and may reduce LDL particle size.[8,18] Unsaturated fats can be divided into two categories: MUF, with one double bond; and polyunsaturated fat (PUF), with more than one double bond. Within the PUF category, fats can be further divided into omega-3 and omega-6 fats, based on the distance of the first double bond from the omega end of the carbon chain. Unsaturated fats of all types reduce LDL-C when they are substituted for saturated fat.[19] Fats of all types raise HDL-C when they are substituted for carbohydrate, but unsaturated fats substituted for saturated fats either reduce or maintain HDL-C.[17,20] Omega-3 fats reduce TGs and have positive nonlipid effects on inflammation, oxidation, and thrombosis (see Chapter 86, The Antiinflammatory Diet).[19] When TG levels are higher than 1000 mg/dL, dietary fat of any form will raise TG levels because of the lack of lipoprotein lipase activity. Limiting total fat intake to 10% to 15% of calories is necessary to reduce TG levels and decrease the risk of pancreatitis in these situations.

The U.S. Department of Agriculture National Nutrient Database is an excellent free resource to determine the fat and other nutrient content of individual foods. Go to http://www.nal.usda.gov/fnic/foodcomp/search/

Saturated Fat

Considering all available evidence, the TLC diet and the 2006 AHA diet goals recommended a saturated fat limit of 7% of calories for management of lipid disorders and intensive reduction of CVD risk.[1] Dairy fat (butter, cream, cheese, ice cream, whole milk), which is approximately 60% saturated, and meat fat (fatty beef or pork, chicken skin, sausage, hot dogs, bologna), which is approximately 30% saturated, are the major sources of saturated fat in the U.S. diet. In addition, the fats found in coconut oil, palm oil, palm kernel oil, and chocolate contain a significant amount of saturated fat. Research has shown that not all saturated fatty acids have the same influence on lipids. Of the four main saturated fats in our food supply (lauric, myristic, palmitic, and stearic), the myristic and palmitic acid found in meats, dairy, and palm oil appear to have the greatest negative lipid effects. Lauric acid, found in coconut and palm kernel oil, raises both LDL-C and HDL-C, whereas stearic acid, found mainly in beef and chocolate, reduces LDL-C.[21] Because foods contain a mixture of saturated fatty acids and because research is currently limited, recommending specific intakes of each fatty acid is not possible.[22–24] Current recommendations to reduce saturated fat from high-fat dairy products, fatty meats, and tropical oils (palm, palm kernel, coconut) are appropriate.

Trans Fat

Trans fats are found in liquid vegetable oils that have been partially hydrogenated to produce a solid or semisolid fat. These fats are popular in the food industry because of their long shelf life, solid consistency, and stability for deep frying. Trans fat should be avoided as much as possible. Food labels have included trans fat content as of January 2006, thus making it easier for the consumer to make choices based on trans fat content. As a result of consumer demand for trans fat–free products, many food producers have nearly eliminated trans fat from their products. Unfortunately, to maintain the desired texture and stability of processed foods, saturated fats are often substituted for trans fat.[25] Reading labels for trans and saturated fat content and limiting the use of processed foods in general are recommended for management of dyslipidemia and reduction of CVD risk.

Unsaturated Fats

The benefits of MUF versus PUF have been debated for many years. Both types of fats appear to reduce LDL-C to approximately the same degree when they are substituted for saturated fat, and although MUFs seem to maintain HDL-C more effectively than PUFs, PUFs are associated with a greater overall reduction in cardiovascular risk.[19] MUFs are found primarily in olive oil, canola oil, avocado, nuts, and olives. PUFs are found in corn, soybean, safflower, sunflower, and flaxseed oil, as well as fish and some nuts and seeds. Because unsaturated fats come primarily from plant foods, some of the cardiovascular benefits noted with higher unsaturated fat intake may possibly relate to other plant constituents.

PUFs can take the form of omega-3 or omega-6 fats and are essential for good health because they cannot be manufactured by the body. The omega-3 fats influence the inflammatory pathways that affect cardiovascular risk and are discussed further in Chapter 86 (The Antiinflammatory Diet). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the primary omega-3 fats obtained from marine sources including fish and fish oil, whereas the omega-3 alpha-linolenic acid can be obtained from plant sources, including flax, canola, walnuts, soy, mustard oil, and hemp. From 2 to 4 g of EPA and DHA per day can lower TG levels by 20% to 40%, usually accompanied by a slight increase in LDL-C and HDL-C.[26–28] The AHA recommends two fish meals per week, with an emphasis on fatty fish.[16] Because many types of fish may be contaminated with polychlorinated biphenyls and heavy metals, recommendations to increase fish intake should be carefully considered, especially for children and for women of childbearing age.[29] Many fish oil capsules are guaranteed for purity and can be safely used to increase EPA and DHA intake. Investigators have estimated that only 10% to 15% of the omega-3 fats from plant sources (alpha-linolenic acid) are converted to EPA or DHA, and whereas alpha-linolenic acid may offer some protection against CVD, the TG-lowering effect of plant omega-3 fats is not as significant as the effect of marine omega-3 fats.[17,30,31]

Dietary Cholesterol

Individual serum lipid response to dietary cholesterol intake varies widely and is difficult to separate from the effects of dietary saturated fat. Dietary cholesterol is found only in foods from animal sources, and the most significant source is egg yolks. Cohort studies have reported no significant relationship between egg intake and heart disease risk, but metabolic studies have shown a 10-mg/dL increase in serum cholesterol with a 200-mg increase in dietary cholesterol.[25] The ATP III TLC diet recommends a daily limit of 200-mg dietary cholesterol, which equates to approximately two egg yolks per week.[1]

Carbohydrate

Carbohydrates provide a ready source of energy and are found in grains, fruits, vegetables, and legumes, foods that also contain various cardioprotective nutrients. The TLC diet guidelines recommend that carbohydrates provide approximately 50% of the calories to achieve optimal lipid levels.[1] As carbohydrate intake increases, TG levels increase and LDL size and HDL-C levels decrease, so diets containing more than 60% of the calories as carbohydrate are not recommended for persons who have elevated TG levels, low HDL levels, or a predominance of small dense LDL particles.[32] The TG-raising effects of carbohydrates are reduced by fiber and are increased by sugar in the diet.

Based on 2000 calories/day, a diet containing 50% carbohydrate would include 250 g of carbohydrate per day:

$$2000 \times 0.5 \div 4 \text{ calories per gram of carbohydrate}$$

Aiming for an even distribution of the carbohydrate intake, meals would contain 60 to 75 g of total carbohydrate, and snacks would contain 15 to 25 g.

Sugar

A diet that contains more than 20% of the calories as sucrose (approximately 8 tablespoons of table sugar per day in a 2000-calorie diet) will raise TG and probably reduce HDL levels.[33] Large amounts of sugar are absorbed so rapidly that the normal pathways for carbohydrate metabolism are overwhelmed, thus leading to greater synthesis of fatty acids.[32] High-fructose corn syrup is a widely available, inexpensive sweetener used in many processed foods.[34] Fructose may have a greater effect on lipids because the metabolism of fructose encourages the production of VLDLs more than other sugars. Sugar alcohols such as mannitol and sorbitol are commonly used in "low-sugar" foods, but because they are converted to fructose, they can also contribute to the overproduction of TG.[33]

For patients with elevated TG levels, aim for the total carbohydrate goals described earlier, with specific limits on sugar-containing beverages (no more than 8 to 12 oz of regular soda, fruit juice, or fruit drinks per day). Modest amounts of desserts and other sweet foods can be incorporated if they fit within the total carbohydrate goals.

Glycemic Index

The glycemic index ranks carbohydrate-containing foods based on their effect on blood glucose when a prescribed dose of a food is eaten in isolation.[35] The glycemic index of a food is influenced by the type of starch it contains, the amount of fiber present, and the other foods eaten at the same time.[36] Studies suggest the risk of CHD is higher for people who consume high–glycemic index foods, especially if those people have underlying insulin resistance or metabolic syndrome[37,38] (see Chapter 85, The Glycemic Index/Load).

Fiber

Dietary fiber can be classified as insoluble (primarily cellulose found in wheat) or soluble (viscous) fibers including beta-glucan, pectin, and gums. Food contains a mixture of fibers, with an average U.S. diet containing approximately two-thirds insoluble and one-third soluble fiber. Although insoluble fibers have significant benefit for digestion and satiety, the beneficial effects of fiber on cholesterol levels are primarily attributed to soluble fibers. The mechanisms are not clearly understood, but they probably include binding of bile acids in the viscous intestinal contents and fermentation of soluble fiber by colonic bacteria, thus leading to inhibition of hepatic cholesterol synthesis.[39] The TLC diet recommends 10 to 25 g of soluble fiber per day, which has been shown to reduce LDL-C by 3% to 10%.[1,40] The most significant dietary sources of soluble fiber are legumes, oats and oat bran, barley, flax, and fruits. One fourth of the fiber in flaxseed is soluble fiber, and consumption of 1 to 2 oz of ground flaxseed per day can reduce total cholesterol and LDL-C by 2% to 3%, with no effect on TG and HDL-C. Flax oil void of lignan fiber does not have the same lipid-lowering effects as ground flaxseed.[41] Studies show that a higher intake of whole grains is associated with a lower risk of CVD, a finding suggesting that components other than soluble fiber (vitamins, minerals, phytoestrogens) are also important.[42]

Adding 1 to 2 teaspoons of a soluble fiber (psyllium, guar gum, ground flaxseed, bran) before meals has multiple benefits. This practice lowers cholesterol, reduces the glycemic index of the carbohydrates eaten (lowers triglycerides), and stimulates satiety by soaking up water in the stomach, with resulting mild weight loss from reduced calorie intake.

Soluble fiber found in legumes, oats, oat bran, barley, and pectin (apples and oranges) has a greater benefit on cholesterol than does insoluble fiber such as cellulose found in wheat.

Protein

For many years, most dietary guidelines assumed that the amount of protein in the diet had no impact on serum lipid levels. Research suggests, however, that if protein low in saturated fat is substituted for carbohydrate, the risk of CHD is reduced, possibly through improved lipid levels.[43]

Soy Foods

Soy protein substituted for animal protein can reduce total cholesterol, with little effect on TG or HDL-C. Cholesterol-lowering effects of soy are greatest in people with the highest initial cholesterol levels.[41] In general, 25 g of soy protein per day reduces LDL-C levels by approximately 5% and may produce a modest reduction in TG.[44] The mechanisms for the LDL-C reduction are not well understood but may include increased excretion and synthesis of bile acids, reduction of cholesterol absorption, and increased LDL receptor activity.[41] Studies to determine whether the soy protein or the isoflavones found in soy (primarily genistein and daidzein) are responsible for hypolipidemic effects have produced mixed results. A meta-analysis found that soy protein containing isoflavones had a greater lipid-lowering effect than soy protein without isoflavones, but soy isoflavones without soy protein showed no significant lipid-reducing effects.[45] For maximum benefit, minimally processed soy foods (soy nuts, tofu, soy burgers, soy milk, tempeh) are recommended as the primary source of soy protein, rather than isolated soy protein or isoflavone supplements.

Alcohol

Consumption of one or two alcoholic drinks per day is associated with a 30% to 50% reduction in CHD risk.[46] About half of the beneficial effect of alcohol is likely the result of an average 12% increase in HDL-C with one or two drinks per day.[47] In susceptible people, however, one or two drinks per day can raise TG levels, increase blood pressure, and provide extra calories that will make weight loss more difficult. Certain alcoholic drinks (red wine, dark beer) contain phytochemicals that have benefits for cardiovascular health but do not alter lipid levels.[47]

Other Bioactive Food Components

Phytosterols

Phytosterols are naturally occurring sterols present in plants that may enhance the cholesterol-lowering effects of vegetable oils.[48] Typical consumption of plant sterols in the United

States is 200 to 400 mg/day, primarily from vegetable oils, legumes, and nuts and seeds.[49] Studies show that approximately 2 g/day of plant sterols can reduce serum cholesterol levels by approximately 10%.[49] Because this dose is impractical to obtain from food on a daily basis, plant sterols are concentrated and added to foods, including some margarines, orange juice, and soy milk. These products are discussed later under Supplements.

Nuts

Nuts are a rich source of unsaturated fatty acids, plant protein, fiber, vitamins and minerals, plant sterols, and flavonoids, all of which may have health benefits. Numerous studies have shown an inverse relationship between nut consumption and CHD risk, with CHD risk reduced by up to 50% by consumption of 1 oz of nuts or more per day.[50] Studies of walnuts, almonds, pecans, peanuts, macadamias, and pistachios showed modest changes in serum lipids when compared with diets with similar fatty acid profiles but showed significant improvement when nuts were substituted for saturated fat or carbohydrate.[51–55] Similar to other foods rich in unsaturated fat, nuts help maintain HDL levels. To control calorie intake, moderate quantities of nuts should be substituted for other foods, because 1 oz of nuts (approximately ¼ cup) contains 170 to 190 calories. Recommend a handful (not a canful) daily.

Garlic

Garlic is valued for the flavor it adds to food and has been assessed for its lipid-lowering effects, but results are difficult to interpret because of the instability of the active ingredients and variations in preparations used in research studies. Garlic cloves (one half to one per day) and garlic oil may reduce LDL-C by up to 10%, probably related to a reduction in cholesterol synthesis and absorption, whereas the effects of garlic powder are more variable.[50,56] In addition to lipid-lowering effects, garlic seems to have a positive impact on platelet aggregation, which may reduce CVD risk.[20,37]

Eating Patterns

Research on specific nutrients is critically important, but the translation of this research into food and eating patterns will ultimately influence CVD risk. The 2006 AHA guidelines focused on a balanced diet emphasizing vegetables, grains, and fruits while simultaneously limiting saturated fat and cholesterol intake.[17] Emphasis on eating patterns acknowledges that people eat food, not nutrients, and encourages recognition of the potential additive and synergistic effects of various dietary components.[57]

Mediterranean Diet

A Mediterranean diet is described as a diet rich in plant foods (vegetables, fruits, legumes, nuts) and including fish, some poultry, limited red meat, and primarily unsaturated vegetable oils. Interest in this diet plan grew when epidemiologic studies noted that populations with this dietary pattern had lower risks of CVD. The macronutrient composition of the Mediterranean diet is variable but is generally 45% to 55% of calories as carbohydrate, 25% to 35% as fat, and 15% to 20% as protein, with a high content of fiber and omega-3 fatty acids, similar to the TLC diet recommendations of the ATP III.[1] The Lyon Diet Heart Study studied diet plans consistent with a Mediterranean diet and found significant reduction in CVD risk, only partially accounted for by lipid improvements.[15] More recently, a study comparing the effects of a plant-based diet having Mediterranean characteristics with a diet higher in refined convenience foods but low in saturated fat and cholesterol found that the plant-based diet offered additional lipid benefits, likely because of constituents of whole plant foods.[57]

Portfolio Diet

The Portfolio diet study used a Mediterranean-type diet enhanced with foods and nutritional supplements to achieve optimal LDL-C reduction. The diet was vegetarian, with less than 7% of calories as saturated fat, and included foods high in soluble fiber (oats, barley, eggplant, okra), 1 oz of almonds per day, and generous amounts of soy protein (approximately 50 g/day). In addition, participants took supplements of plant sterols and psyllium fiber. All foods were provided for the participants in the 1-month study, which produced LDL-C reductions almost equal to those achieved with 20 mg of lovastatin (28.6% versus 30.9%), a response greater than in any previous dietary study.[58] A year-long follow-up study was conducted, with participants preparing their own foods. Adherence to diet varied significantly, and the mean LDL reduction was 12% to 15%; closer adherence led to LDL-C reductions of greater than 20%.[59] Although these results are encouraging, routine adherence to the Portfolio diet requires a committed patient and a wider availability of dietary products similar to those used in the study.

The Portfolio eating plan is a vegetarian/Mediterranean-type diet with less than 7% of calories from saturated fat. It consists of 2000 calories/day and includes the following key ingredients:

- 30 g of almonds (approximately 23 almonds)
- 20 g of viscous fiber from foods such as oats, barley, psyllium, and certain fruits and vegetables
- 50 g of soy protein from foods such as tofu, soy meat alternatives, and soy milk
- 2 g of plant stanols or sterols from supplements, avocado, soybeans, olive oil, and green leafy vegetables

The results of this regimen are equal to the reduction in low-density lipoprotein cholesterol obtained with 20 mg of lovastatin (approximately 30%).[53,54]

Supplements

Plant Stanols and Sterols

The plant sterol mixtures typically used in supplements to reduce cholesterol levels are usually extracted from pine tree wood pulp or soybean oil. Plant sterols are often hydrogenated, forming stanols, and both sterols and stanols can be esterified to make them soluble in fats, forming stanol and sterol esters. Plant stanols and sterols decrease cholesterol absorption by displacing cholesterol from the intestinal micelles and increasing fecal elimination of both dietary and biliary cholesterol.[41] Stanol or sterol esters in doses of 2 to 3 g/day reduce LDL-C by 8% to 14%, with the greatest reductions occurring when they are added to a high-fat diet.[50,60]

Doses higher than 3.4 g/day provide no additional benefit.[61] Supplements of stanol and sterol esters can be obtained in capsules or "chews," as well as in fortified food products, including margarines, juice, and rice or soy milk. The stanol or sterol content of each supplement or fortified food should be checked because some items contain only small amounts and will not provide the desired lipid reductions.

Safety concerns relate to decreased plasma levels of carotenes, tocopherol, and lycopene when stanol or sterol ester supplements are used.[60] At present, the significance of these changes is not known. In addition, concerns exist about the absorption of plant sterols and the resulting elevations in serum sterol levels, which may increase the risk of heart disease. This occurs in people affected by the rare condition (fewer than 100 cases worldwide) sitosterolemia, characterized by an inability to clear dietary sterols, but studies suggest that this situation may also occur to a lesser degree in the general population. The clinical significance of elevations in serum sterol levels is not clear. Plant stanols do not seem to aggravate sitosterolemia or increase serum sterol levels and may be the safer choice.[62,63]

Dosage

The dose of beta-sitosterol is 800 mg to 1 g, taken 30 minutes before meals three times daily. Benecol chews, four chews per day, are spread over the day. Take Control or Benecol margarine is consumed at 2 tablespoons per day (1 g plant sterol or stanol per tablespoon).

Precautions

Stanol and sterol supplements are generally well tolerated. In some patients, they can cause nausea, indigestion, gas, diarrhea, or constipation. Long-term use may negatively affect plasma levels of sterols, carotenes, tocopherols, and lycopene.

Psyllium

The LDL-C–reducing effect of soluble (viscous) fiber found in food can be enhanced by using supplements high in viscous fiber. Psyllium husk is a well-tolerated, readily available source of soluble fiber that has been extensively studied. LDL-C levels were reduced approximately 7% when 10.2 g of psyllium was added to a diet low in saturated fat.[64] Study subjects taking 10 mg of simvastatin achieved an additional 6% LDL-C lowering when they added 15 g of psyllium per day.[65] Psyllium has a minimal effect on HDL-C or TG levels. Because psyllium supplementation can lead to gastrointestinal symptoms, gradual introduction is recommended, starting with 1 teaspoon/day for a week and increasing the dose by 1 teaspoon/day each week until reaching a maximum dose of 4 to 6 teaspoons/day. Each teaspoon of plain (no sugar added) psyllium powder contains approximately 3.4 g of psyllium husk. Adequate fluid intake is important to prevent choking and improve tolerance. Flavored psyllium supplements may contain undesired sugar and calories, but artificially sweetened or unflavored supplements are available. Other soluble fibers, including guar gum and pectin, have been shown to reduce LDL-C but are less readily available to consumers.[50]

Dosage

Numerous sources of psyllium are available: powder, capsules, wafers); 1 teaspoon of unsweetened powder equals 3.4 g of psyllium husk. Slowly titrate up to 15 to 20 g/day (approximately 4 to 6 teaspoons or 1.5 to 2 tablespoons in divided doses daily).

Precautions

Taking soluble fiber with inadequate fluid intake can lead to constipation and possible fecal impaction.

Fish Oil

Omega-3 fatty acids have multiple cardioprotective mechanisms, but their major lipid effects are reduction of TG and increase in HDL-C. The minimal effective dose of EPA and DHA for TG reduction is slightly more than 1 g/day; a dose of 2 to 4 g/day reduces TG by 25% to 50%.[17,66,67] Patients should begin with a dose of 1 to 2 g/day and titrate to the level that provides adequate TG control. Fish oils reduce production of VLDLs, result in smaller VLDL particles by reducing TG transport, and increase VLDL clearance. Fish oil reduces the absorption and synthesis of cholesterol but may produce a slight increase in LDL-C related to down-regulation of LDL receptors.[66]

Consumption of two to three fatty fish meals per week (as recommended by the AHA) provides approximately 250 to 400 mg of EPA and DHA per day, which is less than the dose required for significant TG reduction. Higher dietary intake of fish is a potential source of heavy metals and other contaminants.[17] Fish oil capsules checked for purity can safely be used to achieve higher doses of omega-3 fatty acids. The omega-3 fatty acid content varies with different fish oil preparations but is often 120 mg of DHA and 180 mg of EPA per 1-g capsule. Thus, 7 to 13 capsules per day would be required to achieve a dose of 2 to 4 g of EPA and DHA per day. This sometimes results in gastrointestinal upset, burping, and a fishy taste. Patients can minimize these symptoms by using fish oil capsules with a higher concentration of DHA and EPA, by taking fish oil with meals, by freezing capsules, or by using enteric-coated fish oil capsules. Some fish oil preparations are more concentrated in EPA and DHA, thus making fewer capsules necessary and possibly minimizing side effects. Cod liver oil is a popular fish oil supplement, but it is high in vitamin A and has a lower concentration of EPA and DHA (190 mg/g) than do oils from fish flesh. Consuming the large amount of cod liver oil necessary to meet omega-3 fatty acid goals on a regular basis could lead to dangerously high vitamin A intakes.

Dosage

A dose of 1 to 4 g of EPA and DHA daily is recommended. Higher doses (3 to 4 g) are needed to treat hypertriglyceridemia.

Precautions

Avoid acquiring omega-3 fatty acid from cod liver oil because of the risk of high vitamin A intake with high doses.

Red Yeast Rice

Red yeast rice is the fermented product of rice on which red yeast *(Monascus purpureus)* has grown. Red yeast rice has been used as a preservative, colorant, and spice in China for centuries. Studies in China and the United States have shown that red yeast rice may reduce cholesterol levels by up to 30% and TG levels by approximately 12% to 19%, because of the presence of monaclins.[68] Red yeast rice has the same potential side effects as 3-hydroxy-3-methylglutaryl–coenzyme A (HMG CoA) reductase inhibitors, including a risk of myopathy. In 1998, the

U.S. Food and Drug Administration (FDA) sought to regulate supplements containing red yeast rice because of the presence of lovastatin, which is identified by the FDA as a drug. Red yeast rice supplements are still available to consumers, but the monaclin and lovastatin contents are highly variable and often unknown, thus making dosing difficult and raising safety concerns. In addition, these products contain other inhibitors of the cytochrome P-450 isoenzyme CYP3A4, which can inhibit the metabolism of the statins and other medications.

Dosage

A standard dose is 1200 mg twice daily, with doses ranging from 600 to 3600 mg daily. A dose of 2400 mg of RYR contains approximately 9.6 mg total statins, of which 7.2 mg is lovastatin. Special care should be taken to ensure a product low in citrinin.

Precautions

Because standardized dosing and reliable preparations of red yeast rice and monaclins are not available, red yeast rice should be used with caution for lipid reduction.[31,69] Inappropriate fermentation practices can result in a chemical contaminant, citrinin, that can be nephrotoxic. Although associated with less myopathy, this supplement should be treated like a statin drug and liver enzymes should be monitored with long-term use.

Guggulipid

Guggul gum is an extract from the resin of the mukul myrrh tree that has been widely used in Asia for centuries. The active ingredients are not clearly defined but may be the plant sterols, guggulsterones, or sesamin, a lignan component, suggesting a mechanism involving reduction in cholesterol absorption or bile acid reabsorption.[70] Most of the research on guggulipid has been conducted in India, with few randomized, controlled studies. One controlled study showed reduction in LDL-C, total cholesterol, and TG, whereas a study in the United States showed no improvements in lipid values.[71]

Dosage

The suggested dosage is 75 to 100 mg daily divided into three doses. This supplement likely works similarly to viscous fiber.

Precautions

Guggulipid may cause gastrointestinal upset, headache, and rash.[21]

Pharmaceuticals

Pharmaceuticals for dyslipidemias should be used for patients at moderate risk after an adequate trial of lifestyle changes and supplements, usually 3 to 6 months. High-risk patients, such as those with genetic cholesterol disorders, very high TGs, or atherosclerosis, may require pharmaceutical treatment at the onset of the diagnosis. Treatment should be individualized for patients, depending on personal characteristics such as the following:

- Overall risk
- Type of dyslipidemia
- Associated medical conditions
- Prognosis
- Patient motivation
- Cost of treatments

The cholesterol-lowering medications have specific lipoprotein actions. Currently, four classes of medications are used to treat dyslipidemias: (1) statins (HMG CoA reductase inhibitors), (2) fibrates, (3) niacin, and (4) cholesterol absorption inhibitors (ezetimibe and bile acid resins. Table 39-6 lists the available medications and provides

TABLE 39-6. Cholesterol Medications

MEDICATION	DOSE RANGE	LDL-C REDUCTION (%)	COST	SIDE EFFECTS AND SPECIAL CONSIDERATIONS
Statins[a]				For all statins: most LDL-C reduction with statins occurs with initial dose Increased hepatic, transaminases and other minor GI effects (2%–3%) May continue if liver function tests are elevated but less than two to three times normal—remonitor Myalgias or arthralgias (2%–3%)
Atorvastatin (Lipitor)	10 mg daily min 80 mg daily max	35–38 50–60	$$$–$$$$	
Fluvastatin (Lescol)	20 mg nightly min 40 mg twice daily or 80 mg XL max	20–25 35–38	$$ or more	[b,c] [b,c]

Continued

TABLE 39-6. Cholesterol Medications—cont'd

MEDICATION	DOSE RANGE	LDL-C REDUCTION (%)	COST	SIDE EFFECTS AND SPECIAL CONSIDERATIONS
Lovastatin (Mevacor, Altocor, generic)	10 mg nightly min 80 mg nightly or 40 mg twice daily max	25–30 34–40	$–$$	[b,c]Lovastatin now available as a generic medication
Pravastatin (Pravachol)	10 mg nightly min 80 mg nightly max	25–32 30–35	$$$	[b]Only statin without CYP450 metabolism; less interaction with other medications; now available as a generic medication
Rosuvastatin (Crestor)	5 mg daily min 40 mg daily max	54–61 35–40		
Simvastatin (Zocor)	10 mg nightly min 80 mg nightly max	45–50	$–$$	[b,c]Simvastatin now available as a generic medication
Bile Acid Sequestrants[d]				
Colestipol (Colestid)	4–8 g two to three times daily	10–25	$$$–$$$$	May increase TG; bloating, constipation
Cholestyramine (Questran)	5–10 g two to three times daily (start at low dose)	TG may increase moderately	$$–$$$	Interference with some medications and fat-soluble vitamin absorption
Colesevelam (WelChol)	6–7 capsules daily (3 capsules twice daily or 6 daily with meal)		$$$$	Less GI toxicity and possibly less interference with absorption of other medications
Niacin				
Niacin plain (crystalline)	500–1,500 mg two to three times daily (starting dose: 100 mg)	20–25 (at high dose); also 50% TG reduction	$	Flushing, dry skin, rash, glucose intolerance, hepatitis, elevated uric acid
Extended-release niacin (Niaspan, only SR formulation recommended)	Starting dose 500, max dose 2,000 mg nightly	Also 50% TG decrease and 25% HDL-C increase	$$–$$$	Dyspepsia or ulcer; caution use in diabetes, gout, history of gastritis or peptic ulcers
Fibrates				
Gemfibrozil (generic, Lopid) Fenofibrate (TriCor, Lofibra, Antara, Lipofen, Triglide)	600 mg twice daily 50–201 mg daily	10% increase to 20% decrease; also 50% TG decrease and 5%–20% HDL-C increase	$–$$$ $$–$$$	Nausea, rare hepatitis, myositis (2%–6%) with statins and cyclosporine; caution use in renal failure
Other				
Ezetimibe (Zetia)	10 mg daily	15–20	$$$	Angioedema, pancreatitis, hepatitis, diarrhea, abdominal pain
Red yeast rice	1200 mg twice daily	25–35	$$ (OTC)	Similar to statins; avoid products with the nephrotoxin citrinin
Guggulipid	50–75 mg twice daily	10–12	$ (OTC)	Headache, nausea, loose stools, bloating, hiccups

$ to $$$$, least expensive to most expensive; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; max, maximum; min, minimum; OTC, over the counter; PO, orally; TG, triglyceride.
[a]All statins have moderate TG-lowering (15% to more than 40%) and HDL-raising (5% to 12%) effects.
[b]Increased myositis occurs with gemfibrozil, fenofibrate, and niacin.
[c]Cytochrome P-450 (CYP450) metabolism leads to interactions with other medications that are metabolized there. The results may be higher statin levels and possible myositis or rhabdomyolysis.
[d]This second-line treatment for LDL-C disorders is a potent combination with statins.

information on their use. To treat dyslipidemias effectively, health professionals should become familiar with all the medication classes. Medications within each class have similar intraclass effects and side effects. However, because pharmacokinetics will vary, if side effects occur, medications may be cautiously substituted within a class.

Choosing the Right Medication for Specific Dyslipidemias

The pattern of dyslipidemia dictates the choice of medication for each patient. Figure 39-1, a dyslipidemia treatment summary, can help the clinician choose an appropriate therapy.

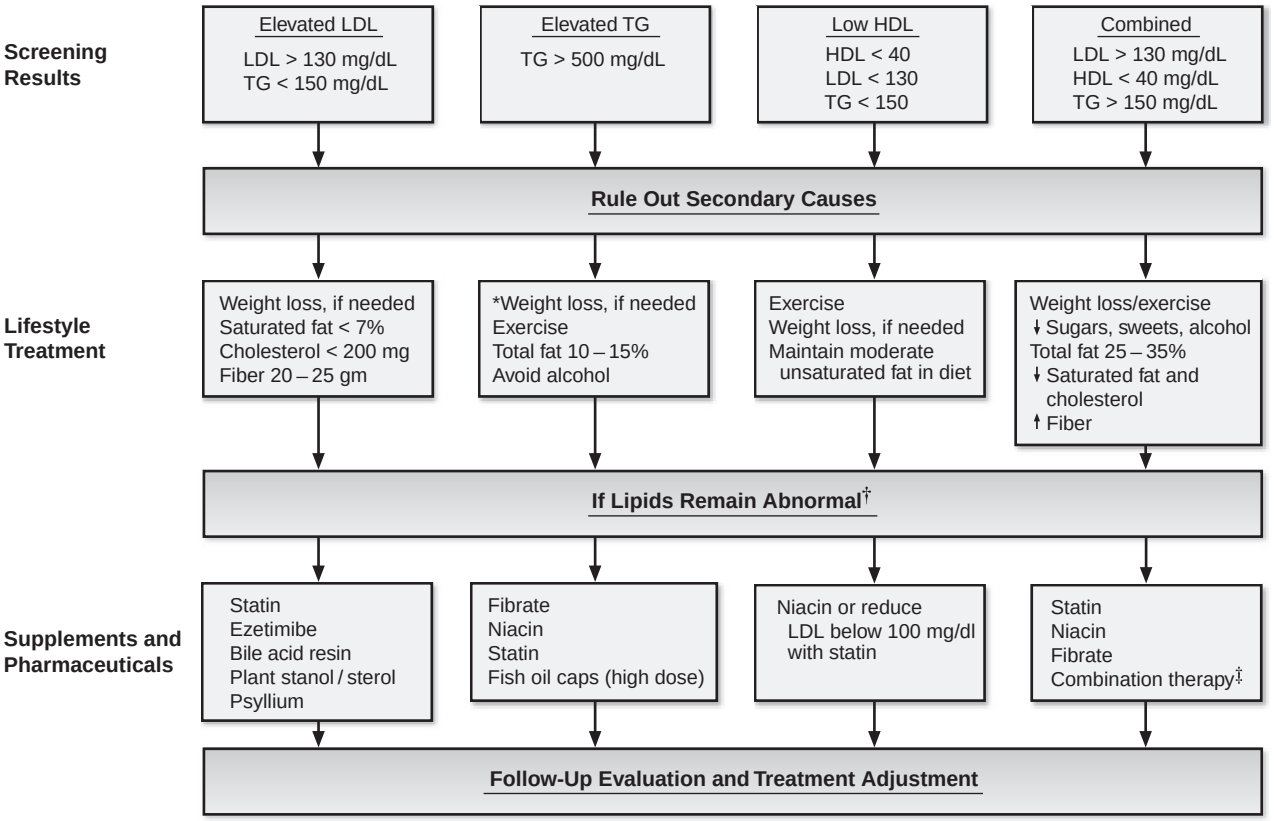
Treating Elevated Low-Density Lipoprotein Cholesterol

- Statins are the most effective treatment for LDL-C elevations, and they also moderately reduce TGs and moderately raise HDL-C.
- Ezetimibe (Zetia) is effective as monotherapy (18% LDL-C reduction) but is more effective in combination with statins (25% LDL-C reduction and 14% TG decrease) and is used only in the 10-mg dose.
- The bile acid resins primarily lower LDL-C but may exacerbate TG elevations.
- Niacin is a potent and inexpensive LDL-C agent, especially in low-dose combination with bile acid resins, but high doses are usually required to lower LDL-C significantly (niacin 2000 mg daily total reduces LDL-C 20% to 25%). The use of niacin is somewhat limited by side effects.
- "No flush" preparations of niacin, such as nicotinamide, have no effects on lipids and should not be substituted for niacin.

Treating High Triglyceride Levels

After secondary causes are evaluated and treated, niacin, gemfibrozil, fenofibrate, and fish oils are the most effective and cost-effective treatments for patients with hypertriglyceridemia (TG higher than 400 mg/dL).

FIGURE 39-1
Dyslipidemia treatment summary. **Exception*: Immediate medication (gemfibrozil or niacin) for patients with triglyceride (TG) higher than 1000 mg/dL because of the high risk of pancreatitis, or low-density lipoprotein cholesterol (LDL-C) higher than 220 mg/dL because of genetic disorders and resistance to nonpharmacologic treatment after ruling out secondary causes. †*Notes*: (1) goal LDL-C lower than 100 mg/dL (70 mg/dL optional) with coronary heart disease (CHD)/noncoronary atherosclerosis, diabetes mellitus, or 10-year CHD risk greater than 20%; (2) goal LDL-C lower than 130 mg/dL if no known CHD or noncoronary atherosclerosis but high risk; (3) goal LDL-C higher than 160 mg/dL with two or more risk factors or LDL-C higher than 190 mg/dL in isolation. ‡*See text*: Statins and fibrates or niacin may be used in combination with close monitoring for hepatitis or myositis (risk of interaction, 2% to 6%). HDL, high-density lipoprotein. (Modified from McBride PE, Underbakke G, Stein DH. Dyslipidemias. In: Taylor RB, ed. *Family Medicine: Principles and Practice*. 6th ed. New York: Springer; 2003:1019–1029.)



Specific guidelines for treating hypertriglyceridemia include the following:

- The fibrates, including gemfibrozil and fenofibrate, primarily reduce TGs and subsequently raise HDL-C. However, they may also elevate LDL-C.
- Fenofibrate is effective for TG, HDL, and LDL if the baseline TG is lower than 200 mg/dL.
- Estrogens, progestins, and other steroids are contraindicated for patients with hypertriglyceridemia because they elevate the TG level and may cause pancreatitis.
- Fibrates are the treatment of choice for hypertriglyceridemia associated with diabetes, gout, gastritis, or ulcer disease because niacin may worsen these conditions.
- Patients with well-controlled diabetes may tolerate niacin without significant worsening of hyperglycemia, but caution and careful monitoring are advised.

Treating Combined Dyslipidemia

The treatments of choice for combined dyslipidemia are statins, niacin, gemfibrozil, and fenofibrate.

- To reduce LDL-C effectively, use a statin, ezetimibe, or bile acid resin.
- Statins may not be effective if the TG level is higher than 300 to 400 mg/dL. In that case, treat with a TG-lowering medication such as niacin (Niaspan), fibrates, or fish oil capsules.

Treating Low High-Density Lipoprotein Cholesterol

Niacin is highly effective in treating isolated low HDL-C (less than 40 mg/dL). Isolated low HDL-C deficiencies are slow to respond to treatment. Patients with documented atherosclerosis and low HDL-C should have a goal LDL-C of lower than 70 mg/dL and may be candidates for prolonged trial of low- to moderate-dose niacin (500 to 1000 mg) to determine whether HDL-C can be increased without significant side effects. Some studies have demonstrated that when HDL-C cannot be raised, using statins to lower LDL-C to less than target levels can reduce CVD.[1,4]

Monitoring Medications

Treatments should be monitored regularly, approximately every 4 to 6 weeks, to adjust the dose and evaluate side effects. Because dyslipidemias are asymptomatic, an initial visit 4 to 6 weeks after therapy is initiated provides an opportunity for valuable patient feedback on medication effectiveness. If patients do not have feedback within that time frame, a significant drop in medication adherence occurs.[1] The following are some additional guidelines for monitoring medications:

- Levels of liver function tests, such as alanine transaminase or aspartate aminotransferase, that are less than two to three times normal and are not progressive are acceptable with the use of cholesterol medications, especially the statins.
- More frequent monitoring is recommended for patients with severe underlying clinical disease, liver enzyme elevations, or underlying liver disease and for patients taking combination therapy.
- Statin drugs lower coenzyme Q10 serum levels, but research has not found that supplementation reduces the incidence of myalgias.
- Because physical activity often causes benign elevations of creatine kinase, measuring creatine kinase levels is recommended only if patients complain of generalized myalgias.
- When lipoprotein levels reach treatment goals, monitoring every 4 to 6 months (to assess the side effects, check laboratory studies, and verify diet and medication adherence) is appropriate.

If a statin is causing myositis, fatigue, or difficulty with memory, consider switching to a water-soluble statin such as pravastatin or rosuvastatin. Also consider adding coenzyme Q10, 100 to 200 mg daily.

Prevention Prescription

- Choose a whole foods, plant-based diet that includes generous amounts of vegetables, whole grains, fruits, and legumes, as well as some fatty fish, nuts and seeds, vegetable oils, and possibly poultry or lean meat.
- Maintain appropriate weight by reducing portions of higher-calorie foods and increasing physical activity.
- Limit foods that are high in saturated fats, trans fats, and cholesterol: fatty meats, butter, cheese, ice cream, other whole milk dairy products, egg yolks, coconut and palm oil, hardened vegetable shortenings, commercially fried foods, snack foods, and bakery items.
- Include food sources of unsaturated fats in moderate quantities: fatty fish, flaxseed, nuts and seeds, and liquid vegetable oils.
- Increase intake of high-fiber foods, especially oats, barley, and legumes, as well as fruits, vegetables, and other whole grains.
- Limit use of high-sugar foods such as sweetened drinks and fruit juices.
- Emphasize vegetable proteins (soy and legumes), and combine protein with carbohydrate at meals and snacks to minimize blood glucose changes and control appetite.
- Use alcohol in moderation, if at all.
- Add plant stanols or sterols, viscous (soluble) fiber, and fish oil supplements as needed to achieve additional cholesterol or triglyceride reduction.
- Add pharmaceutical agents if the foregoing measures do not result in adequate control.

Therapeutic Review

The approach to the therapy of dyslipidemia varies, depending on the patient's cardiovascular disease risk assessment and the severity of the dyslipidemia.

Check for Secondary Causes

- Blood tests for thyroid status, blood glucose, and renal or liver disease
- Review of medications

Lifestyle

- Weight management (initial goal, 5% to 10% weight loss) is a priority for all lipid disorders. A1
- Regular exercise is prescribed, with a goal of 150 minutes of moderate intensity exercise per week. A1

Nutrition

- Emphasize limits on saturated fat (less than 7% of total calories), trans fat, and cholesterol (less than 200 mg/dL), with increases in fiber and soy for low-density lipoprotein (LDL) elevations. A1
- Recommend limits on sugar intake, moderation of total carbohydrate intake, and low–glycemic index foods for triglyceride (TG) elevations. A1
- Encourage substitution of monounsaturated fats for high-carbohydrate foods to maintain or increase high-density lipoprotein (HDL) levels. A1

Supplements

- Add fish oil supplements to reduce TG levels. Start with 1 g of eicosapentaenoic acid and docosahexaenoic acid per day and increase as needed and tolerated. A1
- Use 2 to 3 g/day plant stanols or sterols for LDL-C elevations (1 g before meals). B2
- Add psyllium supplements to increase viscous fiber, including recommended amounts of fluid. Start with 1 teaspoon/day and increase gradually to 4 to 6 teaspoons/day, as tolerated. B2

Pharmaceuticals

- For LDL elevations, consider
  - Statins A2
  - Ezetimibe: 10 mg/day A2
  - And bile acid sequestrants A2
- For TG elevations, consider
  - Niacin: titrated slowly up to 1000 mg A2
  - Fibrates (see Table 39-5) A2
  - Or fish oil: 1 to 4 g/day A2
- For low HDL cholesterol therapy to improve the LDL-to-HDL ratio, consider
  - Niacin A2
  - And/or an additional statin A2
- When TG is higher than 400 mg/dL, TGs must be controlled before total cholesterol and LDL cholesterol can be successfully lowered.

KEY WEB RESOURCES

HeartDecision: www.heartdecision.org	This University of Wisconsin Web site provides a CVD risk calculator, management guidelines, and patient education materials.
National Cholesterol Education Program10-year cardiac risk calculator: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.	This National Institutes of Health site includes guidelines, risk calculator, and patient education materials.
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): www.nhlbi.nih.gov/guidelines/cholesterol/index.htmwww.nhlbi.nih.gov/guidelines/cholesterol/index.htm	
My.AmericanHeart for professionals: my.americanheart.org/professional/guidelines.jsp	This American Heart Association Web site includes a learning library, consensus statements, and guidelines.
HeartHub for patients cholesterol information: www.hearthub.org/hc-cholesterol.htm	This American Heart Association Web site has handouts, videos, and newsletters.
National Lipid Association: http://www.lipid.org	This Web site includes references, tools, protocols, and guidelines.

FamilyDoctor cholesterol information: www.familydoctor.org/online/famdocen/home/common/heartdisease/risk/029.html

This American Academy of Family Physicians Web site has patient education materials.

University of Wisconsin Integrative Medicine program module on nonpharmaceutical methods to lower cholesterol: http://www.fammed.wisc.edu/integrative/modules/cholesterol

This site also includes patient handouts.

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References are available online at expertconsult.com.

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Chapter 40

Irritable Bowel Syndrome

Patrick J. Hanaway, MD

Pathophysiology and Epidemiology

Irritable bowel syndrome (IBS), one of the most common symptom complexes seen by the primary care physician, affects 30 to 50 million people in the United States.[1] Based on the Rome Foundation's Rome III criteria (Table 40-1),[2] the prevalence of IBS has been estimated to range from 10% to 18% in Western countries.[3] IBS has a major impact on modern industrialized societies in terms of economic costs from lost days of employment and health care expenditures, as well as impaired quality of life because of symptoms and impaired psychosocial functioning.[4] In the United States, $10.5 billion is spent each year on direct medical costs and an additional $20 billion on indirect medical costs associated with IBS and related conditions,[5] with an additional $20 billion in indirect costs and absenteeism. Several studies have highlighted that patients with IBS cost insurers 50% more annually than do patients without IBS.[6] Patients with IBS visit their physicians three times more often for symptoms not related to the gastrointestinal (GI) tract than do patients without IBS.[7] Symptoms are reported by 12% to 15% of the U.S. population and are the reason for 30% to 50% of referrals to gastroenterology clinics.[8] IBS is often not seen as a serious medical condition, but patients with the disorder experience a poorer quality of life than described by U.S. norms and than experienced by patients with asthma, diabetes, or migraine headaches.[9]

Functional changes in bowel patterns are the hallmark of IBS, described by Hippocrates as the triad of abdominal discomfort, irregular bowel movements, and various degrees of bloating and rectal urgency. IBS is generally considered a diagnosis of exclusion, defined by the presence of symptoms (abdominal pain or discomfort, bloating, and diarrhea or constipation) and the lack of a known disorder. The Rome III diagnostic criteria are used to define this functional bowel disorder in research, but these criteria are not useful in determining treatment options. As a result, treatment options focus on symptom suppression, rather than on an integrated approach to the person with GI dysfunction that is based on a current understanding of pathophysiologic changes.

The pathogenesis of IBS is multifactorial, with contributions from diet,[10] visceral hypersensitivity,[11] neuroendocrine dysfunction,[12] psychosocial factors,[13] stress,[14] enteric infection,[15] altered GI flora,[16,17] food sensitivities or allergies,[18] and other factors.[19] Research on the treatment of IBS has emphasized diet and nutrition, psychoneuroendocrinologic factors, gut microflora, and the immune system.[20] Research has focused primarily on the gut-brain interactions that highlight visceral perception and autonomic response. However, newer studies of postinfectious IBS, low-grade inflammation, small intestinal bowel overgrowth, and altered gut microflora have yielded more effective clinical improvements.

Gut Microflora and Inflammation

Studies increasingly indicate that a substantial subset (25% to 30%) of patients will develop IBS after an enteric infection.[21] This form of postinfectious IBS is noted to have greater mucosal inflammation extending into the myenteric plexus.[22] The presence of inflammation (even low-grade inflammation) within the GI tract potentiates activation of visceral perception, motility, and hypersensitivity, even after the original infection has cleared.[23]

The role of GI flora in relation to immune activation is currently being explored across the continuum of GI dysfunction, from IBS to inflammatory bowel disease.[24] In IBS, culture and molecular studies have demonstrated decreased diversity of the gut microflora, particularly in aerobic species.[25] Probiotic and dietary prebiotic therapies have been used to correct these deficiencies, with mixed results. Each species and strain of probiotic is unique, with different biochemical effects and specific interactions with the mucosal immune and enteric nervous systems (see Chapter 102, Prescribing Probiotics).

An interesting counterpoint to concerns about gut microflora in IBS is seen in the work of Pimentel et al,[26] who reported that the eradication of bacterial overgrowth of the small intestine eliminated IBS symptoms in 41% of patients. This type of overgrowth could provide a better understanding of the bloating and distention common in IBS.

TABLE 40-1. Rome III Criteria for the Diagnosis of Irritable Bowel Syndrome (IBS)

Symptoms present for at least 3 days per month in the past 3 months (with symptom onset at least 6 months previously) with at least two of the following features:

- Pain improved with defecation
- Onset of pain associated with a change in stool frequency
- Onset of pain associated with a change in stool form

From Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology.* 2006;130:1480–1491.

Additionally, stress produces an inflammatory phenotype in patients with IBS. In response to chronic stress, patients with IBS have helper T cell (Th1 and Th2) suppression and increased interleukin-6. As stress and inflammation increase, so do symptoms. Treatment strategies must consider each of these phenotypic subsets.

Stress

Since the eighteenth century, IBS (formerly known as irritable or spastic colon) was believed to be a nervous disorder that developed in response to external stress and internal neuroses such as depression and anxiety.[27] Early epidemiologic studies demonstrated a 2:1 female-to-male predominance, as well as a higher prevalence of emotional, physical, or sexual abuse in patients with IBS.[28] These vulnerability factors are part of the enhanced stress responsiveness observed in IBS that manifests as an inability to turn off the stress response.[29] Higher cortisol levels in morning urine and saliva have been reported in subjects with IBS than in controls, a finding indicating a state of chronic stress.[30] Stress increases intestinal permeability and susceptibility to colonic inflammation.[14]

The evolution of mind-body medicine and research into psychoneuroimmunoendocrinology helps us better understand the intrinsic relationships among external stressors, emotions, and physiologic changes. Integrative treatment of IBS requires an array of therapeutic approaches that treat the patient on mental, emotional, and physical levels. The studies described here tend to evaluate a single parameter in the treatment of IBS. Intuitively, comprehensive treatment approaches will be of greater benefit.

Enteric Nervous System

Clinicians clearly understand that stress and emotions affect GI function and worsen symptoms in patients with IBS.[31] In addition to elevations in cortisol, patients with IBS have significantly higher postprandial serotonin levels,[32] which are associated with altered gastric emptying, increased small bowel contractions, faster small bowel transit time, and altered pain perception.

Dr. Michael Gershon first described the enteric nervous system as the "second brain"[33] that detects nutrients, monitors the progress of digestion, and modulates the pressure and motility of the GI tract. Alterations in the gut-brain axis observed with positron emission tomography[34] and functional magnetic resonance imaging[35] highlight the role of emotions and mood on the perception of pain in patients with IBS. Studies have recognized the importance of gut microflora, as well as diet, in bidirectional communication with the brain. In other words, brain signaling changes the gut environment, whereas changes in gut microflora can affect both emotions and pain perception by central nervous system signaling through vagal afferent nerves.[36] A synergistic effect on signaling occurs when inflammatory mediators are also present, thus leading to a further increase in visceral hypersensitivity.[37] In addition, 95% of the serotonin (i.e., 5-hydroxytryptamine) in the body is in the GI tract, not in the brain.

Putting it all together: gut signaling arises from gut microflora, serotonin-producing enterochromaffin cells, and localized inflammation. Pharmacologic approaches have focused on the use of agents to bind enteric serotonin receptors, but untoward side effects of these agents create a high risk-to-benefit ratio. Integrative medicine takes the root cause of individual imbalance into account and leads to therapies that focus on the aforementioned areas of diet, inflammation, gut microflora, infection, stress, and mood.

Ninety-five percent of the body's serotonin is in the gut and not the brain.

Diagnosis

Conventionally, the symptom-based determination of IBS is based on the Rome III criteria, as well as a complete history and physical examination. No diagnostic testing is necessary to confirm the diagnosis. Careful attention should be paid to potential alarm signs that should initiate further investigation for cancer or inflammatory bowel disease (Table 40-2). Given the multifactorial nature of IBS, however, this descriptive definition of disease does little to target treatment recommendations. The updated Rome III criteria place greater emphasis on subtypes (IBS-C, constipation; IBS-D, diarrhea; and IBS-M, mixed), which further suggests the importance of symptom-based treatment. More recent studies, however, indicate that IBS subtypes are not stable over time.[38] Similar to the Rome III criteria, this subtype stratification does not facilitate integrative treatment based on the underlying physiologic changes. IBS is diagnosed according to the exclusion of other disease, so it remains necessary to rule out specific illnesses that could mimic IBS. GI imbalances to consider include celiac disease, lactose intolerance, fructose intolerance, food sensitivities, food allergies, small

TABLE 40-2. Alarm Signs in the History of a Patient With Irritable Bowel Syndrome

- Weight loss
- Fever
- Overt or occult blood in stool
- Frequent nocturnal bowel movements
- Abnormal laboratory test results
- Family history of inflammatory bowel disease
- Family history of early colon cancer
- Onset of symptoms after age 50 years

From Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut.* 2000;45(suppl 2): S243-S247.

intestinal bacterial overgrowth, dysbiosis, pancreatic insufficiency, acute infection (bacterial, viral), parasitic infection (acute or chronic),[39] *Clostridium difficile* infection, inflammatory bowel disease, and colorectal cancer.

Diagnostic considerations include, first and foremost, an extensive health history with an understanding of dietary inputs, food intolerances and allergies, and use of antibiotics, laxatives, fiber, and herbs. In addition, the clinician must elicit the current pattern of bowel movements including frequency, history, abdominal pain, gas, bloating, relation to meals, and duration. It is amazing how many patients consider their altered bowel movements to be normal. Western medicine does not have a defined norm of bowel movement frequency, whereas other forms of healing such as Ayurveda and traditional Chinese medicine view the regular functioning of the GI tract to be a critical barometer of health and well-being, with one well-formed bowel movement per day as the norm.[40]

Etiologic factors—infection, parasites, pancreatic insufficiency, celiac disease, food sensitivities, and *Clostridium difficile* infection—should be considered in the differential diagnosis of irritable bowel syndrome before treatment is begun.

Integrative Therapy

We must look beyond symptom-based diagnosis and suppression-based treatment to understand the underlying causes of imbalance and illness. IBS represents an imbalance within the digestive system. The essential components of that system—nutrition, gut flora, immune system, constitution, thoughts, and environment—work optimally when they are in balance and harmony. This integrative approach highlights the unique needs of the individual patient.

Nutrition

Diet

Dietary factors can cause all the symptoms of IBS—pain, bloating, discomfort, and alterations in bowel pattern. More than 70% of patients with IBS describe a worsening of symptoms after meals.[41] Cordain et al[42] described the dietary patterns most common today and compared them with the characteristics of ancestral diets. These investigators noted significant alterations in glycemic load, fiber content, essential fatty acid composition, pH balance, and macronutrient and micronutrient composition. All these factors have tremendous effects on the balance of the commensal flora and the nutrient delivery within the GI tract. This observation is an important reference point, as are the unique and simple food rules that author Michael Pollan has offered: "Eat food. Mostly plants. Not too much."[43] Many patients with IBS experiment with their diet, particularly by removing wheat, corn, dairy, eggs, coffee, tea, and citrus, before they seek medical attention.[44]

Dietary approaches provide the most effective means of returning balance to dysfunction within the GI system, and clinicians have many opportunities to bring these tools to patients. However, the profound dietary changes that humans have adopted over the past 10,000 years, changes that have accelerated over the past 100 years, have created discord with the nutritional input that our genetic structure has evolved to maximize.[42] This discordance creates a much more complex set of clinical opportunities required to regain balance and optimal function.

Food Allergies and Sensitivities

Conventional research has noted that food allergies (mediated by immunoglobulin E [IgE]) and food sensitivities (IgG-mediated) account for approximately 8% of patients with GI symptoms,[45] although many integrative practitioners would remark that the rate of food sensitivity is higher, based on clinical experience. IgE-mediated food allergies can be measured but are present only 2% to 4% of the time. Typically, this diagnosis is made with an elimination diet, during which the symptoms resolve when the patient has removed the offending food and symptoms recur when the offending food is returned to the diet. Atkinson et al[46] used enzyme-linked immunosorbent assay to evaluate food sensitivity in patients with IBS. These investigators used a therapeutic diet in one cohort (based on the IgG assay results identifying foods to which subjects had raised IgG levels) and a sham diet (i.e., the foods eliminated were not those identified as those to which subjects had sensitivities, according to the IgG assay results) in the control population. A 26% decrease in IBS symptoms occurred when test subjects consumed the therapeutic diet, and symptoms returned when they resumed an unrestricted diet.

In a patient with IBS, a diet history should be taken, and a therapeutic diet should be formulated on the basis of results of a targeted elimination-challenge diet (see Chapter 84, Food Intolerance and Elimination Diet).

Gluten Sensitivity and Celiac Disease

Gluten sensitivity is a term used to describe a condition in which gluten leads to a clinical or serologic reaction that improves with gluten elimination. This condition is not exclusive to those who are genetically predisposed through human leukocyte antigen (HLA) DQ2/DQ8.[47] Approximately 4% to 5% of patients with IBS have celiac disease, more than fourfold higher than people without IBS.[48] Investigators have also demonstrated that people without celiac disease who have IgG antigliadin antibody (ABA) feel significantly better when gluten is removed from their diet.[49] Antibody testing for celiac disease is quickly becoming a standard of care in patients with IBS.

Lactose and Fructose Intolerance

The most common form of food intolerance is lactose intolerance, which affects approximately 25% of adults in the United States and 35% to 40% of patients with IBS. Of the patients with IBS who restrict lactose in their diets, more than half will have symptom improvement.[50] Fructose and sorbitol intolerances have also been noted, with similar rates of carbohydrate malabsorption in patients with IBS and controls. However, one study found that patients with IBS had significantly more symptoms because of their carbohydrate malabsorption; these symptoms resolved in 40% of the study subjects after intake of the offending sugar was restricted.[51] The clinician should perform a 14-day trial of a fructose-free, lactose-free, sorbitol-free diet to determine whether the patient's symptoms resolve. Foods with these constituents should be added back with a dietary challenge one at a time every 3 days.

Sorbitol-containing chewing gum can be a common trigger of irritable bowel syndrome, and the clinician should screen for its use when taking the patient's history.

Fermentable Carbohydrates

An extension of the idea to avoid simple sugars is the concept of a diet restricting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMaPs). These fermentable substrates (apples, pears, dried fruit, sugar alcohols, mushrooms, avocado, milk, cheese, wheat, rye, onions, artichokes, and inulin) act as prebiotics and stimulate bacterial growth and gas production.[4] This diet is similar to the specific carbohydrate diet that has been anecdotally effective for IBS and inflammatory bowel disease.[52]

Dietary fiber intake in the United States averages less than 15 g/day, well short of the recommended intake of 25 to 35 g/day, or the 115 g/ day found in the Paleolithic diet. Although fiber seems to ease constipation symptoms in some patients, the ability of dietary fiber to help with abdominal pain and diarrhea has been limited. Multiple randomized controlled trials (RCTs) have failed to show benefit of soluble and insoluble fiber supplementation together for the multiple symptoms of IBS.[53] Many studies have been complicated by the use of significant amounts of wheat bran as a source of fiber; wheat has been noted to be a common source of food sensitivity, thus potentially altering symptom measures in these studies. Partially hydrolyzed guar gum, a soluble fiber derived from ispaghula, has also been shown to reduce IBS symptoms.[54] Soluble fiber and insoluble fiber have been found to have different effects on IBS symptoms. In one study, soluble fiber (psyllium, ispaghula, calcium polycarbophil) led to significant improvement, whereas insoluble fiber (corn, wheat bran), in some cases, worsened the clinical outcome.[55] The clinician should recommend soluble fiber (e.g., 1 tablespoon psyllium seed with 8 oz of water daily) for patients with constipation. This dosage can be titrated to 30 g/day of soluble fiber in food (or as a supplement). The patient should be told to avoid eating insoluble fiber alone or on an empty stomach, but instead to eat it with a larger quantity of soluble fiber.

Soluble fiber (psyllium, ispaghula, calcium polycarbophil) improves symptoms, whereas insoluble fiber (corn, wheat bran) can worsen symptoms in some cases.

Exercise

Regular physical exercise has been demonstrated to improve stress coping, enhance well-being, and decrease feelings of depression and anxiety. Light to moderate exercise is recommended and encouraged for all patients with IBS.

Sleep

Poor sleep quality, which has been reported and quantitated in patients with IBS, further compromises their quality of life. Good sleep hygiene is an important consideration and often requires supporting the entire family unit to adopt this approach.

Supplements

Probiotics

Awareness is growing that the human gut microflora plays a critical role in maintaining host health both within the GI tract and systemically through the absorption of metabolites. An optimal gut microflora establishes an efficient barrier to the invasion and colonization of the gut by pathogenic bacteria, produces a range of metabolic substrates that are used by the host (e.g., vitamins and short-chain fatty acids), and stimulates the immune system in a noninflammatory manner.

The fecal microflora has been shown to be abnormal in IBS. Patients have high numbers of facultative anaerobic organisms and lower amounts of *Lactobacillus* and *Bifidobacterium*. Changes in the colonic flora may lead to altered fermentation and immune dysregulation of the intestinal mucosa.

Trials have focused on altering gut microflora with the therapeutic use of probiotics, which are live microbial organisms that are administered in foods or supplements. Probiotics are nonpathogenic, of human origin, resistant to gastric acid and bile, adhere to intestinal epithelium, and they can colonize the GI tract.[56] Probiotic action appears to decrease fermentation, improve competition against imbalanced and potentially pathogenic flora, and stimulate proper immune functioning. Probiotics have been shown to improve the symptoms of IBS[57] and to balance inflammatory cytokines in patients with IBS.[58] A systematic review in the journal *Gut* evaluated 19 RCTs. Results showed clear benefit, although only one strain (*Bifidobacterium infantis* 35624) demonstrated statistical significance in reductions of pain, bloating, and inflammatory cytokines.[59] Information and studies on clinical utility cannot be transferred across different strains and different bacteria. Initial studies focused on several strains of probiotic, with positive effects reported for *Lactobacillus plantarum, L. plantarum* in combination with *Bifidobacterium breve, Streptococcus faecium,* and VSL#3.[53]

Dosage

Recommend a mixture of 50/50 *L. plantarum with B. breve* at 25 billion colony-forming units (CFUs) twice daily for 6 to 8 weeks; then decrease to 10 billion CFUs/day. Other probiotic combinations may be considered on the basis of fecal flora (see Chapter 102, Prescribing Probiotics).

Precautions

Avoid probiotics in the severely immunocompromised host.

Altered gastrointestinal flora (also known as dysbiosis) is considered a critical factor in immune dysregulation and altered function. Correction of dysbiosis is necessary in the treatment of irritable bowel syndrome.

Prebiotics

Prebiotics are simple carbohydrate molecules that selectively stimulate normal GI flora to proliferate and thus compete with abnormal flora and pathogens for space, food, and adherence. Synbiotics are the combination products of prebiotics and probiotics. Fructo-oligosaccharides and inulin

are the most commonly used prebiotics at this time; they increase bifidobacteria in the stool. Animal studies have demonstrated beneficial effects on microflora balance,[60] and human studies have shown in vivo activation of bifidobacteria,[61] but no improvement in IBS.[62]

Dosage

See the earlier discussion of the FODMaP diet. Do not recommend prebiotics unless or until rebalancing of the gut flora occurs. Common food sources include apples, pears, dried fruit, mushrooms, avocado, milk, cheese, wheat, rye, onions, artichokes, and inulin.

Pancreatic Enzymes

One of the conditions to be considered diagnostically with IBS is pancreatic insufficiency. This disorder can be a primary process, with depletion of exocrine pancreatic function, or it can be secondary to villous atrophy and insufficient cholecystokinin stimulation of the exocrine pancreas. Both conditions lead to a decrease in the production of pancreatic elastase and chymotrypsin in the stool, identification of which will help determine the need for supplemental pancreatic enzymes. Laboratory data reveal that approximately 20% of patients with IBS have mild pancreatic insufficiency, whereas 8% have moderate to severe pancreatic insufficiency. Studies of pancreatic enzyme supplementation in patients with IBS symptoms are now under way.

Testing the stool for pancreatic elastase is a relatively inexpensive way to check for pancreatic insufficiency.

Botanicals

Peppermint Oil

Peppermint *(Mentha piperita)* has been used for GI disturbances for millennia. Menthol and methyl salicylate, the main active ingredients, have antispasmodic actions, with calming effects on the stomach and GI tract. Peppermint also has analgesic properties, mediated through activation of kappa-opioid receptors to help block transmission of pain signals. Peppermint oil has been evaluated in several randomized trials, and a meta-analysis performed by Pittler and Ernst[63] demonstrated a beneficial effect after 2 weeks of therapy. A 2006 Cochrane Review confirmed these initial reports; 79% of patients with IBS noted alleviation of abdominal pain.[64]

Dosage

The recommended dosage is one to two 0.2-mL (200 to 400 mg) enteric-coated capsules three times/day between meals; smaller doses (100 to 200 mg) are effective in children.[65]

Precautions

Non–enteric-coated capsules and peppermint oil can decrease the tone of the lower esophageal sphincter and can lead to heartburn. Skin rash has also been reported approximately 2% of the time.

Fennel

Fennel *(Foeniculum vulgare)* has antispasmodic properties and is particularly helpful in the treatment and prevention of bloating and gas, as a result of the volatile anethole oil.

Dosage

Fennel is best used with food (1 teaspoon), but it can also be taken as a tea, oil capsule, or alcohol extract. Caraway seeds are noted to have similar properties.

Ginger

Ginger *(Zingiber officinale)* can be used nutritionally, in cooking, or as an herbal remedy and has been evaluated in the treatment of postoperative nausea and vomiting. No studies have been conducted with ginger in IBS, although the active gingerols act as an antispasmodic and improve the tone of intestinal muscles. Ginger is available in many forms, and ginger root tea is particularly helpful after overeating.

Dosage

The dose of powdered root is 250 to 500 mg three to four times/day. Prepare ginger tea by chopping a piece of ginger the size of the patient's fifth digit; place in 150 mL of boiling water for 5 to 10 minutes and strain. Drink 1 cup before meals.

Aloe

Aloe (*Aloe spicata* and *Aloe vera*) is commonly considered safe for internal ingestion and is used commonly in patients with IBS. *Aloe vera* is classified by the U.S. Food and Drug Administration (FDA) as a class 1 harsh stimulant laxative because the anthraquinones in aloe significantly increase colonic peristalsis. Aloe should be regarded as being in the same class as other anthranoid laxatives, such as cascara *(Cascara sagrada)* and senna *(Cassia senna)*. Although these agents may be used for short-term relief of constipation, they are not suitable for use in IBS because of their powerful action and tendency for dependency.[66]

Combination Herbal Therapies

Traditional Chinese Medicine

One of the most often cited studies of integrative medicine in IBS was published by Bensoussan et al in *JAMA*.[67] These researchers demonstrated a beneficial effect of a combination Chinese patent medicine (Tong Xie Yao Fang [TXYF], a generic prescription for presumed spleen qi deficiency and liver-spleen disharmony) used for 16 weeks. Symptoms improved significantly during treatment but returned after the medicine was stopped. Individualized herbal therapies demonstrated sustained improvement, however, even 14 weeks after the individualized herbal medicines were stopped. Thus, individualized traditional Chinese medicine treatment is recommended. An additional study of TXYF in 120 patients with IBS showed decreased mast cell activation, but the trial was not placebo controlled.[68]

Padma Lax

Padma Lax is a complex Tibetan herbal formula for constipation; it contains aloe extract, calumba root, cascara bark, frangula bark, rhubarb root (all known laxatives), and other herbs and minerals with antispasmodic and antidiarrheal effects. Several studies have demonstrated the effectiveness of this treatment in constipation-predominant IBS.[69]

Dosage

For IBS with constipation, the dose of Padma Lax is two capsules/day for 3 months; then decrease dosage to one capsule daily if loose stool is noted.

STW 5

STW 5 is a mixture of aqueous ethanolic plant extracts from *Iberis amara* (Clown's mustard), chamomile flower, caraway fruit, peppermint leaves, greater celandine, licorice root, lemon balm leaves, angelica root, and milk thistle fruit. In a 2001 randomized multicenter study of 208 patients with IBS, STW 5 reduced total abdominal symptoms by approximately 54%, compared with 27% for placebo, at 4 weeks.[70]

Dosage

A common brand name of this product is Iberogast. It can be mixed with water in the following dosage:

Adults and children older than 12 years of age: 20 drops, three times/day

Mind-Body Therapy

Mind-body therapy, in the form of relaxation therapy, biofeedback, hypnosis, counseling, or stress management training, has been shown to reduce symptom frequency and severity and to enhance the results of standard medical treatment of IBS. Most of these therapies focus on correcting maladaptive coping skills that engender emotional stress, which then manifests as GI symptoms.

Stress Management

Lifestyle changes that incorporate stress reduction and stress management strategies, along with progressive muscle relaxation, have proved to be more effective than medical therapy[71] (see Chapter 93, Relaxation Techniques).

Hypnosis

Trials conducted in the United Kingdom found that weekly hypnosis sessions, in combination with self-hypnosis techniques for 12 weeks, improved the symptoms of abdominal pain, bloating, and disturbed defecation, as well as anxiety scores, but did not alter rectal tone or pain threshold.[72] Specific gut-directed hypnotherapy programs are now available (see Chapter 92, Self-Hypnosis Techniques).

Psychotherapy and Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) combines cognitive therapy and behavioral therapy. Behavioral therapy helps a person weaken the connections between troublesome situations and habitual reactions to them. Cognitive therapy teaches how certain thinking patterns are causing symptoms. When combined into CBT, these therapies provide powerful tools for eliminating symptoms. CBT has been shown to improve symptoms significantly in patients who had moderate to severe IBS in comparison with education alone.[73] A Cochrane Review confirmed the positive data noted earlier but indicated that more research is needed to draw a conclusion about the effectiveness of hypnotherapy for IBS.[74] Additionally, the review of psychological treatments for IBS stated that most of the studies have been suboptimal, so physicians should choose individualized therapies.[75]

> Persons with irritable bowel syndrome symptoms often have a combination of mental and emotional stressors and alterations in the psychoneuroimmunologic axis. Ensuring a proper gut milieu, along with stress management strategies, is necessary for optimal gut function.

Acupuncture

In 2006, the Cochrane Review analyzed six RCTs using acupuncture in IBS. No evidence supported the use of acupuncture in treating IBS.[76] A more recent study was performed by Lembo et al[77] that demonstrated a benefit of both real and sham acupuncture. The nonspecific placebo effects of acupuncture seemed to be therapeutically effective.[77]

Placebo Effects

The high placebo response rates noted in RCT research in the treatment of IBS have been well documented. Kaptchuk et al[78] developed a unique study to evaluate the benefit of openly offering a placebo treatment, which was found to be efficacious.

Pharmaceuticals

Oral Cromolyn

Several studies compared oral cromolyn with placebo in randomized double-blind crossover trials; in one study, an 8-week treatment resulted in significant symptom reduction and a long carryover effect in the group initially treated with cromolyn.[79] Two large unblinded studies compared oral cromolyn with elimination diet. The largest trial involved 409 patients with well-defined IBS who were monitored for 4 months.[80] Symptom improvement was noted in 60% of patients treated with elimination diet and in 67% of those receiving cromolyn.

Dosage

The recommended dose is 200 to 400 mg (one to two gel caps) four times/day, before meals and 30 minutes before bedtime.

Antibiotics

The "shotgun" use of antibiotic treatments leads to significant alterations in the GI microflora that can be deleterious in the long term.[81] Rifaximin (a nonabsorbable antibiotic) has been demonstrated to improve IBS symptoms significantly.[82] Rifaximin has also been shown to be useful in treatment of small intestinal bacterial overgrowth, a source of bacterial fermentation, gas, and bloating. Small intestinal bacterial overgrowth can be diagnosed with a lactulose or glucose breath test.

Dosage

The recommended dose of rifaximin is 550 mg three times/day for 14 days in patients with small intestinal bacterial overgrowth.

Precautions

Rifaximin is not absorbed systemically, so most of the side effects are related to GI function, including flatulence, abdominal pain, and stool urgency.

Antidepressants

A meta-analysis reported that tricyclic antidepressants significantly lessened abdominal pain and diarrhea in patients who had diarrhea-predominant IBS.[83] Patients who can tolerate these medications are likely to have symptomatic benefit, but many patients experience unacceptable side effects. Although the neuroendocrine role of serotonin in the GI tract is understood, no support exists for selective serotonin reuptake inhibitor treatment of IBS at this time.[84] A Cochrane Review from 2005 found no evidence to suggest that antidepressants are effective for the treatment of IBS.[85]

Therapies to Consider

Betaine Hydrochloride

A basic evaluation of digestion and absorption is often excluded from the initial evaluation of GI function in patients with IBS. Factors that affect digestion of food include mastication, hypochlorhydria, and pancreatic insufficiency. Mastication is a simple clinical point to make with patients and is often overlooked. Pancreatic insufficiency and the benefit of digestive enzyme supplementation have already been discussed. Data indicate that stomach acid declines with age, even as proton pump inhibitor prescriptions are increasing. Decreased pH limits the activation of peptidases and other critical enzymes necessary for digestion and absorption. Betaine hydrochloride can be used as a supplement to support the reactivation of proper digestion.

Dosage

The dose is 325 to 650 mg before a protein-containing meal.

Homeopathy

In classic homeopathy, an extensive historical interview is performed that seeks to identify the totality of the patient on physical, emotional, and mental levels. To this picture the practitioner matches a remedy that best suits the individual patient. This remedy is administered in small and infrequent doses, and follow-up is performed to determine whether the chosen remedy should be repeated, changed, or allowed to continue its work.

Osteopathic Medicine

A common view is that osteopathy and other related manual therapies are used only for musculoskeletal problems. However, recognition of a somatovisceral pathway amenable to manipulation has led to use of these approaches for relief of symptoms in people with IBS. The somatic areas commonly affected include the following: external oblique muscles (especially the lower portion), internal oblique muscles, and rectus abdominis muscle; lower segments of the thoracic spine (T10 to T12); iliocostalis thoracis and lumborum and longissimus thoracis and lumborum muscles; and quadratus lumborum muscles. Persons with this somatovisceral connection are often not aware of these tender points until they are discovered by careful palpation. This indirect technique seeks to release the strained somatic segments through initiation of a reciprocal counterstrain of the antagonist muscles (see Chapter 106, Strain/Counterstrain).

Prevention Prescription

- Primary prevention in the first 2 years of life:
  - Limit or avoid antibiotics and antimicrobial herbs to maximize opportunity for bowel microflora to develop.
  - Practice breast-feeding on demand for the first 12 months of life; avoid formula feeding, if possible.
  - Introduction of solid foods: Delay introduction of grains until after age 6 months, preferably after age 12 months.
  - Carbohydrates: Avoid or delay introduction of simple sugars because they provide the substrate for abnormal bacteria to perpetuate in the GI tract.
- Stress the importance of taking time to eat, preparing food, and eating it with others.
- Promote learning to reduce stress or the internalization of emotion.
- Encourage the use of a Paleolithic diet, with fewer processed foods and fewer grains.
- Treat enteric infections and watch for sequelae, particularly in patients with life stress during infection or a history of trauma.

Therapeutic Review

An initial diagnostic evaluation is necessary to target effective therapies for irritable bowel syndrome (IBS). For the patient with mild to moderate symptoms of no clear cause, this ladder approach is appropriate.

Mind-Body Therapy

- Cognitive-behavioral therapy — B1
- Hypnotherapy — B1

Nutrition

- Elimination/challenge diet (see Chapter 84, Food Intolerance and Elimination Diet) — B1
- For some patients, additional motivation through diagnostic testing (IgG food allergy testing)

Probiotic Supplements

- 50 billion CFUs/day as 25 billion CFUs/day of *Bifidobacterium* and 25 billion CFUs/day of *Lactobacillus*; or *Bifidobacterium infantis* 36524 at 5 billion CFUs/day — A2, A1

- Soluble fiber (psyllium, guar gum): 15 g/day with meals 

Botanicals

- Peppermint oil: one to two enteric-coated capsules 3 times/day between meals 
- Traditional Chinese medicine herbs: Tong Xie Yao Fang 
- Tibetan herbs/Padma Lax for IBS with constipation: two capsules/day for 3months 
- STW 5: 20 drops three times/day for 4 weeks 

Pharmaceuticals

- Oral cromolyn: 200 mg (two capsules) four times/day before meals and before bedtime 
- Antibiotic: rifaximin, 550 mg three times/day for 14 days, if evidence of small intestine bacterial overgrowth[86] 
- Tricyclic antidepressants: lower doses to start, such as amitriptyline at 10 to 25 mg/day 

KEY WEB RESOURCES

International Foundation for Functional Gastrointestinal Disorders: www.iffgd.org.	The aim of this nonprofit education and research organization is to inform, assist, and support people with functional GI disorders. The Web site offers patient information, as well as recent publications and current research on IBS.
Institute for Functional Medicine: www.fxmed.com.	This Web site offers educational opportunities to help health care practitioners develop personalized approaches to understand and find the root cause (i.e., the core clinical imbalances) for various chronic diseases, including IBS.
American Board of Integrative Holistic Medicine: www.holistic-board.org.	This Web site offers digital education tools, online learning modules and educational conferences on integrative (the what) holistic (the how) medicine. In addition, the organization has defined the new standard of care through its Board Certification in Integrative Holistic Medicine process.

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Chapter 41

Gastroesophageal Reflux Disease

David Kiefer, MD

Gastroesophageal reflux disease (GERD) occurs when there is abnormal passage of acidic stomach contents, or refluxate, into the esophagus, causing symptoms or complications. It is one of the primary causes of the informal name and symptom "heartburn," and GERD is a common phenomenon. Estimates are that 15% to 20% of people in the United States have heartburn or regurgitation at least once a week, and 7% of people suffer from those symptoms daily.[1–3]

Symptoms of GERD may include any or all of the following: retrosternal burning, acid regurgitation, nausea, vomiting, chest pain, laryngitis, cough, and dysphagia.[3] The injury to the esophagus can include esophagitis, stricture, the development of columnar metaplasia (Barrett esophagus), and adenocarcinoma.[2] A poor correlation exists between the severity of symptoms and the pathophysiologic findings in the esophagus.[2] For example, GERD is not the only phenomenon in the differential diagnosis of heartburn. Many people with GERD do not have endoscopic evidence of esophagitis, and up to 40% of people with Barrett esophagus in one study did not report heartburn.[2] The confusing nature of this condition makes it a challenge to develop concrete screening recommendations for advanced disease.

People may turn to complementary and alternative medicine to help with their gastrointestinal symptoms. The 2002 National Health Interview Survey, based on 31,044 interviews in the United States, documented that 3.7% of people used complementary and alternative medicine for stomach or intestinal illnesses.[4]

Pathophysiology

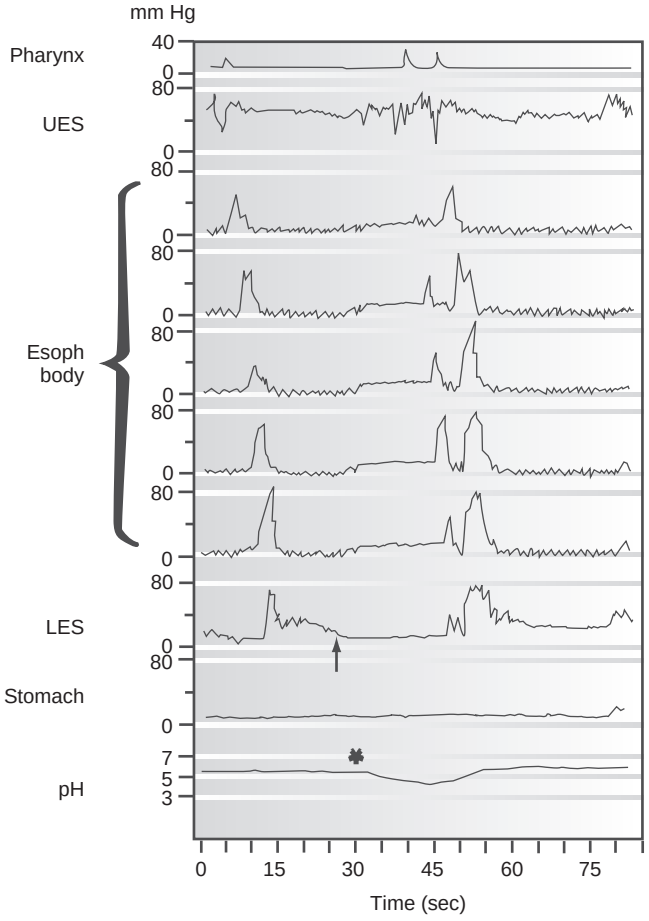
Symptoms of GERD result from the interplay of many factors, including the amount of time the esophagus is exposed to refluxate, the degree of refluxate causticity, and the susceptibility of the esophagus to damage.[5] Three main mechanisms or factors prevent refluxate from entering the esophagus: the lower esophageal sphincter (LES), the crural diaphragm (which acts as an external esophageal sphincter), and the location of the gastroesophageal junction below the diaphragmatic hiatus.[1] Dysfunction or malalignment in any or all of these structures could lead to symptoms of GERD, although the major pathologic mechanism is some abnormality in tone of the LES.

The LES normally exists in a contracted state, but it relaxes during the swallow mechanism to let material into the stomach (Fig. 41-1). The LES also relaxes to vent swallowed air and allow retrograde expulsion of material from the stomach.[5] For approximately an hour after meals, people may normally have up to five transient episodes of reflux, but if these episodes continue, symptoms of GERD may develop.[5]

Decreased tone of the LES occurs with many substances, medications, and other factors (Table 41-1).[1] Certain beverages may exacerbate symptoms of GERD, some by affecting LES tone. For example, coffee, including instant coffee, decaffeinated, and ground coffee, decreases LES initially and, in some people with sustained decreased tone, for up to 90 minutes after ingestion. Caffeinated coffee seems to cause more gastric acid production,[6] and it decreases LES tone more at lower pH.[7] Another study found an association between pH and titratable acidity and the frequency with which some beverages, such as juices, sodas, coffee, and tea, caused heartburn symptoms in 394 people with GERD.[8] Caffeine itself has some ability to decrease LES tone.[9]

Symptoms of GERD may result from other factors. For example, increased intra-abdominal and gastric pressure, such as from obesity, ascites, pregnancy, or even tight clothes, may lead to GERD.[1,10] In addition, GERD may occur when the gastric contents are located near the gastroesophageal junction, such as in the recumbent position, while bending

FIGURE 41-1
Normal swallow mechanism. A continuous tracing of esophageal motility showing two swallows, as indicated by the pharyngeal contraction associated with relaxation of the upper esophageal sphincter (UES) and followed by peristalsis in the body of the esophagus. The lower esophageal sphincter (LES) also displays transient relaxation *(arrow)* unassociated with a swallow. An episode of gastroesophageal reflux *(asterisk)* is recorded by a pH probe at the time of the transient LES relaxation. (From Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics.* 17th ed. Philadelphia: Saunders; 2004.)



over, or in patients with a hiatal hernia.[1] Furthermore, any conditions that decrease the production of saliva may predispose to GERD because of the neutralizing effect of saliva on acid.[1]

People report that stress exacerbates GERD, a finding that has borne out in clinical trials. For example, stress was shown to increase GERD symptom reports, without necessarily being correlated with objective physiologic changes such as increased esophageal acid exposure or duration of acid exposure.[11,12] This phenomenon occurs especially in people with high levels of anxiety.[12]

Diagnostic testing can be used to determine the cause of a patient's symptoms and any pathophysiologic correlates. For example, barium swallow, upper endoscopy, ambulatory pH, and a trial of proton pump inhibitor (PPI) medications are the most commonly used diagnostic tests.[13] Ambulatory pH testing, estimated to have a sensitivity of 79% to 96% and a specificity of 85% to 100% for GERD, may also be used with impedance testing to explore the correlation of symptoms with refluxate volume regardless of acidity (weakly acidic or nonacid reflux).[2,13] One approach is to consider diagnostic testing (upper endoscopy, ambulatory pH, or impedance testing) if a patient is unresponsive to PPI therapy.[13]

TABLE 41-1. Factors Associated With Decreased Tone of the Lower Esophageal Sphincter

FACTOR	EXAMPLES
Dietary supplements	Arginine may cause lower esophageal sphincter relaxations through the nitric oxide system Carminative herbs such as peppermint (*Mentha piperita*), spearmint (*Mentha spicata*), and other mint family (Lamiaceae) plants Essential oils (high doses)
Foods and beverages	Alcohol Chocolate (probably through the methylxanthines) Coffee (caffeinated more than decaffeinated) Cow's milk Fat Orange juice Spicy foods Tea Tomato juice
Lifestyle	Smoking
Medications	Aminophylline Anticholinergics Beta-adrenergic agents Calcium channel blockers Nitrates Phosphodiesterase inhibitors, including sildenafil
Physiologic, by stomach dilatation	Acid hypersecretion After meals Gastric stasis Pyloric obstruction
Trauma, irritation, and miscellaneous factors	Esophagitis Scleroderma-like diseases Surgical damage

Data from references 1, 16, 17, and 27.

Special Considerations for Pediatrics

In children, GERD is the most common esophageal disease.[5] In infants, symptoms often peak at 4 months of age and resolve by 12 to 24 months, whereas in children, the clinical course may wax and wane, resolving in about half the cases.[5] Infants may present with postprandial regurgitation, irritability, arching, choking, gagging, feeding aversion, failure to thrive, obstructive apnea, or stridor; signs and symptoms in older children are abdominal pain, chest pain, asthma, laryngitis, and sinusitis.[5] Studies in infants with suspected GERD have found both a high incidence of allergy to cow's milk protein[14] and symptomatic improvement when infants with intractable symptoms were changed to a diet free of cow's milk protein.[15]

Cow's milk protein is a common cause of gastroesophageal reflux disease in infants, and a trial of elimination should be considered.

Integrative Therapy

Lifestyle

In mild cases of GERD, lifestyle modifications are the first line of therapy and can lead to improvement or elimination of symptoms. For example, GERD symptoms may improve if smokers quit and if obese patients lose weight.[1,16] Patients should avoid the foods and supplements and, if possible, the medications mentioned in Table 41-1 because of their relaxing effect on the LES. In addition, patients should avoid eating large meals or consuming large quantities of fluids with meals.[1]

If nighttime symptoms are present, patients should elevate the head of the bed 4 to 6 inches, by using blocks under the bed posts rather than extra pillows. Use of extra pillows could compress the abdomen and increase intra-abdominal pressure, thereby exacerbating symptoms.[1,2,16]

Demulcent Botanicals

Several types of botanical treatments are useful for GERD (Table 41-2). Demulcent, or mucilaginous, botanical medicines can be used as mucoprotection of the esophageal mucosa, both to soothe irritated tissues and promote healing.[16,17]

Licorice (Glycyrrhiza glabra)

Licorice is a well-known demulcent botanical used for GERD, gastritis, and duodenal and peptic ulcers. For long-term use, it should be prescribed as deglycyrrhizinated licorice, to prevent the side effects of one of its phytochemicals, glycyrrhizin (see later).

Dosage

Two to four 380-mg tablets of deglycyrrhizinated licorice should be taken before meals.[18]

The prolonged use of decoctions or infusions of dried, unprocessed licorice root can cause hypertension, hypokalemia, and edema because of the mineralocorticoid action of a saponin glycyrrhizin, also called glycyrrhizic acid.[19]

Slippery Elm (Ulmus fulva) *Root Bark Powder*

Slippery elm root bark powder is one demulcent botanical that can be used for symptomatic relief and promotion of healing of irritated esophageal or gastric mucosa. Most health food stores, integrative pharmacies, and herbal dispensaries with botanical products for sale in bulk will have slippery elm.

Dosage

One to two tablespoons of the powder should be mixed with a glass of water and taken after meals and before bed. The proportions should be carefully titrated because the preparation can be very thick and difficult for some people to tolerate. To increase palatability, this supplement can be sweetened slightly with honey or sugar.

Precautions

This botanical is described by most sources as very safe, although the hydrocolloid fibers may bind simultaneously administered medications and decrease their absorption.[19]

TABLE 41-2. Botanical Medicines Useful in Gastroesophageal Reflux Disease

COMMON NAME	SCIENTIFIC NAME (FAMILY)	MECHANISM OF ACTION	DOSE	ADVERSE EFFECTS
Chamomile	*Matricaria recutita* (Asteraceae)	Antiinflammatory, antispasmodic	1–3 g of an infusion of the flowers three to four times daily	Occasional allergic reactions in people allergic to plants in the daisy family (Asteraceae)
Licorice	*Glycyrrhiza glabra* (Fabaceae)	Mucoprotective	Two to four 380-mg DGL tablets before meals	Mineralocorticoid side effects avoided when DGL form is used
Marshmallow	*Althea officinalis* (Malvaceae)	Mucoprotective	5–6 g of tea daily, in divided doses	Decreased drug absorption
Skullcap	*Scutellaria lateriflora* (Lamiaceae)	Antianxiety	1–2 g of the herb as infusion three times daily, 1–2 mL tincture three times daily	Confusion, stupor, and twitching with high doses
Slippery elm	*Ulmus fulva, Ulmus rubra* (Ulmaceae)	Mucoprotective	1–2 tablespoons per glass of water, three to four times daily	Decreased drug absorption
Valerian	*Valeriana officinalis* (Valerianaceae)	Antianxiety	1–2 g root infusion two to three times daily, or 150-mg capsule two to three times daily	Possibly increased effects of alcohol, barbiturates, benzodiazepines

DGL, deglycyrrhizinated licorice.

Marshmallow (Althea officinalis)

Marshmallow is another mucilaginous herb for GERD symptomatic relief. Its demulcent properties also make it useful for pharyngitis, wound healing, cough, and bronchitis.

Dosage

It is usually taken at 5 to 6 g daily, in divided doses, as an infusion of the leaves or root.[18]

Precautions

As with slippery elm, a decrease in absorption of orally administered drugs taken simultaneously with marshmallow may occur.[19]

Antiinflammatory Botanicals

Antiinflammatory herbs are often used for GERD symptom relief and to improve healing of the irritated esophageal mucosa.[17] Examples are meadowsweet *(Filipendula ulmaria),* which also reduces acidity, chickweed *(Stellaria media),* and chamomile *(Matricaria recutita).*

Chamomile (Matricaria recutita)

Chamomile is well known for its mild sedative actions and for its antispasmodic effects on the gastrointestinal tract. In GERD, it is used as a nondemulcent antiinflammatory agent.[16,17]

Dosage

Chamomile is most commonly prepared as a hot water infusion (tea) of 1 to 3 g of the flowers, steeped in a cup covered with a saucer, taken three to four times daily.[18]

Precautions

Chamomile is generally well tolerated, although individuals allergic to other plants in the daisy family (Asteraceae) may experience an exacerbation of their allergic symptoms with consumption of chamomile.

Antianxiety Botanicals

Many herbal experts recommend botanicals as part of an overall approach to anxiety management, given the connection between anxiety and GERD. Examples are valerian *(Valeriana officinalis)* and skullcap *(Scutellaria lateriflora)*[17] (see Chapter 5, Anxiety).

Pharmaceuticals

Both histamine-2 (H_2) receptor antagonists or blockers (H2Bs) and PPIs are commonly used for the symptoms of GERD. A meta-analysis showed that both H2Bs and PPIs are effective in GERD symptomatic improvement, but PPIs are significantly more effective than H2Bs.[20] PPIs are also used in a 1-week therapeutic trial to test and diagnose GERD empirically.[1] The optimal dosing time for PPIs is 30 minutes before a meal, although adherence to the ideal dosing regimen may or may not lead to better symptom control.[21] Some clinicians use H2Bs or PPIs indefinitely as necessary to control symptoms.[2]

Aggressive, long-term acid suppression can decrease the absorption of vitamin B_{12}.[1] Consider regular intramuscular injections of vitamin B_{12} for those individuals requiring long-term treatment with histamine-2 receptor blockers or proton pump inhibitors. Use of these drugs can also lead to iron malabsorption, increased risk of hip fracture, and community-acquired pneumonia.

In one study, between 10% and 40% of people who took PPIs for GERD failed to respond symptomatically, partially or completely, whereas another study found that 85% of people taking PPIs had persistent GERD symptoms even though 73% of those patients were still satisfied with the treatment.[21] Some debate exists about the reasons that certain patients may not respond to PPIs. Investigators have theorized that these patients may actually have functional or nonerosive reflux disease, or they may have weakly acidic or alkaline refluxate.[21]

Some nuances with the prescribing of the two primary classes of pharmaceuticals for GERD, PPIs and H2Bs, are noted in Table 41-3. Box 41-1 describes the protocol for tapering PPIs.

Biomechanical Therapy

Some naturopathic physicians recommend hernial reduction adjustments, an abdominal manipulation technique, when GERD symptoms are complicated by the presence of a hiatal hernia.[16] Although no clinical trials have examined this treatment, referral to an experienced practitioner could be considered for patients with a documented hiatal hernia and symptoms of GERD. Aside from surgery, no documented allopathic interventions exist for the treatment of hiatal hernia.

Mind-Body Therapy

Relaxation training can improve symptoms of GERD, by addressing the issue that stress exacerbates GERD symptoms, especially in people suffering from chronic anxiety.[21]

Other Therapies to Consider

Homeopathy

Homeopathy can be a therapeutic consideration. Many of the symptoms associated with GERD, such as indigestion and heartburn, or even associated disorders such as hiatal hernia, are mentioned in homeopathy sources and treated with a wide variety of short-term remedies, such as phosphorus, nux vomica, pulsatilla, carbo vegetabilis, arsenicum, bryonia,

TABLE 41-3. Proton Pump Inhibitors versus Histamine-2 Receptor Blockers for Gastroesophageal Reflux Disease

PPIs	H2Bs
Greater rate of healing from esophagitis than H2Bs	Greater rate of healing from esophagitis than placebo
Slight benefit in healing esophagitis with twice the standard dose	
Unclear whether PPIs heal heartburn, as a symptom, more than H2Bs	Both PPIs and H2Bs heal heartburn more than placebo
Complete resolution of heartburn in approximately 40% of people (compared with 15% for placebo)	

Data from Kahrilas PJ. Gastroesophageal reflux disease. *N Engl J Med.* 2008;359:1700–1707.
H2Bs, histamine-2 receptor blockers; PPIs, proton pump inhibitors.

BOX 41-1. Helping Taper off a Proton Pump Inhibitor

For those patients who have made positive lifestyle changes and may not need continued chronic acid suppression, it can often be difficult to discontinue proton pump inhibitors (PPIs) because they often cause rebound hyperacidity even if the underlying condition has resolved.[1]

Plan:

1. Slowly taper off the PPI over 2 to 4 weeks (the higher the dose, the longer the taper).
2. While the taper is being completed, use the following for bridge therapy to reduce the symptoms of rebound hyperacidity:

   Encourage regular aerobic exercise.

   Encourage a relaxation technique such as self-hypnosis for gastrointestinal disorders (see Chapter 92, Self-hypnosis Techniques) or meditation (see Chapter 98, Recommending Meditation).

   Suggest acupuncture one to two times per week.[2]

   Add one or more of the following:

   Deglycyrrhizinated licorice, two to four 380-mg tablets before meals or Sucralfate (Carafate) 1 g before meals.

   Slippery elm, 1 to 2 tablespoons of powdered root in water three to four times per day

   A combination botanical product, Iberogast (Clown's mustard, German chamomile, angelica root, caraway, milk thistle, lemon balm, calendine, licorice root and peppermint leaf), 1 mL three times per day[3]
3. If the taper is successful, slowly taper the foregoing supplements (except for positive nutritional changes, exercise, and stress management). If symptoms return, start with one of the foregoing or a histamine-2 receptor blocker. If symptoms are still difficult to control, consider adding back the PPI.
4. Ideally, it is beneficial to avoid long-term acid suppression if possible because this can be associated with malabsorption of vitamin B_{12} and iron,[4] increased risk of community-acquired pneumonia,[5] hip[8,9] and spine[10,11] fracture, and *Clostridium difficile* diarrhea.[12]

china, anacardium, argentum, sepia, lycopodium, graphites, and kali bichromium[22] (see Chapter 111, Therapeutic Homeopathy).

Traditional Chinese Medicine

Traditional Chinese medicine, which provides a complete assessment based on a unique cultural, diagnostic, and therapeutic approach, may offer relief for people suffering from GERD. In a study comparing acupuncture with doubling the dose of a PPI for GERD, acupuncture was found to be more effective in reducing symptoms.[23] With treatment suggestions incorporating diet, lifestyle, botanical medicines, and acupuncture or acupressure,[24] traditional Chinese medicine should be considered a therapeutic option, based either solely on a patient's personal preference or on the need for adjuncts to incomplete or ineffective allopathic therapeutics.

Surgery

Surgical treatment is considered by many experts to be an option for people in whom lifestyle modification or adequate medical therapy fails or who are unwilling to take long-term medication.[1,3,25] The most common surgical procedure is the Nissen fundoplication, either open or laparoscopic, whereby the fundus of the stomach is wrapped wholly (total fundoplication) or partially (partial fundoplication) around the lower esophagus to create an area of high pressure meant to prevent refluxate from entering the esophagus and causing symptoms. Laparoscopic fundoplication provides long-term disease control similar to that seen with the open approach but with fewer incisional hernias.[25] One review examined health-related quality of life and GERD symptoms after 1 year in 4 studies involving 1232 people who underwent medical management versus laparoscopic surgical management.[3] Overall, the surgical approach seemed to improve symptoms of GERD more effectively than did medical management, although in some cases dysphagia (8% to 12% postoperatively),[25] costs after 1 year, and adverse effects were more pronounced in the surgical group. One review and meta-analysis found that the partial laparoscopic fundoplication was associated with less postoperative dysphagia than was total fundoplication.[25]

Special Considerations in Pediatrics

The treatment of GERD in infants usually involves dietary interventions such as the normalization of feeding techniques, volumes, and frequency, if these are abnormal.[5] Formula can be thickened with a tablespoon of rice cereal per ounce, to decrease the number of regurgitation events, increase calorie density, and reduce the number of crying times.[5] One meta-analysis supported the concept that thickened feedings improves GERD symptoms in infants.[26] A short trial of a hypoallergenic diet, in particular to exclude milk and soy, can be helpful in children suspected of having allergies to those foods. Older children with GERD are advised to avoid tomatoes, chocolate, mint, and classically offending beverages (juices, sodas, caffeinated beverages) and to lose weight, if applicable.

With respect to positioning during meals, infant GERD is worse when infants are seated, supine, or on their side and better when they are prone or carried upright. Because of the risk of sudden infant death syndrome, a prone position cannot be recommended for sleep.[5] Older children may have some relief from GERD when they lie on their left side or with the head of the bed elevated. As with adults, children experience some symptomatic improvement with H2Bs and PPIs; the dose of PPIs is higher per kilogram than for adults (0.7 to 1.5 mg/kg/day).[5]

Prevention Prescription

- Avoid foods and supplements, and, when possible, medications known to decrease lower esophageal sphincter tone (see Table 41-1).
- Maintain ideal body weight.
- Reduce stress as much as possible, through lifestyle change and stress management and mind-body techniques.
- Avoid large meals and consuming large quantities of liquids with meals.

Therapeutic Review

This summary of possible therapies is for patients with mild to moderate, short-term GERD. Patients with long-standing, more severe GERD should undergo an appropriate diagnostic workup, which may include a referral to a gastroenterologic specialist and upper endoscopy to rule out esophagitis, ulcers, Barrett esophagus, or adenocarcinoma.

Removal of Exacerbating Factors

- Avoid foods, supplements, and, when possible, medications known to decrease lower esophageal sphincter tone (see Table 41-1).
- If applicable, quit smoking.
- If applicable, lose weight.

Lifestyle

- For nocturnal symptoms, elevate the head of the bed 4 to 6 inches. C 1
- Avoid large meals and consuming large quantities of liquids with meals. C 1

Mind-Body Medicine

- Practice stress management and relaxation techniques. B 1

Botanical Medicines

- Deglycyrrhizinated licorice: two to four 380-mg tablets before meals C 1
- Slippery elm: 1 to 2 tablespoons of powdered root in a glass of water, three to four times daily C 1
- Other botanical medicines that have potential benefit include chamomile, marshmallow, skullcap, and valerian (see Table 41-2).

Pharmaceuticals

- Start with a proton pump inhibitor, both for symptomatic relief and for diagnostic purposes. A 2
- Histamine-2 receptor antagonists A 2
- Over-the-counter antacids, such as calcium carbonate, aluminum hydroxide, and magnesium hydroxide, can be helpful. C 1

Surgery

- For people with intractable symptoms, fundoplication should be considered. B 3

KEY WEB RESOURCES

American College of Gastroenterology clinical updates: www.acg.gi.org/physicians/clinicalupdates.asp.
This collection of allopathic, evidence-based reviews covers numerous topics relevant to GERD, including diagnosis, management, reflux testing, and surveillance of Barrett esophagus.

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Chapter 42

Peptic Ulcer Disease

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Pathophysiology

Peptic ulcer disease (PUD) is caused by disturbances of the gastrointestinal (GI) mucosa secondary to loss of protective elements or to damaging insults, resulting in mucosal erosions, most commonly located in the duodenum or stomach. People with PUD most often complain of epigastric pain (especially a few hours after meals), bloating, nausea, early satiety, altered bowel habits, and heartburn. Pain is often improved with food or antacids. PUD can also occur without symptoms, especially in older adults. Peptic ulcers can cause GI bleeding, which is potentially a life-threatening emergency necessitating urgent endoscopy and intensive care unit consideration. Rarely, ulcers can also perforate, leading to intense pain and acute peritonitis, which is a surgical emergency. Patients with significant weight loss and PUD symptoms also deserve endoscopy to investigate for potential malignant diseases.

Loss of mucosal integrity is usually multifactorial, with diminished protective elements (mainly decreased acid buffering, reduced immune system functioning, and slowed wound healing) and increased insults (primarily *Helicobacter pylori* infection, nonsteroidal antiinflammatory drugs [NSAIDs], increased acidity, and inflammation). Treatment efforts are focused on restoring these protective factors and reducing harmful affronts.

> Nonsteroidal antiinflammatory drugs should be avoided in patients with a history of peptic ulcer disease (PUD) and also minimized in people with PUD symptoms who lack a formal ulcer diagnosis.

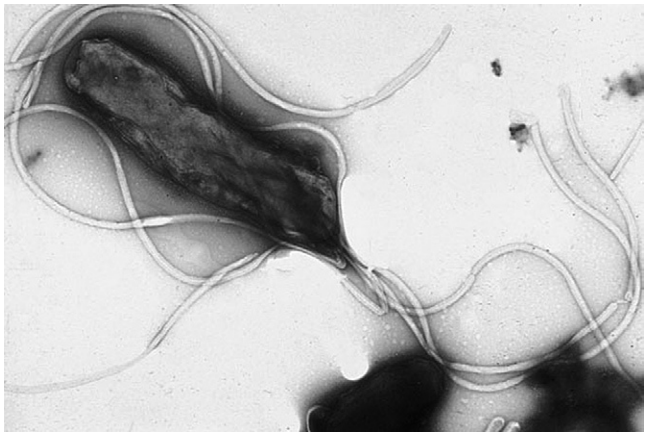
Approximately half a million people in the United States are newly diagnosed with PUD each year.[1] Peptic ulcers can occur at any time in life, although the incidence gradually increases with age.[2] In the early twentieth century, PUD was diagnosed in men at twice the rate as in women, yet it is now nearly equally distributed by gender; gastric ulcers tend to be more common in women, and duodenal ulcers occur more often in men.[3]

Historically, investigators knew that smoking, stress, NSAIDs, and family history (risk increases three times with an afflicted first-degree relative)[4] contributed to peptic ulcer formation. Before the late 1970s, however, allopathic medicine had limited success in addressing PUD until the arrival of two revolutionary developments: the invention of pharmaceuticals that reduced the amount of acid the stomach produced and the discovery of *H. pylori* (Figure 42-1).

The development of gastric acid–suppressing medications, with the advent of histamine-2 receptor antagonists (H_2 blockers) in the late 1970s and proton pump inhibitors (PPIs) in the late 1980s, heralded a new chapter in Western medicine's management of PUD. Previous efforts had focused on reducing risk factors, giving acid buffers (e.g., calcium carbonate) for symptom relief, and surgery (with significant morbidity and mortality). With the invention and administration of acid-reducing medications, most cases of PUD were quickly attenuated. This drastically reduced the need for surgery and dramatically increased the role of pharmaceuticals in PUD therapy.

H. pylori was identified in 1982 (a discovery for which Drs. J. Robin Warren and Barry J. Marshall won the Nobel Prize for medicine in 2005), and the more the medical world learned about this unique bacterium, the more it revolutionized how we thought about PUD. Having an *H. pylori* infection has been shown to increase the rate of PUD by at least four times.[5] Living in the harsh acidic environment of the human stomach, *H. pylori* seems to increase the risk of PUD by directly damaging the protective mucus lining of the GI tract and allowing for more acidic damage. *H. pylori* also triggers an immune response that causes damaging inflammation. Rates of *H. pylori* infection are stratified worldwide by age and economic status. Younger, more affluent people have rates as low as 20%, whereas up to 60% of all people in the developing world and 50% of people who are older than 60 years in the United States are colonized by the bacterium.[6] With an estimated 4 billion people infected worldwide, the goal of complete global eradication is likely logistically impractical, if not impossible, even though *H. pylori* only

FIGURE 42-1
Helicobacter pylori, the discovery of which revolutionized medical understanding and management of peptic ulcer disease. (Courtesy of Yutaka Tsutsumi, MD.)



resides in humans. The drastic impact of *H. pylori* on PUD has triggered management strategies focused on eradication with antibiotics. However, only 10% to 20% of *H. pylori*–infected people ever develop PUD.[5]

Altogether, *H. pylori* and NSAIDs account for most peptic ulcers.[1] The remainder is attributed to other risk factors and a few "zebras," such as Zollinger-Ellison tumors, carcinoid syndrome, other drugs, radiation, cytomegalovirus, and systemic mastocytosis.

These two developments, pharmaceutical acid suppression and the discovery and subsequent antibiotic treatment of *H. pylori*, had PUD morbidity and mortality riding off into the sunset near the end of the twentieth century. Yet more recent discoveries (increasing resistance of *H. pylori* to antibiotics and further knowledge of the harms of long-term pharmaceutical acid suppression, mixed with more evidence of botanical anti-*H. pylori* approaches and growing patient preference for more alternative therapeutic options) promise an increasing need for more integrative PUD approaches in the years and decades ahead.

Diagnosis

The overlapping constellation of PUD symptoms with such diseases as gastritis, irritable bowel syndrome, gastroesophageal reflux disease, Crohn disease, pancreatitis, gallstones, and malignancies makes a first-time diagnosis of PUD challenging, especially because the best current standard diagnostic test is endoscopy (an invasive, costly procedure) and the next best tool for diagnosis is a barium GI series (with resulting radiation, cost, and potential inaccuracy). One study even showed that a physical examination finding of epigastric tenderness to palpation lessens the likelihood of PUD.[7] Thus, it is not surprising that many practitioners, as well as patients without signs of serious disease (bleeding or weight loss), hesitate to pursue these invasive diagnostic measures. The likely result is that most cases of PUD are never diagnosed with certainty. More frequent *H. pylori* testing increases the number of people diagnosed with *H. pylori* infection, but a positive test result indicates only bacterial infection (and 80% to 90% of *H. pylori*–infected people will not develop ulcers).[5] Once a diagnosis of PUD is established, recurrence is reported in up to 74% of patients.[8] Much PUD management therefore focuses on prevention and symptomatic treatment, a good fit for an integrative approach (Fig. 42-2).

Integrative Therapy

Nutrition

Diet was linked to PUD long before the discovery of *H. pylori*, and with research demonstrating the anti–*H. pylori* properties of certain foods, nutrition is even more of a key component of ulcer prevention and symptom management.

Meal timing has a reported relation to PUD. Skipping breakfast is an established risk factor,[9] and consuming large meals shortly before bedtime can also increase the chance of PUD.[10]

Fruit and vegetable intake reduces the risk of developing ulcers, and epidemiologic studies demonstrated that a diet high in plant-based fiber and vitamin A (e.g., carrots, spinach, mango, sweet potatoes, apricots) helps protect against PUD.[11] Flavonoids, which are compounds found throughout the plant world, show anti–*H. pylori* properties and are present in concentrated amounts in citrus, berries, onions, parsley, green tea, red wine, and dark chocolate.[12] Sulforaphanes, which are phytochemicals found in vegetables such as Brussels sprouts, cabbage, cauliflower, bok choy, turnips, radishes, and in especially high concentrations in broccoli sprouts, also have anti–*H. pylori* properties.[13]

Foods containing capsaicin (chili) are shown to be protective against ulcers,[14] and chilies (fruit of the plant genus *capsicum*) are reviewed in the botanical section of this chapter for acute symptom relief. Other foods demonstrating anti–*H. pylori* properties include honey and garlic.[15]

> Foods found to be associated with a reduced risk of *Helicobacter pylori* infection include fruits and vegetables rich in carotenoids (yellow, orange), flavonoids (purple, blue, red wine, green tea), sulforaphanes (cruciferous veggies, including cabbage and broccoli), capsaicin (chili), and fermented foods rich in probiotics (yogurt, miso, aged cheese, and sauerkraut),

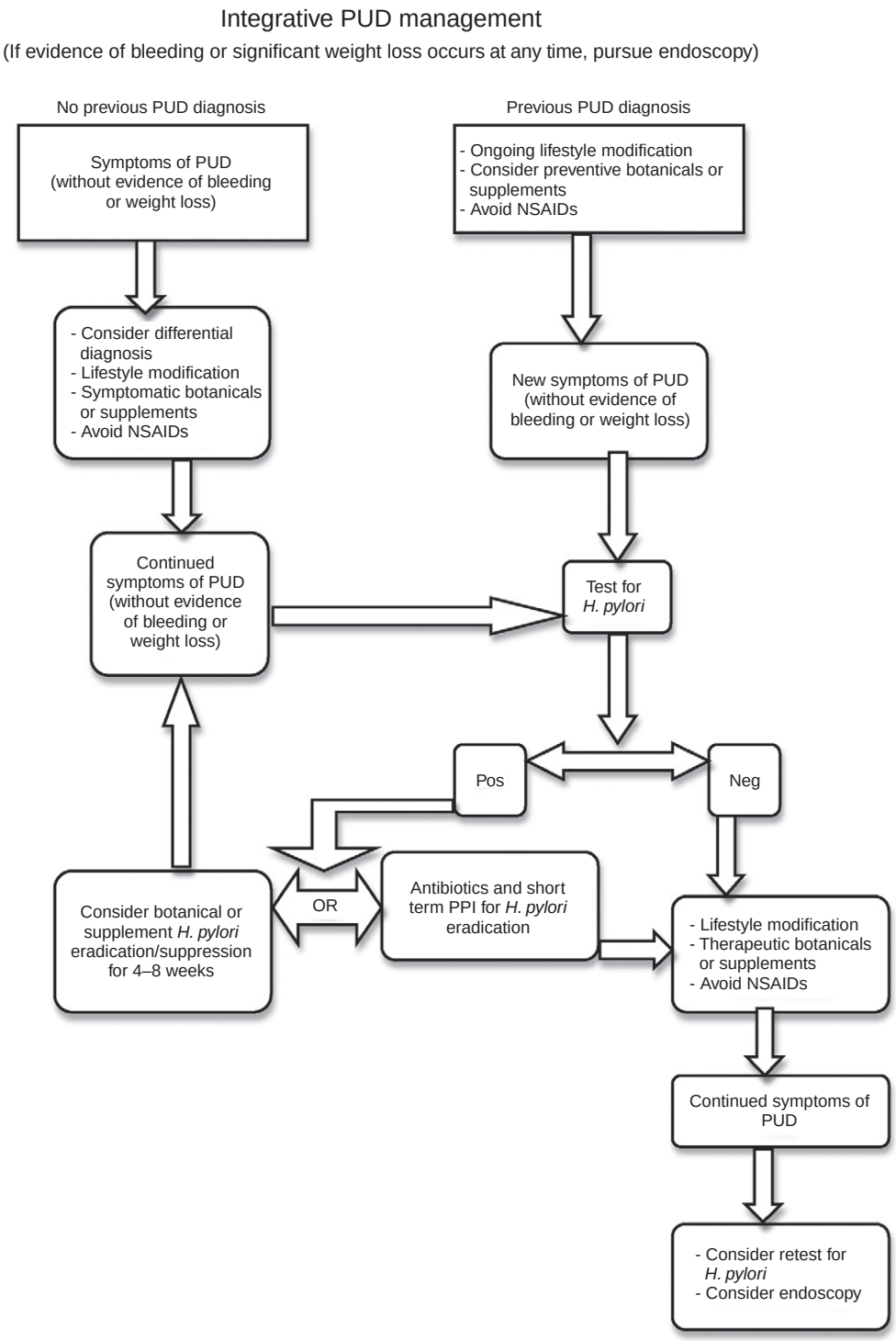
Milk increases PUD risk, likely because of increased stimulation of acid production.[16] Nonetheless, fermented dairy products and other food with probiotics, such as yogurt, aged cheeses, and sauerkraut, are shown to be protective against *H. pylori*.[17,18]

Coffee and caffeine, long thought to be risk factors for PUD, have so far eluded convincing data to that effect but are known risk factors for reflux disease.

Physical Activity

Multiple studies have demonstrated that regular physical activity, when compared with a more sedentary lifestyle, is protective against PUD.[19,20] One study specifically

FIGURE 42-2
Integrative management flow chart for peptic ulcer disease (PUD). Neg, negative; NSAIDs, nonsteroidal antiinflammatory drugs; Pos, positive; PPI, proton pump inhibitor.



demonstrated that the risk for duodenal ulcers was 62% less in men who cumulatively walked or ran more than 10 miles per week.[20] Routine exercise should be recommended for almost all patients, especially those with a previous history of PUD.

Stress Reduction

The relationship between stress and PUD is a classic example of why clinicians must keep in mind the social determinants of health (Fig. 42-3), over which our patients have varying degrees of control. Stress is largely a product of this social and environmental milieu, and convincing evidence

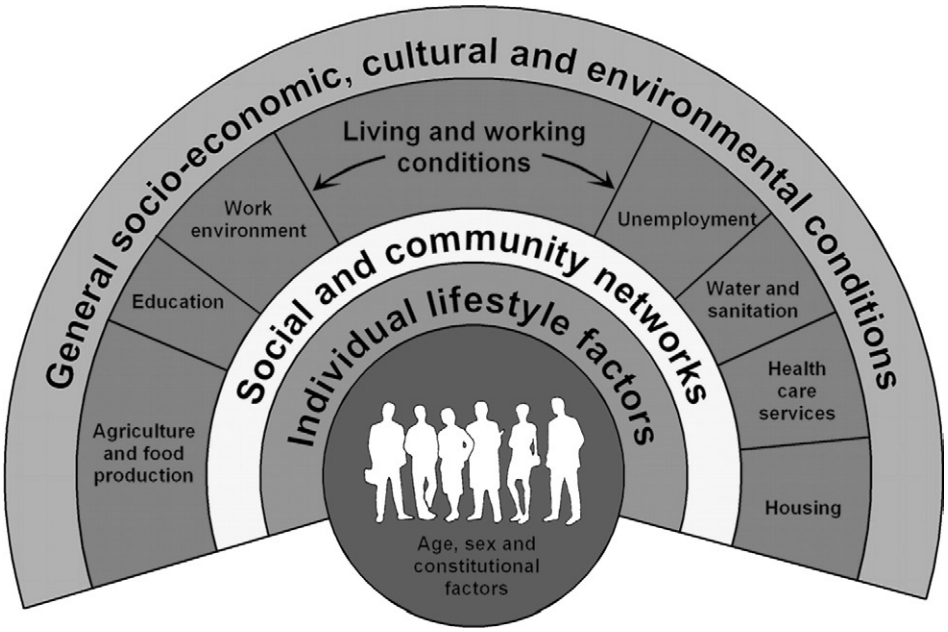


FIGURE 42-3
Social determinants of health diagram. (From Dahlgren G, Whitehead M. *Policies and Strategies to Promote Social Equity in Health*. Stockholm: Institute for Futures Studies; 1991.)

indicates that stress plays a role in PUD. This connection is established early in life. Childhood stress, in the form of traumatic events such as an illness of a family member, financial strain, or family conflict, causes nearly 50% higher rates of PUD in adulthood.[21] Studies have also shown that GI ulceration increases with both chronic stress and in times of acute stress, such as during an earthquake or war (e.g., during the bombing of London in World War II).[22,23] A multipronged approach to stress reduction, in comparison with any single method, appears to provide more protection against PUD.[24] As a clinician, recommending individually tailored stress reduction programs, including yoga, tai chi, and other coordinated movements, as well as meditation, focused breathing, and any other culturally applicable relaxation methods, will likely be beneficial (see Chapter 93, Relaxation Techniques, and Chapter 98, Recommending Meditation).

Sleep

Inadequate sleep is a risk factor for PUD.[9] This is probably the result of increased stress levels, which cause immune dysfunction and impaired lifestyle decisions. Maintaining good sleep hygiene is an important key to ulcer avoidance (see Chapter 8, Insomnia).

Tobacco Cessation

Smoking increases rates of PUD up to four times when compared with nonsmokers.[19] This added risk is likely because of decreased wound healing in smokers. Accordingly, smoking cessation is essential in addressing PUD.

Alcohol Avoidance or Moderation

Alcohol, in large amounts, has been shown to be a risk factor for ulcers, likely because of mucosal damage. One epidemiologic study showed that people who had more than 42 drinks per week had more than 4 times the rate of bleeding ulcers compared with people who had 1 drink per week or less.[25] However, red wine has anti–*H. pylori* properties in animal models, possibly because of bioactive compounds such as flavonoids.[26] Avoiding large quantities of ethanol, especially higher-percentage drinks, is prudent in patients with a history or symptoms of PUD, whereas moderate red wine consumption should not necessarily be discouraged.

Nonsteroidal Antiinflammatory Drugs

Evidence shows that NSAID use increases baseline risk of PUD by up to five times, and it also increases the risk of bleeding ulcers in patients with established PUD by five times.[27] NSAIDs inhibit prostaglandin production and thus decrease mucoprotective elements in the GI tract. Although evidence indicates that administration of medications such as sucralfate or misoprostol with NSAIDs can help ease ulcer symptoms and prevent ulcer recurrance,[28,29] NSAIDs should be avoided as much as possible in patients with PUD symptoms and an existing history of PUD disease. More than 80% of people taking NSAIDs never develop PUD,[30] and thus these drugs should not necessarily be avoided in patients who do not have PUD.

Supplements

Probiotics

These helpful microorganisms have proven versatile in the realm of PUD. They have been shown to reduce ulcer recurrence,[31] and people with higher intakes of probiotics have correspondingly lower rates of *H. pylori* infection.[17] Although no clinical trials currently exist with convincing evidence that probiotics eradicate *H. pylori* by themselves, probiotics can reduce the severity of infection.[32] Probiotics are likely effective in combating *H. pylori* as a result of increased GI mucus production, competition for mucosal binding sites, and production of anti–*H. pylori* compounds,

and they were also shown in animal models to decrease the inflammatory response from *H. pylori*.[32] Most studies were conducted with *Lactobacillus* strains commonly found in yogurt, yet evidence indicates that other strains of probiotics are also helpful.[33] Thus, incorporating yogurt and other probiotic-containing foods, such as aged cheeses and sauerkraut, into a diet on a regular basis can be beneficial for PUD prevention and avoidance of ulcer recurrence. Probiotics, including both *Lactobacillus* and *Saccharomyces boulardii,* have also demonstrated synergy with antibiotic for *H. pylori* eradication and can decrease antibiotic side effects such as diarrhea[29,34,35] (see chapter 102, Prescribing Probiotics).

Dosage
During *H. pylori* eradication antibiotic therapy, the regimen is as follows: either *Lactobacillus (acidophilus* or GG) capsules, containing at least 1 billion organisms, twice daily, or *Saccharomyces boulardii,* 500 mg, twice daily.

Prevention
Probiotic-containing foods are recommended on a regular basis for people with a previous history of PUD, a family history of ulcer disease, or other risk factors for PUD.

Precautions
Patients sensitive or intolerant to lactose may have GI discomfort with dairy products containing probiotics.

Vitamin C
Ascorbic acid (vitamin C) has been shown to have potential for *H. pylori* eradication; one study demonstrated a 10% eradication rate with 2 weeks of 1000 mg daily.[36] Vitamin C also has additive effects on antibiotic regimens for *H. pylori* eradication.[37] This anti–*H. pylori* capability has been supported by in vitro studies.[38] A 5-year Japanese study demonstrated lower PUD rates in persons taking vitamin C supplementation.[39] A steady dietary intake of vitamin C is recommended for anyone with current symptoms, a previous history or a family history of PUD, or other risk factors for ulcer disease.

Dosage
For *H. pylori* eradication or suppression (in addition to daily dietary intake), the dose is 500 mg twice daily.

Prevention
Eat foods containing vitamin C on a regular basis, including citrus, kiwi, broccoli, strawberry, and cauliflower.

Precautions
Dose-related potential adverse effects include kidney stones, diarrhea, nausea, and gastritis. Use with caution in patients with kidney disease.

Zinc
A clinical trial showed zinc to accelerate the healing of gastric ulcers up to three times faster than seen with placebo.[40] This finding was also supported by more extensive animal studies.[41] Enhanced healing is likely the result of the fundamental role of zinc in repair of damaged tissue. A compound not available in the United States, zinc acexamate, has been used in East Asia and Europe for PUD and has been found effective in numerous studies.[42]

Dosage
For gastric ulcer treatment, the dose is 40 mg daily for 4 weeks.

Precautions
Potential effects include nausea, vomiting, diarrhea, and altered taste. Zinc inhibits the absorption of other minerals, particularly copper.

Polyunsaturated Fatty Acids
Multiple polyunsaturated fatty acids (PUFAs) have been shown to have anti–*H. pylori* effects in vitro (including alpha-linolenic acid, eicosapentaenoic acid [EPA], gamma-linolenic acid [GLA], and linoleic acid).[43] A clinical study administering 2 g a day of a 1:1 mixture of fish oil (EPA and docosahexaenoic acid) and black currant seed oil (GLA), for 8 weeks, cleared *H. pylori* in more than 50% of patients.[44] Although elimination rates are significantly lower for PUFAs when compared with antibiotics, PUFAs are reasonable to recommend for patients desiring *H. pylori* eradication without antibiotics.

Dosage
For *H. pylori* suppression or elimination, 1 g of fish oil and 1 g of GLA-containing oil (evening primrose, black currant seed, borage, or hemp seed oils) are taken daily for 8 weeks.

Precautions
PUFAs may cause GI upset. Higher doses of omega-3 fatty acids (more than 3 g/day) may increase the risk of bleeding from anticoagulant effects.

Glutamine
In clinical trials, glutamine has been shown to prevent and cure PUD. A study of patients with burn injury demonstrated that glutamine can help prevent stress ulcers.[45] Another trial showed more rapid healing of peptic ulcers in patients given 400 mg of glutamine four times a day.[46] This limited clinical research has also been supported by animal studies.[47,48] Glutamine supplementation is likely successful because it is a necessary amino acid for the repair and new growth of cells lining the GI tract. Dietary sources of glutamine include beef, chicken, fish, eggs, wheat, cabbage, beets, beans, spinach, and parsley.

Dosage
For PUD treatment, the dose is 400 mg of glutamine powder in water four times daily.

Precautions
No significant adverse effects have been reported.

Botanicals

Turmeric (Curcuma longa)
Turmeric has been used for centuries in Chinese and Ayurvedic medicine for treatment of dyspepsia and epigastric pain. One clinical trial administered 600 mg of turmeric root five times daily to people with PUD and demonstrated 48% ulcer resolution at 4 weeks and 76% at 12 weeks.[49] The same study also showed that turmeric markedly improved symptoms of dyspepsia in 1 to 2 weeks.[44] Turmeric and

curcumin, a commercially available turmeric derivative, are known to have anti–*H. pylori* properties in vitro.[50,51] One clinical trial failed to show turmeric's ability to eradicate *H. pylori* completely, yet it demonstrated relief of dyspeptic symptoms.[52] Turmeric has been found to have H_2 blocking properties, which likely also explains much of its healing potential.[53]

Dosage
For PUD treatment and for symptoms of PUD, the dose of whole turmeric root or powder (capsules) is 600 mg five times daily for 12 weeks.

Precautions
Turmeric potentially can cause nausea, diarrhea, heartburn, or kidney stones. Some evidence exists that it may increase the risk of bleeding secondary to antiplatelet activity.

Mastic (Pistacia lentiscus)
Mastic is a member of the pistachio tree family found throughout the Mediterranean, and its resin has been harvested for more than 2000 years as a spice, for chewing gum, and for medicinal purposes. A double-blind placebo-controlled trial of 350-mg capsules, taken three times a day for 3 weeks, demonstrated clinically significant improvement of dyspepsia.[54] Mastic is known to have anti–*H. pylori* properties in vivo and in vitro.[55] A separate double-blind trial showed that mastic significantly improved duodenal ulcer healing when compared with placebo.[56]

Dosage
For dyspepsia, the dose is 350-mg capsules three times a day for 3 weeks. For duodenal ulcer healing, the dose is 500-mg capsules twice daily for 2 weeks.

Precautions
Avoid in people with pistachio allergies. Use with caution in patients taking angiotensin-converting enzyme inhibitors because it may cause hypotension.

Cabbage (Brassica oleracea)
Clinical studies in the 1950s demonstrated the effectiveness of cabbage juice for gastric and duodenal ulcer healing. Participants drank 1 L of fresh cabbage juice over the course of a day for 10 days.[57,58] Because this research was completed more than 50 years ago, and in light of subsequently improved diagnostic studies and further understanding of PUD, new studies in the years ahead are warranted. Because of its safety profile and accessibility, however, cabbage still deserves recommendation for PUD treatment. Cabbage has been shown to be a rich source of glutamine and sulforaphanes, likely accounting for much of its healing power.

Dosage
For PUD, the dose is 1 L of fresh juice (pasteurized juice was found ineffective) divided over the course of a day for 10 days.

Precautions
Because of its vitamin K content, cabbage can potentially decrease the anticoagulant efficacy of warfarin.

Deglycyrrhizinated Licorice (Glycyrrhiza glabra)
Licorice has been used for medicinal purposes, including epigastric pain and dyspepsia, since ancient Egyptian times and for at least 4000 years in China.[59] Deglycyrrhizinated licorice (DGL) does not include the adrenocorticoid effect of glycyrrhiza (sodium retention leading to hypertension) and is less hepatotoxic than the native plant. A small clinical trial demonstrated DGL to be as effective as H_2 blockers for duodenal ulcer resolution at 12 weeks, with fewer episodes of relapse.[60] Licorice derivatives also have anti–*H. pylori* properties in vitro.[61] This effect is possibly explained by the bioactive flavonoids found in licorice. Many good-quality studies have compared licorice, in combination preparations with other botanicals, with placebo in the treatment of PUD. Determining the efficacy of a single ingredient or estimating their synergistic properties is impossible, however, because all these combination products have three or more ingredients. More placebo-controlled individual studies are warranted.

Dosage
For PUD, the dose is 380 mg three times per day for 12 weeks.

Precautions
Use with caution in patients with liver disease, renal insufficiency, and hypokalemia. Avoid in pregnancy because of a theoretical risk of preterm labor.

Chili (Capsaicin)
Capsaicin is the active component of chili peppers (the fruits of plants of the genus *Capsicum*). Historically, chilies were thought to exacerbate PUD, but more recent research is proving the opposite. Epidemiologic studies have shown that people with higher dietary intakes of capsaicin have correspondingly lower rates of PUD.[14,62] A double-blind trial, in which patients took 2.5 mg of chili pepper in capsules daily for 5 weeks, demonstrated that chili was effective for epigastric pain and other symptoms of functional dyspepsia.[63] Animal models also showed capsaicin, by decreasing gastric acidity, to be protective against ulcer formation.[64]

Dosage
For epigastric pain and functional dyspepsia, the dose is 2.5 mg daily of chili pepper capsules (can divide doses) for 5 weeks. For PUD prevention, patients should follow a diet rich in capsaicin, as tolerated.

Precautions
Avoid in people with pepper allergies. Use with caution in patients with diabetes (may cause hypoglycemia) and heart disease (may increase blood pressure). Chilies may cause GI upset. Skin contact may cause irritation.

Cranberry (Vaccinium oxycoccos)
A double-blind clinical trial in *H. pylori*–positive patients demonstrated the ability of cranberry to suppress and eradicate *H. pylori* in patients who drank 500 mL of cranberry juice for 90 days. Although the study demonstrated only a 14% eradication rate, that rate was many times higher than results seen with placebo.[65] In vitro studies of human gastric cells showed cranberry's ability to impair *H. pylori* adhesion to gastric cell walls, similar to its ability to prevent *Escherichia coli* from binding to the bladder wall in the prevention of urinary tract infections.[66]

Dosage
For *H. pylori* suppression or eradication, the dose is 500 mL of cranberry juice daily for 90 days.

Precautions
Patients with diabetes should consider sugar-free juice. High doses may cause stomach distress. Cranberry may affect warfarin efficacy.

Neem (Azadirachta indica)
In Ayurvedic medicine, the neem tree has been used for thousands of years for multiple purposes, including for epistaxis, parasites, asthma, diabetes, fever, and epigastric pain. This versatility has earned neem the nickname "the village pharmacy."[67] Clinical studies demonstrated that 30 mg of neem bark extract, taken for 10 days, reduced gastric acid secretion by 77% while additionally causing significant duodenal ulcer healing when taken for 10 weeks.[68] Animal studies also demonstrated the antiulcer properties of neem,[69] and they elucidated that neem inhibits the proton pump, similar to pharmacologic PPIs.[70]

Dosage
For duodenal ulcers, the dose is 30 mg bark extract twice daily for 10 weeks.

Precautions
Use cautiously in patients with liver disease. Avoid use in pregnant women (because of abortifacient properties). Avoid in infants and children because of potential toxicities.

Additional Botanicals
Some other botanicals demonstrate in vitro anti–*H. pylori* properties. The list keeps growing, and more clinical trials are needed. These botanicals include the following: broccoli sprouts *(Brassica oleracea),*[13] peppermint *(Mentha piperita),*[71] silver wormwood *(Artemisia ludoviciana),*[71] garlic *(Allium sativum),*[72] yarrow *(Achillea millefolium),*[73] chamomile *(Matricaria recutita),*[73] ginkgo *(Ginkgo biloba),*[73] nutmeg *(Myristica fragrans),*[73] ginger *(Zingiber officinale),*[73] hops *(Humulus lupulus),*[74] goldenseal *(Hydrastis canadensis),*[75] sage *(Salvia officinalis),*[75] green tea *(Camellia sinensis),*[76] and red ginseng *(Panax ginseng).*[76]

Additional mucoprotective therapies, which are traditionally used and have animal model evidence but lack sufficient clinical trials, include the following: pectin,[77] aloe *(Aloe vera),*[12] fenugreek *(Trigonella foenum-graecum),*[78] banana powder *(Musa paradisiaca),*[79] and mugwort *(Artemisia douglasiana)*[80].

Pharmaceuticals

Antibiotics
Overwhelming evidence indicates that *H. pylori* eradication with antibiotics, in patients with PUD, dramatically improves symptom resolution and reduces ulcer recurrence.[81] Recommended eradication regimens usually include two to three antibiotics and a PPI and historically demonstrated up to an 80% to 90% eradication rate.[82] Years after antibiotic treatment of *H. pylori* began, however, the bacterium has proven tenacious and has developed more and more resistance to standard regimens. With traditional three-drug therapies, most studies now show less than 80% eradication rate, with some less than 50%.[82] Specifically, metronidazole and clarithromycin have demonstrated marked resistance, thus necessitating newer and potentially more toxic antibiotics.[83] Because of the significant geographic differences in resistance patterns, prescribers should be aware of local susceptibilities before patients are administered one of the numerous anti–*H. pylori* antibiotic regimens.[84] In light of this trend of increasing resistance, it is becoming more practical to look to other methods of *H. pylori* eradication or suppression, such as the integrative therapies discussed in this chapter.

Dosage
A typical *H. pylori* eradication regimen is as follows: amoxicillin, 1 g; clarithromycin, 500 mg; and omeprazole, 20 mg; this combination is taken twice per day for 14 days. (Probiotics are also recommended as adjuvant therapy.) Check regional susceptibilities when choosing antibiotics.

Precautions
Common side effects of antibiotics used include diarrhea, altered taste, headache, and allergic reactions.

Acid-Suppressing Drugs
Since their introduction in the late 1970s, gastric acid suppression medications, in the form of H_2 blockers and later PPIs, have dramatically assisted in the relief of PUD symptoms and ulcer healing. PPIs have been shown to be more effective than H_2 blockers and are used more frequently today.[85] Accumulating evidence, however, shows that chronic acid suppression (longer than 2 to 3 months) has potential adverse effects, including increased rates of pneumonia, *Clostridium difficile* infections, and bone fractures; these drugs also decrease absorption of certain minerals and nutrients, specifically calcium, vitamin B_{12}, iron, and magnesium.[86–88] Animal models also demonstrated an increased gastric cancer rate with extended periods of gastric acid suppression.[87]

Dosage
For PUD and PUD symptoms, the regimen is as follows: PPI (e.g., omeprazole, 20 mg) or H_2 blocker (e.g., ranitidine, 150 mg) once or twice daily, per individual drug, for up to 8 weeks.

Precautions
Potential adverse effects of H_2-blockers include nausea, headache, dry mouth, rash, and confusion. PPIs can cause headache and nausea. Extended use may cause the adverse effects discussed earlier.

> Long-term pharmaceutical acid suppression (especially with proton pump inhibitors) is increasingly associated with adverse effects, such as infections and decreased nutrient absorption, and should be limited to 8 weeks or less.

Antacids
Likely millions of years ago, our ancestors figured out that eating chalk or other natural acid buffers relieved epigastric pain and symptoms of PUD. Antacids are still potentially useful today in helping with symptom relief, and they are found in various nonprescription forms, including calcium

carbonate, aluminum hydroxide, magnesium hydroxide, and sodium bicarbonate. Theoretically, antacids cause increased gastric acid production as a result of rebound, and although some studies support this hypothesis, the research demonstrates antacids to be safe in recommended doses.[89]

Dosage
For PUD symptoms, patients may take over-the-counter antacids according to individual product instructions.

Precautions
High doses of calcium-containing antacids may cause kidney stones, constipation, renal failure, alkalosis, or hypercalcemia. Carbonate-containing antacids may cause alkalosis. Aluminum antacids, in high doses, may cause hypophosphatemia, osteomalacia, constipation, and renal insufficiency. Magnesium antacids should be used in caution in people with renal disease, and they may cause hypermagnesemia.

Sucralfate
An older synthetic compound, sucralfate, has been shown effective in promoting ulcer healing and has been used since the late 1960s as a PUD treatment. It has an impressively complex chemical formula of $C_{12}H_{54}Al_{16}O_{75}S_8$, yet most of its beneficial effects are attributed to two properties: its ability to act as an acid buffer and its ability to bind to ulcer sites, thus protecting them from further insult. In clinical trials, sucralfate has been shown to be as effective as H_2 blockers for treatment of duodenal ulcers.[90]

Dosage
For duodenal ulcers, the dose is 1 g four times daily, 1 hour before meals and bedtime, for up to 8 weeks.

Precautions
Sucralfate can cause bezoar formation and constipation.

Acupuncture
Controlled trials have shown that acupuncture is an effective treatment for epigastric pain.[91] Case studies and animal models have also shown acupuncture to be specifically useful for PUD and prevention of ulcer recurrences, yet more clinical trials are needed.[92]

Therapies to Consider

Traditional Chinese Medical Massage
In a limited study, 74.5% of patients with PUD who received 20 sessions (every other day) of traditional Chinese medical massage demonstrated complete ulcer resolution.[93] This trial was not randomized, however, and more rigorous investigations are warranted.

Osteopathy
Although adequate clinical trials are lacking, osteopathy has potential in PUD for symptom relief and prevention. Manual medicine, in theory, can help the GI system to maintain sympathetic and parasympathetic balance, thus reducing excess acid production and restoring homeostasis. Osteopathy can also lead to relief of symptoms by manipulating somatovisceral pathways, and it is worth considering in patients with access to clinicians experienced in these techniques.

Prevention Prescription

- Eat a diet rich in fruits and vegetables (especially those containing vitamins A and C).
- Eat foods containing capsaicin (chili), as well as those with flavonoids and sulforaphanes.
- Eat probiotics: yogurt, sauerkraut, active yeasts, and aged cheeses.
- Avoid nonprobiotic dairy products such as milk.
- Eat breakfast every day, and avoid eating large meals shortly before sleeping.
- Minimize use of nonsteroidal antiinflammatory drugs.
- Avoid smoking cigarettes.
- Avoid excessive alcohol consumption.
- Maintain a moderate exercise routine.
- Obtain adequate sleep.
- Develop and incorporate stress reduction activities.

Therapeutic Review

The following integrative therapeutic options are useful for different niches on the peptic ulcer disease (PUD) spectrum, from prevention, symptom relief, and *H. pylori* elimination to active ulcer healing. Being mindful of the individual end goals of therapy will guide clinical choices. Evidence of a bleeding ulcer or significant weight loss is a reason to refer patients for endoscopy and can constitute a medical emergency.

Lifestyle
- Tobacco cessation — A
- Adequate sleep — B
- Routine exercise — B
- Stress reduction interventions — B
- Abstention from heavy ethanol intake — B

Nutrition
- Eat breakfast daily. — B
- Avoid eating shortly before sleeping. — B
- Avoid milk. — B
- Eat probiotic-containing foods, such as yogurt, aged cheeses, miso, and sauerkraut. — B
- Eat foods containing chili (capsaicin). — B
- Eat fruits and vegetables, especially those with vitamins A and C. — B

Continued

Supplements

- Probiotics during *H. pylori* antibiotic therapy: either *Lactobacillus (acidophilus* or GG) capsules, containing at least 1 billion organisms, twice daily, or *Saccharomyces boulardii,* 500 mg, twice daily 
- Vitamin C for *H. pylori* suppression: 500 mg twice daily 
- Zinc for gastric ulcers: 40 mg daily for 4 weeks 
- Polyunsaturated fatty acids for *H. pylori* eradication: 1 g of fish oil and 1 gram of gamma-linolenic acid–containing oil (evening primrose, black currant seed, borage, or hemp seed oils) taken daily for 8 weeks 
- Glutamine for peptic ulcers: 400 mg four times daily 

Botanicals

- Turmeric for peptic ulcers and PUD symptoms: whole root or root powder (capsules), 600 mg five times daily for 12 weeks 
- Mastic for dyspepsia: 350-mg capsules three times a day for 3 weeks 
- Mastic for duodenal ulcers: 500-mg capsules twice daily for 2 weeks 
- Cabbage for duodenal or gastric ulcers: 1 L of fresh juice divided over the course of a day for 10 days 
- Deglycyrrhizinated licorice for duodenal ulcers: 380 mg three times per day for 12 weeks 
- Chili (*Capsicum* fruit) for epigastric pain and dyspepsia: 2.5 mg daily of chili pepper capsules for 5 weeks 
- Cranberry for *H. pylori* eradication: 500 mL of cranberry juice daily for 90 days 
- Neem for duodenal ulcers: 30 mg bark extract twice daily for 10 weeks 

Pharmaceuticals

- Eliminate nonsteroidal antiinflammatory drugs for patients with PUD 
- Antibiotics and proton pump inhibitors (PPIs) for *H. pylori* eradication: amoxicillin, 1 g; clarithromycin, 500 mg; and omeprazole, 20 mg; combination to be taken twice daily for 14 days (check regional bacterial susceptibilities) 
- Acid suppression therapy for PUD and PUD symptoms: PPI (e.g., omeprazole) or histamine-2 (H_2) receptor blocker (e.g., ranitidine) once or twice daily, per individual drug, for up to 8 weeks 
- Antacids for PUD symptoms: over-the-counter antacids, per individual product instructions 
- Sucralfate for duodenal ulcers: 1 g four times daily for up to 8 weeks 

Acupuncture

- Acupuncture for epigastric pain 

Therapies to Consider

- Traditional Chinese medical massage for peptic ulcers 
- Osteopathy for PUD 

KEY WEB RESOURCES

http://digestive.niddk.nih.gov/ddiseases/pubs/hpylori/index.aspx	National Digestive Diseases Information Clearinghouse updated allopathic information on PUD
www.umm.edu/altmed/articles/peptic-ulcer-000125.htm	University of Maryland Medical Center integrative info on PUD for patients
http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/ warren-slides.pdf	2005 Nobel Prize for Medicine winner, Dr. J. Robin Warren's, slide-show on the discovery of H. pylori

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Chapter 43

Cholelithiasis

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Pathophysiology

According to the third National Health and Nutrition Examination Survey, more than 20 million people in the United States have gallbladder disease.[1] The occurrence of gallstones varies greatly, ranging from 2% to 70% among different populations. The highest incidence is among Pima Indian women older than 30 years of age.[2]

Bile aids in the digestion and absorption of lipids from the intestines. Made by the liver, bile is composed of bile acids, cholesterol, and phospholipids, and it is stored in the gallbladder until stimulation by cholecystokinin causes its release. Conditions that lead to gallstone formation include supersaturation of bile with cholesterol, decreased bile acids that dissolve cholesterol, excess mucus production, and gallbladder dysmotility and stasis (Fig. 43-1). Gallstones are classified as either cholesterol or pigment. In industrialized countries, cholesterol stones account for up to 85%. Most people with gallstones remain asymptomatic. Approximately 20% will develop true biliary symptoms, such as severe pain in the right upper quadrant that can radiate to the back or shoulder, and 1% to 2% will develop a complication that requires surgery.[2]

Epidemiologic research has revealed many risk factors for gallstones. Some of these conditions are not modifiable: sex, age, and ethnicity. Many conditions can be changed, however, such as obesity, physical inactivity, medications, nutrition, and stress.[2,3] Table 43-1 provides a list of conditions that increase risk.

Integrative Therapy

Lifestyle

Gallstones can be added to a long list of diseases heavily influenced by lifestyle. The profound rise in chronic conditions, such as diabetes, hypertension, and heart disease, has caused Western medicine to reevaluate its treatments and enhance prevention methods. The causes of these conditions are multifactorial, but a lifestyle of inadequate physical activity and the standard U.S. diet are major culprits. These chronic conditions are not isolated; they have similar causes, related to a proinflammatory state of imbalance. Gallstones can be grouped with these other diseases such as diabetes and heart disease, because evidence shows that lifestyle factors such as diet (macronutrient and micronutrient intake) and exercise are also linked to gallbladder disease.

Maintenance of a Healthy Weight

Obesity, especially abdominal, is a well-known risk factor for gallstones. It is associated with increased cholesterol secretion into bile.[2] Gradual weight loss is important for obese individuals because rapid weight loss may also promote gallstone formation secondary to increased biliary cholesterol and bile stasis from gallbladder hypomobility. Weight loss should not exceed 1.5 kg (3.3 lb) per week to avoid this risk.[4]

Exercise

Physical activity is a necessary component of a healthy lifestyle and has a significant impact on many diseases. Studies have also shown that exercise can increase gallbladder motility.[5] In postmenopausal women, physical activity is inversely related to the development of gallstone disease.[6] In one report, women who sat for more than 60 hours a week were 2.32 times more likely to have a cholecystecomy.[7] Fortunately, even modest amounts of physical activity have a positive effect; an observational study of more than 2000 people found that just 2 hours of activity a week reduced the risk by 40%.[8]

Stress Reduction

Even without having randomized placebo-controlled trials to prove it, stress is likely a factor in most diseases. Evidence indicates that stress causes gallbladder dysfunction and bile stasis in animal studies.[3] The general benefits of stress reduction on both mind and body may extend to the gallbladder, too; after all, it is all connected. Consider recommending counseling, meditation, or other stress reduction techniques as appropriate.

FIGURE 43-1
Pathophysiology of gallstones.

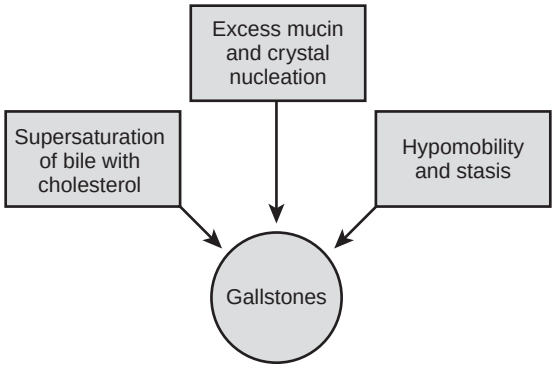

TABLE 43-1. Conditions That May Increase the Risk of Gallbladder Disease

Increased cholesterol saturation	Estrogen (endogenous: pregnancy; or supplemented: hormone replacement therapy, oral contraceptives) Obesity High-cholesterol diet
Decreased bile salts (or increased ratio of secondary bile acids)	Low-fiber diet Ileal inflammation (Crohn disease) Cirrhosis Cystic fibrosis Fibrates Age
Stasis of bile flow	Parenteral nutrition Low-fat, weight loss diets Hypertriglyceridemia (impaired motility) Physical inactivity Ceftriaxone (biliary sludge)[2] Octreotide[2] Stress[3] Iron deficiency anemia[51]

Nutrition

Several areas of nutrition overlap in gallbladder disease. For example, vegetarians have a lower rate of cholelithiasis.[9] The reason could be related to higher consumption of fruits and vegetables, which are good sources of vitamins, minerals, fiber, and antioxidants, all of which have been linked to inhibition of gallstone formation. In a study looking at diet differences, patients with gallstones consumed less fish, fruit, fiber, folate, magnesium, calcium, and vitamin C; they also ate more cereal, sugar, calories, and saturated fat.[10] Specific components of diet are separated for research, but of course the sum is likely greater than the individual parts. Encouraging healthy, well-balanced nutrition (e.g., the Mediterranean diet) full of colorful vegetables and including healthy fats may be a good place to start.

Fats

The type of fats consumed is important in gallbladder disease. The diet should be low in saturated fats, but it should have sufficient sources of polyunsaturated fats and omega-3 fatty acids. Animal studies showed that monounsaturated and polyunsaturated fats act as inhibitors of cholesterol cholelithiasis.[11] Fish oil can decrease biliary cholesterol saturation and enhance bile flow.[12] A study comparing fish oil with fibrate therapy in men with hypertriglyceridemia showed that both approaches lowered triglyceride levels, but only the fish oil increased bile acid synthesis. The same research also demonstrated that fish oil increased the ratio of cholic acid to chenodeoxycholic acid, which improves cholesterol solubility.[13] Proinflammatory, arachidonic acid–rich saturated fats can increase cholesterol saturation and disrupt the gallbladder epithelium.[14] Another study revealed that men with the highest consumption of long-chain saturated fatty acids (which includes arachidonic acid) had a 40% increased risk of cholecystectomy.[15] The goal is to replace this fat with the antiinflammatory effects of healthy fats, such as omega-3 fatty acids (see Chapter 86, The Antiinflammatory Diet).

Fiber

A higher intake of fiber is associated with a lower prevalence of gallstones. Fiber reduces the absorption of deoxycholic acid by decreasing its formation by intestinal bacteria. Deoxycholic acid is a secondary bile acid, and it increases the lithogenicity of bile.[16] Water-soluble fiber found in fruits, vegetables, pectin, oat bran, and guar gum can bind this acid and may be helpful in preventing and treating gallstones.[14] A prospective study of 77,000 women demonstrated that those consuming the most fruits and vegetables reduced their risk of gallstones by 21%.[17]

A good source of fiber is to mix 1 teaspoon of ground flaxseed (lignan) into 8 oz of apple juice or applesauce (pectin) and consume daily. This recipe has the added benefit of being a good source of omega-3 fatty acids.[14]

Legumes are a good source of fiber, yet their role in gallbladder disease is uncertain. They have been shown to increase biliary cholesterol saturation and decrease phospholipids, which can lead to gallbladder disease.[16] However, a case-control study found a negative association with legume intake and gallbladder disease, but the population studied had a relatively small legume intake.[18] The risk that legumes may cause gallstone disease should be weighed against their other known health advantages when considering recommendations.

Nuts

In the Nurses' Health Study, a large prospective study, women who consumed nuts frequently had a more than 20% reduced risk of cholecystectomy. This relationship persisted after controlling for multiple confounding variables, including fat intake.[19] Other research showed similar results in men. Men who frequently ate nuts had a reduced risk of gallstone disease. This inverse relationship existed independently of consumption of peanuts, other nuts, or a combination of both.[20]

Simple Sugars

Refined sugars increase the cholesterol saturation of bile and reduce the ratio of beneficial cholic acid to deoxycholic acid.[21] Although consumption of refined sugars is also a factor in obesity, evidence indicates that simple sugars (monosaccharides and disaccharides) promote gallstone formation independent of obesity.[15] A relationship also appears to exist between glucose intolerance and gallstones.

Hyperinsulinemia may cause supersaturation of cholesterol in bile and gallbladder dysmotility. The prevalence of cholesterol gallstones is higher in diabetic patients; even in women without diabetes, fasting serum insulin levels are positively associated with gallstones.[22] Sugar intake is positively related to triglycerides and inversely related to high-density lipoproteins, and this effect on lipoprotein metabolism may contribute to gallstone formation.[23] Additionally, diets with high glycemic load have been linked to increased rates of cholecystectomy in women[24] (see Chapter 31, Insulin Resistance and the Metabolic Syndrome, and Chapter 85, The Glycemic Index/Load).

Foods associated with a reduced risk of gallstones include fiber-rich fruits and vegetables, whole grains, nuts, coffee, and moderate alcohol.

Coffee

Often, people with gastrointestinal symptoms are told to avoid coffee. Interesting research has demonstrated that coffee can play a role in preventing gallstones, however, and numerous epidemiologic studies support this finding.[2] Coffee and its components have been shown to stimulate cholecystokinin release, enhance gallbladder contractility, and decrease cholesterol crystallization in bile.[25] A large prospective study demonstrated a 40% lower risk of cholecystectomy in men who drank 2 to 3 cups of coffee a day over a 10-year period.[26] Other prospective research found that intake of caffeinated coffee was associated with a significantly reduced risk of cholecystectomy in women. This is not the case for other caffeinated beverages; in fact, a positive association was noted with caffeinated soft drinks.[22] Some studies have not demonstrated this link,[27,28] but many have, and so it is reasonable to continue coffee according to a patient's preference.

Food Allergy

Interest is growing in food allergies and the effects they may have on health and wellness. A small amount of research from as early as the 1940s noted that food allergy is a cause of gallbladder disease.[16] In an uncontrolled study of 69 patients with gallstones or postcholecystectomy syndrome, 100% of these patients reported symptom resolution after 1 week of starting an elimination diet. The foods that most commonly evoked symptoms were eggs, pork, onions, fowl, milk, coffee, citrus, corn, beans, and nuts.[29] Thus, the clinician should keep in mind, when giving dietary advice to patients with gallstones, that it may not be as simple as saying "avoid fatty foods." An elimination diet may be a good option for those patients with biliary colic who want to avoid surgery (see Chapter 84, Food Intolerance and Elimination Diet).

Water

Drinking 6 to 8 cups of clean water a day will ensure the water content of the bile and help prevent crystal agglomeration.[14]

Alcohol

Epidemiologic evidence shows that gallstones are among a handful of diseases that are less common in people who consume a moderate amount of alcohol.[1,30] A large prospective study found that moderate alcohol intake was associated with a decreased risk of cholecystectomy in women.[31] Health benefits are associated with regular consumption of small amounts of alcohol, rather than heavy sporadic drinking. The many hazards and potential health consequences of alcohol consumption must also be considered. Any recommendation for moderate alcohol intake must be evaluated carefully for each person.

Supplements

Vitamin C

Ascorbic acid is involved in the conversion of cholesterol to bile acids, and vitamin C deficiency has been associated with gallstones in numerous studies.[32,33] Vitamin C supplementation, at a dose of 500 mg four times a day for 2 weeks, was shown to prolong the time needed for cholesterol crystal formation significantly.[34] In an observational study of more than 2000 people, the prevalence of gallstones was half of what it was in study participants who did not supplement.[8] Good sources of vitamin C include red pepper, kiwi, broccoli, strawberries, and citrus.

Dosage

The dose is 200 mg twice daily.

Precautions

Gastrointestinal disturbance may occur, including diarrhea, nausea, vomiting, heartburn, and abdominal cramps. Other side effects include fatigue, flushing, headache, hyperoxaluria, and predisposition to urinary tract stones.[13]

Magnesium

People who consume sufficient magnesium have lower rates of gallstones.[10] Additionally, magnesium deficiency is a common mineral deficiency in people consuming the standard American diet, also a risk factor for gallstones. A diet rich in magnesium may be a factor in preventing gallstones. Magnesium is found in green leafy vegetables, nuts, and whole grains. A study showed that men consuming high amounts of magnesium through diet and supplements (average, 454 mg/day) were 28% less likely to have gallstone disease compared with men consuming low amounts (average, 262 mg/day).[35]

Dosage

The dose is 300 mg daily.

Precautions

Gastrointestinal discomfort such as diarrhea, nausea, and abdominal cramping may occur. Magnesium should be used with caution in patients with renal failure. Toxic levels cause muscle relaxation and loss of deep tendon reflexes.

Vitamin E

Animal studies showed that a cholesterol-free diet deficient in vitamin E can lead to cholesterol gallstones.[36] Moreover, when animals were given a high-fat diet along with vitamin E, they did not develop gallstones.[37] Therefore, supplementation with vitamin E may possibly help to prevent gallstones.

Dosage

Vitamin E (mixed tocopherols): 400 units/day.

Precautions
Side effects are rare but include nausea, diarrhea, intestinal cramps, fatigue, weakness, headache blurred vision, rash, and creatinuria. Long-term use may increase cardiovascular risk in persons younger than 65 years old.

Calcium
Calcium preferentially binds secondary bile acids, such as deoxycholic and chenodeoxycholic acid, in the small intestine. These bile acids reduce the solubility of cholesterol, so once it is bound and excreted, the risk of gallstones is reduced. In a study that monitored the dietary intake of 860 men, calcium intake was inversely associated with gallstone disease.[23]

Dosage
Calcium gluconate or citrate: 1000 to 1500 mg/day with meals. Calcium citrate is better absorbed in older adults, but it costs more.

Precautions
Calcium can cause constipation and gastrointestinal irritation. It should not be taken with iron supplements because it decreases absorption of iron.

Lecithin
Phospholipids, such as lecithin, increase the solubility of biliary cholesterol, and one study suggested that they are just as important as bile acids in this process.[36] Supplementation of lecithin is associated with an increase in biliary phospholipids and a decrease in cholesterol. Studies also showed that supplementing causes higher concentrations in bile.[38] No strong evidence indicates that lecithin is effective in treating gallstones, but it may aid in prevention.

Dosage
Lecithin 500 to 1000 mg/day.

Precautions
Diarrhea, nausea, and abdominal pain or fullness may occur.

Olive Oil or Gallbladder "Flush"
The gallbladder flush (or liver flush) is a common remedy that is said to cause gallstone passage. Several versions of the treatment exist, including combinations of olive oil, lemon juice, and apple juice. Proponents of this treatment claim that it causes the passage of gallstones. However, when what is thought to be gallstones are chemically analyzed, they turn out to be saponified complexes of olive oil, minerals, and lemon juice.[39] Possibly, the monounsaturated fat in olive oil could stimulate the gallbladder to expel stones, but these stones could then become lodged in the common bile duct. Ideally, this approach would be avoided until ultrasound evaluation reveals the size and number of stones.

Botanicals: Choleretic Herbs

Herbal medicine has been used to treat gallbladder disease and is a good option for patients with small stones and mild symptoms. Choleretic herbs can stimulate bile production, flow, and solubility.[14,39] Their effects can be enhanced by combining them with terpenes (e.g., peppermint oil, discussed later) that can help with gallstone dissolution.

Milk Thistle (Silybum marianum)
The following list of choloretic herbs may be used individually, or an herbologist may mix a combination together in a tea. They can be combined with peppermint oil for synergistic effect.

Dosage
Standardized 70% silymarin extract, starting at 150 mg twice daily and increasing to three times daily if needed

Precautions
Milk thistle may have a laxative effect. It should be used with caution in patients allergic to plants in the Asteraceae/Compositae family (ragweed, daisies, marigolds).

Dandelion (Taraxacum officinalis)
The following list of choloretic herbs may be used individually, or an herbologist may mix a combination together in a tea. They can be combined with peppermint oil for synergistic effect.

Dosage
Give 4 to 10 g of dried leaf or 2 to 8 g of dried root, three times/day. Tea is made by steeping the same amount in 150 mL of boiling water for 10 to 15 minutes and then straining. One cup of tea should be consumed three times/day. The most convenient dosing is a 1:5 tincture, 5 to 10 mL three times/day.

Precautions
Dandelion can cause gastric hyperacidity. If used topically, it may cause contact dermatitis. Patients who are allergic to plants in Asteraceae/Compositae family (ragweed, daisies, marigolds) should be cautious. Dandelion also can have hypoglycemic effects.

Globe Artichoke (Cynara scolymus)
Dosage
The dose is 1 to 4 g of the leaf, stem, or root three times/day. Do not confuse this plant with Jerusalem artichoke.

Precautions
If used topically, may cause contact dermatitis. Again, caution in those allergic to Asteraceae/Compositae family (ragweed, daisies, marigold).

Turmeric (Curcuma longa)
An animal study demonstrated that mice fed a lithogenic diet had the incidence of gallstones reduced by 73% when these animals were supplemented with curcumin. Curcumin also reduces biliary cholesterol concentration.[40]

Dosage
The dose is 450 mg of curcumin capsule standardized extract or 3 g turmeric root daily in divided doses.

Precautions
Turmeric has blood thinning effects, so patients should be careful if they are taking other blood thinning medications. Turmeric should be used with caution in patients allergic to yellow food colorings or plants belonging to the Zingiberaceae (ginger) family.

Botanicals: Gallstone-Dissolving Herbs

Monoterpenes are a class of hydrocarbon molecules found in the essential oils of many plants. These compounds have choleretic properties and inhibit formation of cholesterol crystals.[16] A combination of monoterpenes, mainly consisting of menthol and pinene, is effective for stone dissolution.[41] A double-blind study concluded that the addition of menthol to ursodeoxycholic acid (UDCA) improved outcomes compared with UDCA alone, and that menthol was equally effective as the monoterpene combination.[42]

Peppermint Oil (Mentha Piperita)

Dosage

One or two enteric-coated capsules (0.2 mL/capsule) three times/day between meals

Precautions

Peppermint oil relaxes the lower esophageal sphincter, and this may lead to reflux or heartburn. (Enteric-coated capsules are used to avoid this effect.) It may also cause allergic reactions, flushing, and headache.

Pharmaceuticals

Treatment with bile acids can be used for gallstone dissolution. These acids work by inhibiting biliary secretion of cholesterol and increasing bile secretion from the liver. They may also improve gallbladder motility. They are most effective when used in patients with small stones, mild symptoms, and good gallbladder function. Patients with calcified or pigment stones are usually poor candidates for bile acid therapy. Incomplete dissolution and stone recurrence are both significant drawbacks to the therapy.

Ursodeoxycholic Acid (Ursodiol)

UDCA is a bile acid that lowers bile cholesterol saturation. Numerous studies have shown UDCA to prevent the formation of gallstones in obese patients undergoing rapid weight loss, either through calorie-restricted diets or bariatric surgery.[43] Maintenance therapy may also be effective for gallstone recurrence.[44]

Dosage

UDCA 300 mg twice daily.

Precautions

Possible adverse effects include hepatic impairment, elevation of liver enzymes, and gastrointestinal upset.

> Lifestyle is the key to treatment. Except for surgery, all treatments are associated with a high 5-year recurrence rate if lifestyle modifications are not made.

Estrogen Supplementation

A systematic review of multiple studies found that estrogen supplementation in postmenopausal women increased the likelihood of gallstones.[45] In addition, two randomized placebo-controlled studies also showed an increased risk of biliary disease with supplementation.[46] Both oral and transdermal estrogen supplements can increase biliary cholesterol saturation and decrease cholesterol nucleation time, which could raise the risk of gallstones.[47] The Heart and Estrogen/progestin Replacement Study revealed that supplementation in postmenopausal women with known coronary artery disease resulted in a significant increased risk for biliary surgery.[48] This additional risk should be considered when women elect hormone replacement therapy.

Surgery

Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy is the recommended treatment for patients with symptomatic stones and gallbladder wall inflammation. However, it is not recommended for most patients with asymptomatic gallstones unless they are at risk for gallbladder carcinoma. A major advantage of surgical treatment is the avoidance of recurrence, but it must be weighed against other harms of surgery and anesthesia.

Extracorporeal Shock-Wave Lithotripsy

Lithotripsy can be an effective treatment for gallstones, especially when it is combined with bile acid therapy. Lithotripsy is rarely used for gallstones, however, despite its being a common treatment for renal stones.

Therapies to Consider

Homeopathy

Homeopathy has been used as a safe treatment for more than 2 centuries, despite a lack of scientific evidence. It may provide benefit when other treatment options have failed. After consultation, a professional homeopath may recommend various remedies, including Chelidonium, Colocynthis, or Lycopodium.

Acupuncture

Acupuncture, as part of traditional Chinese medicine treatment, can include addressing energy flow through the liver and gallbladder. This technique may be helpful for gallbladder function, as well as for alleviating discomfort caused by gallbladder disease.

Osteopathy

Although manual therapy is effective for treating musculoskeletal complaints, it is also used to treat other body systems. Osteopathy can help to regulate physiology and aid the body in establishing homeostasis. Viscerosomatic reflexes are changes in the musculoskeletal system that reflect visceral disorders. These reflexes are mediated by afferent neurons of the sympathetic nervous system. They are helpful in diagnosis, but they also can have treatment benefit by balancing the nervous system and influencing the viscera. Manual therapy does not replace others mentioned, but it may be a useful adjunct.

Percutaneous Solvent Dissolution Therapy

Organic solvents such as methyl-ter-butyl ether can be used to dissolve cholesterol gallstones when these agents are directly instilled into the gallbladder by percutaneous catheter through the liver.[14] This labor-intensive and invasive procedure is rarely performed.

Fatty Acid Bile Acid Conjugates

Fatty acid bile conjugates are novel synthetic lipid molecules made of fatty acids linked to cholic acid. They were developed after investigators noted that phospholipids are major cholesterol solubilizers in bile and possess anticrystallizing activity. When given orally, these conjugates are absorbed and secreted into bile. Animal studies showed that these substances can prevent cholesterol crystal formation and also dissolve existing ones.[36,49,50]

Prevention Prescription

Preventing gallstones is easier than treating them. The same principles of prevention apply to many common chronic diseases (diabetes, heart disease) for an added benefit.

- Maintain a healthy weight, with slow gradual weight loss if body mass index is elevated.
- Exercise. Get moving in a way that is enjoyable and sustainable for you, at least 30 minutes five times weekly.
- Find a stress-reducing practice.
- Encourage a diet high in fiber, vegetables, fruit, nuts, and omega-3 fatty acids.
- Maintain a low intake of saturated fats, refined sugars, and high–glycemic load foods.
- Remember hydration. Drink at least 6 to 8 cups of clean water daily. Consider coffee if you enjoy it, 2 to 3 cups daily. A moderate intake of alcohol may be suitable for some patients.
- Consider an elimination diet.
- Consider supplementation: vitamin C, 200 mg twice daily; magnesium, 300 mg/day; vitamin E, 400 units/day with meals; calcium, 1000 to 1500 mg/day; and lecithin, 500 to 1000 mg/day.
- Avoid medications associated with gallstone risk: estrogen, ceftriaxone, octreotide, and fibrates. Take precautionary measures if taking these medications, have excessive weight loss, or are receiving total parental nutrition (TPN).

Therapeutic Review

Immediate surgical referral is warranted in the setting of severe recurring symptoms, elevation in liver enzymes, amylase, or white blood cell count. In patients with asymptomatic or mild cases and normal liver function, proceed with the therapies listed here.

Lifestyle

- Maintain a healthy weight. B1
- Exercise at least 30 minutes a day, five times a week. B1
- Participate in stress-reducing activity. C1

Nutrition

- Diet should be high in fiber, fruits, and vegetables. B1
- Consider supplementing with fiber and flaxseed.
- Recommend diet low in saturated fat, rich in omega-3 fatty acids. B1
- Drink 6 to 8 cups of water daily. C1
- Avoid refined sugars. B1
- Avoid excess intake of legumes. C1
- Consider an elimination diet. B1

Supplements

- Vitamin C: 200 mg twice daily B2
- Calcium: 1000 to 1500 mg/day B2
- Magnesium: 300 mg/day B2
- Vitamin E: 400 units/day C2

Botanicals

- Milk thistle (*Silybum marianum*) standardized to 70% silymarin extract: starting at 150 mg twice a day and increasing to three times/day if needed C1
- Dandelion (*Taraxacum officinalis*): 1:5 tincture, 5 to 10 mL three times/day C2
- Artichoke (*Cynara scolymus*): 1 to 4 g of leaf, stem, or root three times/day C1
- Turmeric (*Curcuma longa*): 450-mg curcumin capsule, or 3 g root daily C1
- Peppermint oil (*Mentha piperita*): one to two enteric-coated capsules three times/day between meals B2

Pharmaceuticals

- Ursodiol (ursodeoxycholic acid): 300 mg twice daily with meals B2

Surgery

- Laparascopic cholecystectomy A3
- Patients with common bile duct obstruction (elevation of liver enzymes, lipase, and bilirubin, right upper quadrant pain, jaundice, and common bile duct dilation on ultrasound) may need either endoscopic retrograde cholangiopancreatography for stone removal or surgical exploration.

KEY WEB RESOURCES

National Center for Complementary and Alternative Medicine, National Institutes of Health: http://nccam.nih.gov.
National Digestive Diseases Information Clearinghouse, National Institutes of Health: http://digestive.niddk.nih.gov.
American Gastroenterological Association: www.gastro.org.

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Chapter 44

Recurring Abdominal Pain in Pediatrics

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Pathophysiology

Recurrent abdominal pain (RAP) in children was first defined by Apley and Naish in 1958 as consisting of least three episodes of pain over a 3-month period that is severe enough to interfere with normal activities. RAP is one of the most common reasons to seek medical attention.[1] It affects approximately 10% to 15% of all school-age children and is responsible for 2% to 4% of all pediatric outpatient visits.[2] Fewer than 10% of children with RAP are ever found to have an organic cause for pain; however, substantial morbidity, such as depression, anxiety, lifetime psychiatric disorders, social phobia, and somatic complaints, still occurs.[3] In addition, significant health care costs are associated with this disorder, not only from medical evaluations and medications, but also from missed work and productivity.[4] Children with RAP, on average, miss 26 days per year of school compared with only 5 days in children who do not have abdominal pain.[5] Absenteeism has been identified as a precursor to undesirable outcomes, including poor academic performance, increased rates of school dropout, substance abuse, and violence in adolescents.[6] Parents, teachers, and physicians frequently reinforce pain behavior by excusing these children from chores and other responsibilities, allowing absences from school, or providing medications.

We have traditionally recognized that the etiology and pathogenesis are multidimensional in that biologic, psychological, and social factors can all play significant roles in the presentation of RAP in children. With advances in our understanding of pain physiology, more mechanisms that explain the underlying processes will help how we approach the treatment of this condition.

A significant increase in the onset of new RAP cases in children occurs weeks to months after bacterial intestinal infections, and most of these children manifest symptoms consistent with irritable bowel syndrome (IBS).[7] Bacteria interact with intestinal epithelial cells and generate inflammatory mediators that stimulate the sensory nerve endings lying in the gut mucosa. Bacteria also affect intestinal permeability by allowing chemicals and antigens access from the gut lumen into and between the cell walls.[8] Knowing this, we may approach treatment to address lumen physiology and integrity, to decrease the inflammatory response that triggers neuronal sensitization and pain.

Imbalances of neurotransmitters may also contribute to RAP. In the brain-gut axis, which links together the neuroendocrine, immune, and enteric nervous systems, the brain and the gut share identical neurotransmitters because they both originated from the same cells embryologically. Low levels of serotonin have been associated not only with depression and headaches, but also with abdominal pain.[9] Along this line, dysregulation of the autonomic nervous system with an increased auditory startle reflex and low vagal tone has been demonstrated in children with RAP.[10,11] Therefore, therapies that decrease sympathetic arousal, normalize levels of circulating neurotransmitters, and balance the autonomic nervous system may be indicated.

Food sensitivity mediated immunologically by immunoglobulin G (IgG) antibodies has been identified as another trigger for RAP. Rather than the classic IgE food allergy response, which is more immediate, an IgG-mediated response is delayed following exposure to a particular antigen.[12] The most common IgG responses are to wheat, dairy, eggs, corn, and soy. This type of food sensitivity creates a low-level, chronic inflammatory response that triggers gut neuronal sensitivity and pain. This does not, however, trigger excessive calprotectin, a cytosolic protein in granulocytes produced in high levels in inflammatory bowel disease.[13]

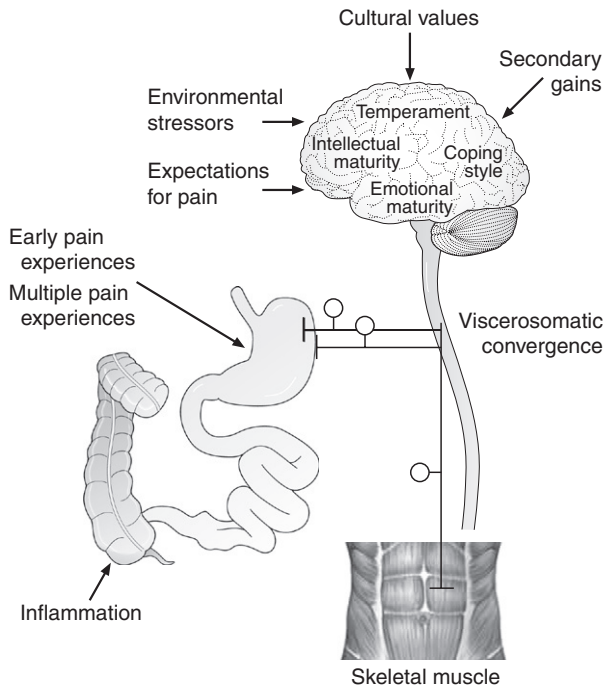
Fructose malabsorption, a condition that causes gas, bloating, and cramping, has also been found to cause RAP in

children who tested positive on breath hydrogen testing for fructose intolerance.[14]

Even obesity has been linked to a greater incidence of constipation, gastroesophageal reflux disease, IBS, encopresis, and functional abdominal pain. This association may be related to food choices (processed foods versus whole fruits and vegetables, higher intake of soda with high-fructose corn syrup), physical activity levels, hormonal status, or emotional state.[15] A thorough diet history is important in identifying possible triggers for RAP.

Another known factor relating to the incidence of RAP in children is the behavior profile of the patient and his or her genetic vulnerability. Some of these children exhibit anxiety, mild depression, withdrawal, and low self-esteem. Investigators have postulated that this behavior profile is frequently fostered within a family structure characterized by parental depression, enmeshment, overprotectiveness, rigidity, and lack of conflict resolution. These factors may influence the way in which the disorder is experienced and addressed.[16] Figure 44-1 nicely displays how all these factors contribute to the clinical expression of chronic pain.[17]

FIGURE 44-1
Pathogenesis of visceral hyperalgesia and clinical expression of chronic pain. Primary hyperalgesia develops when sensory neurons with cell bodies in dorsal root ganglia are recruited and sensitized after early or multiple pain experiences. Secondary hyperalgesia occurs when biochemical changes in pathways from the spinal cord to cerebral cortex result in increased pain perception. *Viscerosomatic convergence* refers to somatic and visceral afferent nerves terminating on the same spinal interneurons, so that the affected individual is unable to define a discrete pain location on the body. Psychological and developmental factors (within the brain) and psychosocial factors (*arrows* pointing to the brain) alter clinical expression of pain. (From Hyams JS, Hyman PE. Recurrent abdominal pain and the biopsychosocial model of medical practice. *J Pediatr*. 1998; 133:473–478.)



Children with RAP may demonstrate one of the classic presentations, as defined by the Rome Foundation's pediatric Rome III criteria, which may help guide the choice of therapies.[18]

1. Functional abdominal pain or syndrome; must include all the following:
- Episodic or continuous abdominal pain
- Insufficient criteria for the functional gastrointestinal disorders
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process
- Some loss of daily functioning
- Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

2. IBS; must include all the following:
- Abdominal discomfort or pain associated with two or more of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency or form of stool
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process

3. Functional dyspepsia; must include all the following:
- Persistent or recurrent pain or discomfort centered in the upper abdomen
- Pain not relieved by defecation or associated with change or form of stool
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process

4. Functional constipation; must include two or more of the following:
- Two or fewer defecations per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet

5. Abdominal migraine; must include all the following:
- Paroxysmal episodes of intense, acute periumbilical pain that lasts more than 1 hour
- Intervening periods of usual health lasting weeks to months
- Pain interfering with normal activities
- Pain associated with two or more of the following:
  - Anorexia
  - Vomiting
  - Photophobia
  - Nausea
  - Headache
  - Pallor
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process

6. Cyclic vomiting
- Two or more periods of intense nausea and unremitting vomiting or retching lasting hours to days
- Return to usual state of health lasting weeks to months

7. Aerophagia; must include two of the following:
- Air swallowing
- Abdominal distention because of intraluminal air
- Repetitive belching or increased flatus

Serious organic disease can be ruled out by a thorough history and physical examination and basic laboratory investigations. Pertinent positive results in this evaluation considered "red flags" include the following:

1. A family history of inflammatory bowel disease, ulcer disease, or significant psychosocial disorder
2. Pain that wakes the child from sleep
3. History of weight loss or growth delay
4. Blood in stool or bile-stained emesis
5. A history and physical examination revealing fevers, rashes, joint involvement, or perianal disease
6. Abnormal complete blood count, urinalysis, sedimentation rate, C-reactive protein, or stool for occult blood

If indicated by a positive history, the clinician may have to consider further testing (i.e., serologic testing for *Helicobacter pylori,* serum transaminases, amylase, lipase, stool for pathogens, and endoscopy).

Rather than a diagnosis of exclusion, recurrent abdominal pain should be presented as a positive diagnosis identified as the most common cause of chronic abdominal pain in children. Parents can further be reassured that serious disease is unlikely if the history and physical examination are normal.

Integrative Therapy

Nutrition

Diet manipulation has been attempted for years as a treatment for RAP either through the elimination of certain foods (e.g., lactose-containing foods) or the addition of others (e.g., high-fiber foods). Research into these dietary interventions has had varying results.[19,20]

Fiber

Although fiber studies have been small and the evidence is weak, some investigators found that additional fiber may be beneficial to some children, especially those with constipation. This goal can be accomplished by increasing the amounts of fruit, vegetables, legumes, and whole grains in the diet. Breakfast cereals can also be a good source of fiber, especially cereals made with bran (Table 44-1).

If a child has difficulty obtaining adequate fiber through the diet, psyllium powder, 1 teaspoon (2 g) in 8 oz of cool water or juice, may be given up to three times a day. An increase in water intake is strongly recommended along with the increased fiber, to prevent constipation.

Age of the child + 5 = recommended minimum daily grams of fiber. More fiber can be added as needed.

Food Elimination

If certain foods seem to exacerbate pain, the patient should certainly avoid them. If symptoms are suggestive or if the patient has a family history of lactose intolerance, initiate a 2- to 4-week trial of cessation of all dairy products (milk, cheese, yogurt, ice cream, and so forth). If no changes are noted after 2 weeks, then consumption of dairy products can be resumed. If some improvement was noted, then have the patient slowly reintroduce dairy in small quantities as tolerated. Reduce the intake of highly processed foods, especially those with refined carbohydrates (e.g., snacks, candy, cookies) because the fermentation of these sugars increases gas production. Studies showed that ingestion of various sugars, such as lactose, fructose, sorbitol, or fructose plus sorbitol, causes an increase in measured breath hydrogen and clinical symptoms in patients with RAP.[21,22] Subsequent reduction of these sugars caused a reduction in symptoms in 40% to 60% of the subjects studied. Fructose is readily available in sweetened soft drinks and juices. Sorbitol is the leading sweetener used in "sugar-free" foods.

Food allergy has been implicated in abdominal pain; however, attempts to test for this by the presence of IgE-mediated antibody responses has not been helpful. One study, however, focused on food elimination based on IgG antibodies detected by enzyme-linked immunosorbent assay. These antibodies may cause delayed sensitivity and irritation of the gastrointestinal tract. In a randomized, controlled trial, compliant patients who were placed on a food elimination diet that was based on high levels of IgG antibodies had a 26% greater reduction of symptoms compared with patients receiving a sham elimination diet[23] (see Chapter 84, Food Intolerance and Elimination Diet).

TABLE 44-1. Fiber Content of Various Foods

FOODS	PORTION SIZE	FIBER (g)
High Fiber		
All-Bran cereal	½ cup	10
Figs, dried	3	10
Kidney beans	½ cup cooked	9
Baked beans	½ cup cooked	8
Broccoli	¾ cup cooked	7
Spinach	½ cup cooked	7
Yam baked in skin	1 medium	7
Whole wheat bread	2 slices	6
Baked potato with skin	1 medium	5
Blackberries	½ cup	5
Apple with skin	1 medium	3.5
Raspberries	½ cup	3.5
Lentils	½ cup cooked	3.5
Whole wheat spaghetti	1 cup	3.5
Wheaties cereal	1 oz	2.5
Low Fiber		
Bagel	1	Less than 1
Cornflakes	1 oz	Less than 1
Grapes	20	Less than 1
Watermelon	1 cup	Less than 1
Lettuce	1 cup	Less than 1

Behavior Modification

Reinforcing pain behavior is often done unknowingly but with good intentions toward the child. Help families recognize that special attention or treatment with pain episodes (i.e., staying home from school, being dismissed from chores or responsibilities, having one-on-one attention from a parent) may foster ongoing pain behavior and diminish the child's self-reliance. Encourage school attendance as well as completion of personal responsibilities. Physicians can also facilitate a return to a normal lifestyle by offering a thorough explanation of the diagnosis and pathophysiology, reassurance, and options for management and adaptation to the disorder.

Poor sleep can heighten the perception of pain; therefore, working on strategies to promote restorative sleep is important. Eliminate all stimulants in the evening before bedtime. This includes caffeine, decongestants, television, computer or video games, and arguments. Practice dusk simulation by dimming lights around the house 1 hour before bedtime and shifting to quieter activities. The child should take a warm bath with Epsom salt to relax tense muscles before bedtime. Make sure the bedroom environment is conducive to sleep—dark, quiet, and cool. If the child has difficulty falling asleep, have him or her practice the self-regulation techniques listed earlier. Also consider using calming herbs such as chamomile.

Botanicals

Chamomile (Matricaria recutita)

The active ingredients in chamomile include the volatile oils alpha-bisabolol and bisabolol oxide and the flavonoids apigenin, luteolin, and quercetin. These constituents have antiinflammatory effects that inhibit phospholipase A, cyclooxygenase, and lipoxygenase pathways.[24] Bisabolol has effects in the gastrointestinal tract receptors, thus causing relaxation of the smooth muscle. Apigenin works on the central nervous system benzodiazepine receptors with anxiolytic effects similar to those of diazepam (Valium) and alprazolam (Xanax) but without the sedative effects.[25,26] Chamomile can be given as a tea, as an extract, or by capsule in standardized preparations. Glyceride extracts of chamomile can be found for use in children to offset any concerns of preparations extracted with alcohol. One study done in infants with colic used an herbal tea preparation that included chamomile. This preparation was found effective in reducing colic episodes.[27]

Dosage

Adults weighing approximately 150 lb: 3 g three to five times per day
Children weighing approximately 75 lb: 1.5 g three to five times per day
Children weighing approximately 35 lb: 0.75 g three to five times per day

One heaping teaspoon of chamomile flowers steeped in hot water yields approximately 3 g. The extracts may come in 1 g/1 mL (1:1) dilution or 1 g/4 mL (1:4) dilution. Use the following doses as a guide:

150 lb
1:1—15 to 30 drops three to five times per day
1:4—2 teaspoons three to five times per day
75 lb
1:1—8 to 15 drops three to five times per day
1:4—1 teaspoon three to five times per day
35 lb
1:1—4 to 8 drops three to five times per day
1:4—½ teaspoon three to five times per day

Precaution

Chamomile is generally safe, although anyone allergic to ragweed, asters, or chrysanthemums should take it with caution. Chamomile is a member of this daisy family and has contributed to allergic reactions in rare cases.

Peppermint (Mentha piperita)

Analysis of peppermint oil typically shows more than 40 different compounds; however, the principal components are menthol, methone, and methyl acetate. The pharmacology focuses almost entirely on peppermint's menthol component, which has carminative effects (elimination of intestinal gas), antispasmodic effects, and choleretic effects (bile flow stimulant). The mechanism of action is thought to be inhibition of smooth muscle contractions by blocking calcium channels.[28] Many studies have been conducted using peppermint oil as a treatment for IBS, including one study in children.[29] Even though peppermint did not alter the associated symptoms of IBS, such as urgency of stool, stool patterns, or belching, it did reduce the pain. Peppermint is most widely used as a tea. Because of its calcium channel blockage effects, it may cause relaxation of the lower esophageal sphincter and lead to an increase in heartburn symptoms for some patients. An enteric-coated capsule is available for use in the treatment of IBS. With its delayed release in the small intestine, peppermint has little effect on the lower esophageal sphincter; therefore, it is less likely to cause heartburn.

Dosage

Tea: 1 to 2 teaspoons dried leaves steeped in 8 oz of hot water as needed
Enteric-coated capsules (200 mg or 0.2 mL):
Two capsules three times a day for children weighing more than 100 lb
One capsule three times a day for children weighing 60 to 100 lb

Precaution

Peppermint is generally regarded as safe; however, hypersensitivity reactions have been reported.

Because of its smooth muscle–relaxing properties, peppermint has its greatest effect on pain related to abdominal spasm.

Ginger (Zingiber officinale)

Ginger contains many volatile oils (sesquesterpenes) and aromatic ketones (gingerols). Gingerols are believed to be the more pharmacologically active constituents. Historically, ginger has been used as far back as the fourth century BC for stomach aches, nausea, and diarrhea. It also has been used as a carminative, appetite stimulant, and choleretic. Ginger can simultaneously improve gastric motility and

exert antispasmodic effects.[30] Studies have shown that ginger's antispasmodic effects on the visceral smooth muscle are likely the result of antagonism of serotonin receptor sites. One study, with a double-blind randomized crossover design, found that the use of ginger brought about a significant reduction of nausea and vomiting in women with hyperemesis gravidarum.[31] Because of its safety profile, ginger is regularly used in pregnancy, with no untoward fetal effects.

Dosage

Adults weighing approximately 150 lb: 1 to 2 g dry powdered ginger root per day (10 g fresh)
Children weighing approximately 75 lb: 0.5 to 1 g dry powdered ginger root per day (5 g fresh)
Children weighing approximately 35 lb: 0.25 to 0.5 g dry powdered ginger root per day (2.5 g fresh)

Ginger can improve gastric motility while also exerting an antispasmodic effect. The pharmacist can dissolve ginger capsules in an 8.4% bicarbonate suspension with good stability and bioavailability for use in children unable to swallow pills.

A one-fourth inch slice of fresh ginger root is approximately 10 g. This is equivalent to 1 to 2 g of a dry powder form of ginger that is a more concentrated form found in capsules. Fresh ginger can be brewed as a tea sweetened with honey or can be chopped and added to foods, soups, or salads.

Precautions

Ginger is well tolerated when used in typical doses. At higher doses, side effects may include heartburn, abdominal discomfort, or diarrhea. Ginger may have antiplatelet effects and therefore may increase the risk of bleeding in some people.

A general rule of thumb for estimating the amount of fresh ginger to use in children is to use the child's "pinky" finger (fifth finger) as the guide to the size of ginger to chop up and steep for tea.

Slippery Elm (Ulmus fulva)

Slippery elm has demulcent properties that can be used to protect the gastrointestinal tract from irritation. When used internally, slippery elm causes reflex stimulation of the nerve endings in the gastrointestinal tract that produces mucus secretion.[32] This effect may be particularly helpful in children with functional dyspepsia.

Dosage

A tea can be made with 1 cup boiling water and 1 tablespoon of powdered bark. Use 2 to 5 mL three times a day.

Precautions

No contraindications are associated with slippery elm. Spontaneous abortions have been reported with its use; therefore, it should not be used during pregnancy.

Lemon Balm (Melissa officinalis)

Lemon balm contains volatile oils and constituents that relax muscles, particularly in the bladder, stomach, and uterus, and thereby relieve cramps, gas, and nausea. This herb is generally regarded as safe and is one of the components of the product Iberogast, used widely for gastrointestinal problems. A meta-analysis of the double-blind randomized controlled trials conducted on Iberogast found significant improvements compared with placebo in patients with functional dyspepsia.[33]

Dosage

Capsules: 100 to 200 mg dried lemon balm three times daily or as needed
Tea: 0.5 to 1.5 g (¼ to 1 teaspoon) of dried lemon balm herb in hot water. Steep and drink up to four times daily.
Tincture: 0.5 to 1 mL (15 to 30 drops) three times daily

Precautions

Although no scientific evidence supports this, lemon balm may interact with sedatives and thyroid medications.

Supplements

Probiotics

The human intestinal tract is populated with various microbial species that are nonpathogenic and necessary for normal digestive functioning. The microorganisms, or probiotics, are now recognized as a way to fight disease and improve health. Studies in children showed a significant reduction of diarrhea symptoms, both from rotavirus infection and from antibiotic use, when these children were given probiotics.[34,35] Probiotics increase the number of rotavirus-specific IgA secreting cells and serum IgA levels. Probiotics are thought to be possibly helpful in treating RAP by degrading dietary antigens, restoring normal intestinal permeability, and alleviating intestinal inflammation that can trigger pain.[36] Two double-blind randomized placebo-controlled trials found that *Lactobacillus* GG reduced the frequency and intensity of pain in children with RAP/IBS when this probiotic was given over the course of 4 to 8 weeks.[37,38] One of these studies also demonstrated a decrease in the number of patients with abnormal intestinal permeability testing after treatment with *Lactobacillus* GG, but not with placebo.

Dosage

Use 10 to 100 billion colony-forming units (CFUs) per serving once or twice a day. These preparations can be of a single strain, such as *Lactobacillus* GG, or made of multiple strains such as *Bifidobacterium bifidus, Lactobacillus acidophilus,* or *Lactobacillus reuteri,* to treat both the small and the large intestine.

Precautions

Probiotics are considered safe for use. *Lactobacillus* sepsis associated with probiotic therapy was reported, but this adverse effect occurred in children who were considered immunocompromised and at high risk because of central line placement.

Pharmaceuticals

Despite a lack of controlled studies with established efficacy for many drugs used in functional bowel disorders,[39,40] these agents continue to be prescribed. For this reason, as well as

worrisome side effects (for metoclopramide, irritability and dystonic reactions; for cisapride, arrhythmia and adverse outcomes in prolonged QT syndrome; for anticholinergics, constipation, blurred vision, tachycardia, and sedation; for tricyclic antidepressants, sedation, agitation, acute mental disturbance, and reduction in seizure threshold), these particular drugs cannot be safely recommended for use in children.

Histamine-2 (H_2) Receptor Antagonists and Proton Pump Inhibitors

For patients with dyspepsia as their primary symptom, histamine-2 (H_2) receptor antagonists and proton pump inhibitors can be used if other strategies are unsuccessful. Studies in children supporting such therapy are few, but these drugs may be beneficial and are relatively safe in the short term (6 to 8 weeks).[41]

Dosage

Cimetidine (Tagamet): 10 mg/kg/dose given four times daily; comes in 100-mg over-the-counter (OTC), 200-, 300-, 400-, and 800-mg tablets and 300-mg/5-mL suspension by prescription

Ranitidine (Zantac): 2 to 4 mg/kg/dose given twice daily; comes in 75-mg OTC, 150-, and 300-mg tablets, 150-mg granules, and 75-mg/5-mL suspension

Famotidine (Pepcid): 0.5 to 3.5 mg/kg/day divided two times a day; comes in 10-mg OTC, 20-, or 40-mg tablets and 40-mg/5-mL suspension

Omeprazole (Prilosec): 0.2 to 3.5 mg/kg/day daily or divided twice a day; comes in 10-, 20-, and 40-mg capsules

Lansoprazole (Prevacid): 1 to 2 mg/kg/day given daily; comes in 15- and 30-mg capsules

Precautions

Headaches, diarrhea, abdominal pain, and elevated liver function tests have been reported.

> Prolonged acid suppression can lead to malabsorption of key nutrients including vitamin B_{12}, iron, and calcium.

Cyproheptadine

This drug (also known by the brand name, Periactin), which has antihistamine effects, was studied through a double-blind randomized controlled trial conducted over 2 weeks in 29 children. The intensity and frequency of abdominal pain reported by the children were significantly improved in the treatment group compared with the control group.[42] This medication has historically been used as prophylactic treatment for migraine because of its effects on serotonin and histamine. These effects may have some benefit in children with abdominal migraines over a short period, although more studies need to be done.

Dosage

Children 7 to 14 years of age: 4 mg two or three times daily (maximum, 16 mg/day)

Children 2 to 6 years of age: 2 mg two or three times daily (maximum, 12 mg/day)

Precautions

The main side effects have been increased appetite and weight gain. Sedation and sleepiness have also been reported.

Biomechanical Therapy

Massage

Massage can ease pain by calming sympathetic arousal often found in children with RAP. With decreased sympathetic drive comes an improvement in gastrointestinal motility. Massage, either of the abdomen directly or indirectly by reflexology, is helpful in alleviating ileus and constipation and overall can be very comforting.[43]

Osteopathic Manipulative Therapy

Understanding somatovisceral pathways has led to the treatment of RAP with osteopathic manipulative therapy. Trigger points along the spine and in the large muscles of the back and trunk (e.g., external and internal oblique, rectus abdominis, iliocostalis thoracis and lumborum muscles) can cause referred pain to the abdominal region that mimics visceral disease. Release of these trigger points through manipulation decreases this reflex effect and therefore lessens the pain.[44]

Surgery

Exploratory surgery is not warranted unless strong indications are revealed through the history, physical examination, and laboratory investigations.

Bioenergetic Therapy

Traditional Chinese Medicine and Acupuncture

The philosophy of traditional Chinese medicine is that of restoring balance to the body through its flow of energy. Although large clinical trials have not been conducted using traditional Chinese medicine and acupuncture in children with RAP, one study measured the effects of hand acupuncture in reducing intermittent abdominal pain in 40 children. Pain intensity and medication use were considerably lower in the treatment group.[45] In a randomized double-blind placebo-controlled study using Chinese herbs, patients receiving herbs noted significant improvement in bowel symptoms, global well-being, and return to normal life activities compared with the group receiving placebo.[46] Although children may be fearful of needles, when acupuncture is performed by an experienced professional, many children have reported that it does not hurt. Acupressure or electroacupuncture may also be used as alternatives to needles.

Reiki and Healing Touch

Like traditional Chinese medicine, Reiki and healing touch are based on the concept of restoring normal energy flow through the body. In patients with disease or pain, this energy may be blocked or stagnant, thus disrupting its normal flow. Through energy work, this energy flow can be restored. Many randomized controlled studies have suggested that energy healing can be effective for pain, anxiety, depression, wound healing, and other problems.[47] Although no specific studies have been conducted in children with RAP, this therapy has no serious side effects and is considered safe (see Chapter 112, Human Energetic Therapies).

Mind-Body Therapy

Because of our knowledge of the brain-gut axis and the associated interactions, it is only logical that mind-body therapy be used in RAP. Studies published primarily in psychiatric journals supported the efficacy of interventions that teach stress management, progressive muscle relaxation, or coping behaviors or use cognitive-behavioral therapy.[48,49] One study showed that significant pain reduction occurred when biofeedback, cognitive-behavioral therapy, or parental support was added to fiber therapy in the multimodal treatment of RAP.[50]

Progressive Muscle Relaxation and Breathing Exercises

Both progressive muscle relaxation and breathing exercises, used alone or together, are forms of self-regulation that help decrease sympathetic arousal to promote comfort. Progressive muscle relaxation is a way for children to learn to feel the difference between tense and relaxed muscles and to use this knowledge to cope with abdominal pain. Progressive relaxation reduces anxiety associated with pain by demonstrating the mind-body phenomenon and patients' capacity for self-regulation. The benefits of these approaches are that they are easily taught, especially to school-age children, and they can be used anywhere. Scripts can be given to parents to use, or a tape can be made or purchased for home use (see Chapter 92, Self-Hypnosis Techniques and Chapter 93, Relaxation Techniques).

Biofeedback

Biofeedback is a form of relaxation using physiologic feedback instruments to reinforce behavior. As relaxation occurs, warmth can be brought to the fingertips, thus increasing the distal temperature. This temperature can be monitored by sensors placed on the fingers and can reinforce the positive behavior of relaxation as the temperature rises. Biofeedback may be beneficial for a person who is somewhat skeptical about the ability to control body functions with the mind. Someone trained in biofeedback who has the equipment readily available can best teach this modality.

In a study using heart rate variability biofeedback, children with functional abdominal pain were able to reduce their symptoms significantly in relation to increasing their autonomic balance, also significantly. The investigators believed that change in vagal tone was the potential mediator for this improvement.[51]

Hypnosis and Guided Imagery

With hypnosis and guided imagery, one achieves a state of focused attention in which the mind is more receptive to suggestion. The technique has been used successfully for all types of pain syndromes including RAP and is easily used in children older than 4 years of age (see Chapter 93, Self-Hypnosis Techniques, and Chapter 95, Guided Imagery).[52,53]

A randomized controlled trial on the use of therapist-directed guided imagery with progressive muscle relaxation found a significant decrease in the number of days with pain and missed activities compared with controls.[54] A similar study using audio-recorded guided imagery treatment also found benefit, with treatment effects maintained for over 6 months.[55] Gut-directed hypnosis therapy was found to be superior to standard medical therapy in reducing pain scores in children with long-standing abdominal pain in yet another randomized controlled trial.[56]

Psychotherapy

In children or families with significant psychosocial dysfunction, counseling by a child psychiatrist or clinical psychologist may be the best therapy. Cognitive-behavioral family intervention therapy, which often includes teaching specific coping skills, social skills, and relaxation, has been shown to be efficacious in studies of children with RAP.[57,58]

Prevention Prescription

- Encourage liberal amounts of water and fiber, in the form of natural fruits and vegetables, to promote daily bowel movements.
- Promote probiotics if the patient has a history of antibiotic, steroid, or nonsteroidal antiinflammatory drug use.
- Ask the patient to practice breathing and relaxation exercises or other self-regulation techniques to reduce stress.
- Encourage healthy sleep habits to promote restorative sleep.
- Consider avoiding high amounts of processed foods and simple sugars including sorbitol.
- Encourage regular movement and exercise.

Therapeutic Review

Once a child has been thoroughly evaluated and organic disease has been ruled out, any of these therapies can be used in an age-appropriate manner.

Nutrition

- Avoid foods that have sorbitol and high-fructose corn syrup or are a source of refined carbohydrate because these are poorly digested.
- Prescribe a 2- to 4-wk trial of cessation of all dairy products if the history suggests lactose intolerance (see Chapter 84, Food Intolerance and Elimination Diet).
- Increase fiber by at least 10 g/day through the addition of fruits, vegetables, legumes, and whole grains or with psyllium, 1 teaspoon/8 oz cool water once to three times daily.
- Increase water intake along with the increase of fiber.

Behavior Modification

- Encourage attendance at school and other usual activities.
- Offer strategies to overcome the reinforcement of illness behavior at school and at home.
- Improve restorative sleep.

Botanicals

- Chamomile 
  - 3 g three to five times/day (150-lb patient)
  - 1.5 g three to five times/day (75-lb patient)
  - 0.75 g three to five times/day (35-lb patient)
- Peppermint tea 
  - 1 to 2 teaspoons dried leaves/8 oz hot water as needed
  - Enteric-coated capsules (200 mg)
  - Two capsules three times/day (approximately 100-lb patient)
  - One capsule three times/day (60- to 99-lb patient)
- Ginger 
  - 10 g fresh (or 1 to 2 g dry powdered)/day (150-lb patient)
  - 5 g fresh (or 0.5 to 1 g dry powdered)/day (75-lb patient)
  - 2.5 g fresh (or 0.25 to 0.5 g dry powdered)/day (35-lb patient)
- Slippery elm 
  - Make tea with 1 cup boiling water and 1 tablespoon powdered bark. Give 2 to 5 mL three times a day
- Lemon balm 
  - 100- to 200-mg capsules three times/day
  - 0.5 to 1.5 g tea three times/day
  - 0.5 to 1 mL (15 to 30 drops) tincture three times/day

Supplements

- Probiotics: 10 to 100 billion CFUs once or twice/day 

Pharmaceuticals

- Histamine-2 (H_2) receptor antagonists or proton pump inhibitors for maximum of 6 to 8 weeks if dyspepsia is the primary complaint (see text for dosing) 
- Cyproheptadine: 2 to 4 mg two to three times/day for abdominal migraine 

Biomechanical Therapy

- Massage 
- Osteopathic manipulative therapy 

Bioenergetic Therapy

- Traditional Chinese medicine and acupuncture 
- Reiki and healing touch 

Mind-Body Therapies

- Progressive muscle relaxation and breathing exercises (see Chapter 89, Breathing Exercises) 
- Biofeedback 
- Hypnosis and guided imagery (see Chapter 92, Self-Hypnosis Techniques, and Chapter 95, Guided Imagery) 
- Psychotherapy 

KEY WEB RESOURCES

YourChild: http://www.med.umich.edu/yourchild/topics/abpain.htm.

This University of Michigan Web site provides information for parents on abdominal pain in children.

HeartMath: http://www.heartmath.com; StressEraser: http://stresseraser.com; and Wild Divine: http://www.wilddivine.com.

These Web sites offer biofeedback devices that can help stimulate parasympathetic activity toward a reduction in abdominal pain.

Health Journeys: http://www.healthjourneys.com; Kaiser Permanente Healthy Living to Go audio library: https://members.kaiserpermanente.org/redirects/listen/?kp_shortcut_referrer=kp.org/listen; and Guided Imagery: http://www.guidedimageryinc.com/store/children_teens_products.aspx.

These Web sites are resources for guided-imagery recordings.

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Chapter 45

Constipation

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Pathophysiology

Constipation is estimated to affect up to 28% of the population, most commonly older adults, women, and children, and results in more than $6.9 billion in medical costs.[1] The symptom is usually intermittent and self-limiting, although some patients require intervention to achieve resolution. Table 45-1 demonstrates defining criteria for constipation,[2] but in practical clinical terms, the complaint of constipation and even the diagnosis are often made more subjectively. Asking what patients mean by the statement "I am constipated" may be the most important first step to management.[3] Most patients complaining of constipation describe a perception of difficulty with bowel movements or a discomfort related to bowel movements. The most common terms used by young healthy adults to define constipation are straining (52%), hard stools (44%), and the inability to have a bowel movement (34%).

> Routine diagnostic testing is not recommended for patients with no alarm symptoms and no signs of organic disorder.[4]

Functional constipation can most often be classified into three different categories:

1. Normal-transit constipation: Also known as functional constipation, this is the most common type. In functional constipation, stool passes through the colon at a normal rate, and bowel movement frequency is normal.[5] In this group of patients, constipation is likely the result of a perceived difficulty with evacuation or the presence of hard stools.[2]
2. Slow-transit constipation: This type is characterized by prolonged delay of transit of stool through the colon. Patients may complain of abdominal bloating and infrequent bowel movements.[6] The causes are unclear.
3. Pelvic floor dysfunction: These patients have uncoordinated evacuation of stool through the rectum. They are more likely to complain of a feeling of incomplete evacuation, a sense of obstruction, or a need for digital manipulation.[6]

Physicians should keep secondary causes of constipation (the most common being hypothyroidism) in mind, as well as medications that can cause constipation. In one study of more than 20,000 patients, certain drugs were found to have a two- to threefold increased risk of constipation.[7] Although the list of drugs that can cause constipation is quite lengthy, Table 45-2 [7,8] provides some of the most common offenders.

Integrative Therapy

Physical Activity

The generally accepted view is that increasing the amount of physical activity can be a preventive measure of constipation. In fact, a subset of the Nurses' Health Study showed that in more than 62,000 women, physical activity two to six times a week was associated with a 35% decrease in risk of constipation.[9] A previous National Health and Nutrition Examination Survey showed a twofold increased risk of constipation in persons with a low physical activity level. Despite these findings, data in support of exercise as an actual treatment for constipation have not been consistent. Nevertheless, many patients who comply with dietary and exercise recommendations have an improvement in symptoms.[10]

Nutrition

Fiber

Although dietary modification may not always succeed, all constipated patients should be advised initially to increase their dietary fiber intake as the simplest, most physiologic, and cheapest form of treatment.[1] Patients should be encouraged to ingest 20 to 25 g of fiber daily by eating whole grain breads, unrefined cereals, plenty of fruit and vegetables, or flax meal or bran. A careful meta-analysis showed that in 18 of 20 studies stool weight was increased by adequate fiber supplementation, and fecal transit was accelerated.[11,12] Dietary fiber appears to be less effective in severe constipation, especially of the slow-transit variant, in evacuation disorders, (fiber may actually worsen these two types), or

TABLE 45-1. Rome II Criteria for Functional Constipation

Adults*

- Two or more of the following six must be present:
  - Straining during at least 25% of defecations
  - Lumpy or hard stools in at least 25% of defecations
  - Sensation of incomplete evacuation for at least 25% of defecations
  - Sensation of anorectal obstruction/blockage for at least 25% of defecations
  - Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  - Fewer than three defecations/wk

Infants and Children

- Pebble-like, hard stools for a majority of stools for at least 2 consecutive wk
- Firm stools up to twice/wk for at least 2 wk
- No evidence of structural, endocrine, or metabolic disease

From Lembo A, Camilleri M. Chronic constipation. *N Engl J Med.* 2003;349:1360–1368.
*Loose stools are rarely present without the use of laxatives; criteria for irritable bowel syndrome are not fulfilled.

TABLE 45-2. Medications Associated With Constipation

- Aluminum-containing antacids
- Diuretics
- Antidepressants
- Antihistamines
- Anticholinergics
- Nonsteroidal antiinflammatory agents
- Iron supplements
- Opioids
- Anticonvulsants
- Calcium channel blockers
- Beta blockers

in constipation secondary to medications.[13–15] In one study, women who engaged in regular physical exercise and who had a higher fiber intake (approximately 20 g/day) had a threefold lower prevalence of constipation compared with women who rarely exercised and had approximately 7 g of fiber a day.[9] If ensuring proper intake of fiber is difficult, a commercially packaged fiber supplement may also be used (discussed later under Supplements).

Increasing fiber intake too quickly can cause abdominal bloating or flatulence. To optimize compliance, increase fiber gradually over at least 2 to 3 weeks to 20 to 25 g/day and ensure increased fluid intake to avoid these symptoms.
An example of a 20-g fiber breakfast: ½ cup bran (10 g), three dried figs (10 g). Make palatable with 1 cup soy or almond milk (1 g fiber), 1 tablespoon brown sugar for taste, and 1 tablespoon of cinnamon (slows absorption of sugar).
Other high-fiber foods: 1 large apple or pear (5 g), ½ cup raspberries (9 g), 1 cup Raisin Bran (5 g), 2 Brazil nuts (2.5 g), 23 almonds (3.5 g), 1 cup peas (16 g), 1 cup black beans (15 g), 1 artichoke (10 g), 1 cup cooked broccoli (5 g)

In pediatric populations, decreased fiber intake has also been found to be a risk factor for chronic constipation.[16] One safe and effective dietary fiber recommendation for many children is the *age + 5 = daily grams of fiber* guideline.[17] According to this guideline, the amount of dietary fiber recommended daily is the sum of the child's year in age plus five.

In pregnant women, fiber supplements in the form of bran and wheat fiber were found to increase bowel frequency, soften stool, and be better tolerated than were stimulant laxatives.[18]

Food Triggers

A large body of evidence indicates that cow's milk and dairy products may be risk factors for chronic constipation in some children.[19–21]

Evidence supports a 4- to 6-week trial of elimination of dairy products as a component of the integrative treatment of childhood constipation.

Fluids

Although the generally accepted belief is to increase fluids both as a preventive measure and as treatment for constipation, supporting data are conflicting.[22] One study did show that increasing fluids with an increased fiber intake (25 g/day) led to greater stool frequency and decreased laxative use compared with increased fiber alone.[23] To date, no child studies have demonstrated the benefits of increasing fluid intake in states other than severe dehydration.[24] However, carbohydrates and especially sorbitol, found in some juices such as prune, pear, and apple, can cause increased frequency and water content of stools.[25]

Supplements

Commercially Packaged Fiber Supplements

These supplements include psyllium, methylcellulose, and polycarbophil and are bulking laxatives. More information, including dosing, is available in Table 45-3 and is provided later under Pharmaceuticals. Psyllium is an efficacious method to increase stool frequency and weight and improve stool consistency in idiopathic constipation.[26]

One double-blind multicenter study showed psyllium (5.1 g twice daily) to be superior to docusate sodium (100 mg twice daily) for softening stools by increasing stool water content and to have greater overall laxative efficacy in subjects with chronic idiopathic constipation.[27]

Probiotics

Lactobacillus reuteri, administered at a dose of 10^8 colony-forming units to infants older than 6 months of age, was found to increase bowel frequency.[28] A high-grade systematic review showed that use of probiotics in adults and children augmented the number of stools and reduced the number of hard stools.[29] These results were statistically significant but clinically only

TABLE 45-3. Agents for Treatment of Constipation in Adults

TYPE	GENERIC NAME	DOSAGE	ACG GRADE	COMMENTS
Bulking Laxatives				
	Psyllium (Metamucil)	Titrate up to 30 g/day in divided doses	B	Taken from the ground seed husk of the ispaghula plant; needs to be taken with plenty of water to avoid intestinal obstruction; undergoes bacterial degradation that may contribute to side effects of bloating and flatus; allergic reactions, such as anaphylaxis and asthma, reported but are rare
	Methylcellulose (Citrucel)	Titrate up to 6 g/day in divided doses	B	Semisynthetic cellulose fiber relatively resistant to colonic bacterial degradation; tends to cause less bloating and flatus than psyllium
	Polycarbophil (FiberCon)	Titrate up to 4 g/day in divided doses	B	Synthetic polymer of acrylic acid that is resistant to bacterial degradation
Osmotic Laxatives				
	Magnesium hydroxide (Milk of Magnesia)	30–60 mL/day	B	Small percentage actively absorbed in the small intestine; remainder draws water into the intestines along an osmotic gradient
	Polyethylene glycol (MiraLax)	17–34 g once to twice/day	A	Organic polymer that is poorly absorbed and not metabolized by colonic bacteria
	Lactulose	15–30 mL once to twice/day	A	Synthetic disaccharide consisting of galactose and fructose linked by a bond resistant to lactase and therefore not absorbed by the small intestine; undergoes bacterial fermentation in the colon resulting in formation of short-chain fatty acids; bacteria in the colon can metabolize up to 80 g of lactulose each day; gas and bloating common side effects
Stimulant Laxatives				
Anthraquinones	Sennosides (senna)	8.6–30 mg once to twice/day	B	Anthraquinones converted by colonic bacteria to their active form, which increases electrolyte transport into the bowel and stimulates intestinal motility; may cause melanosis coli, a benign condition usually reversible within 12 months; no definitive association established between anthraquinones and colon cancer or myenteric nerve damage
Diphenylmethane derivatives	Bisacodyl (Dulcolax)	10–15 mg/day orally 10-mg rectal suppository/day	B	Hydrolyzed by endogenous esterases; stimulates secretion and motility of small intestine and colon
Stool Softeners				
	Docusate sodium	50–100 mg once to twice/day	B	Ionic detergents that soften the stool by allowing water to interact more effectively with solid stool; may have modest effects on fluid absorption and secretion; efficacy in constipation not well established
	Docusate calcium	5–45 mL orally nightly	B	Alters stool by being emulsified into the stool mass and providing lubrication for passage of the stool; long-term use can cause malabsorption of fat-soluble vitamins, anal seepage, and lipoid pneumonia in patients predisposed to aspiration of liquids
Emollients				
	Mineral oil	5–45 mL orally nightly	B	Alters stool by being emulsified into the stool mass and providing lubrication for passage of the stool; long-term use can cause malabsorption of fat-soluble vitamins, anal seepage, and lipoid pneumonia in patients predisposed to aspiration of liquids

TABLE 45-3. Agents for Treatment of Constipation in Adults—cont'd

TYPE	GENERIC NAME	DOSAGE	ACG GRADE	COMMENTS
Chloride Channel Activator				
	Lubiprostone	8 mcg twice/day for IBS-C; 24 mcg twice/day for chronic constipation	Not graded	Activates ClC-2s in the intestine and causes fluid secretion and possible secondary effects on motility; nausea common; administer with food and water; approved for use in adults with chronic constipation and in women older than 18yr old with IBS-C

From Eoff JC III, Lembo A. Optimal treatment of chronic constipation in managed care: review and roundtable discussion. *J Manag Care Pharm.* 2008;14(suppl A):1–15.
ACG, American College of Gastroenterology; bid, twice daily; ClC-2, type-2 chloride channel; IBS-C, irritable bowel syndrome with constipation; PEG, polyethylene glycol; po, by mouth; qd, every day; qhs, every night.

modest. The most thoroughly studied strains are *Bifidobacterium* and *Lactobacillus* (most specifically *Lactobacillus casei Shirota*). Probiotics may be useful to relieve constipation, but the effect may depend on the probiotic dose, the bacterial strain used, and the population studied.[12] More investigation is needed to evaluate specific recommendations on dosing and strain type (see Chapter 102, Prescribing Probiotics).

Mind-Body Therapy

Behavioral Training in Childhood Constipation

Education for parents and children is an important component of treatment of functional constipation.[30] The child's fear of a painful bowel movement is the most common motivating factor for fecal retention.

In childhood constipation, explain the physiologic changes that occur as a consequence of chronic constipation, including a diminished ability to recognize the need to stool or that soiling has occurred.[31] Explain that this condition is common and is multifactorial in origin for most children and stress the need to avoid demeaning or embarrassing the child.

Biofeedback

In an instrument-based training program, patients receive auditory or visual feedback, or both, to help train the pelvic floor and relax the anal sphincter while simulating defecation. Biofeedback also improves rectal sensation to assist in proper evacuation.[10] Biofeedback is the preferred treatment for pelvic floor dysfunction, in which it has a success rate of 70% to 81% and is superior to standard treatment (laxatives, fiber, and education).[32–34] Randomized controlled trials (RCTs) showed that five biofeedback sessions are more effective than continuous polyethylene glycol (PEG) administration for treating pelvic floor dysfunction, and benefits last at least 2 years.[35] Although biofeedback is not an effective treatment for slow-transit constipation, it should be considered first-line treatment for pelvic floor dysfunction.

Hypnotherapy

Substantial evidence supports the use of hypnotherapy in constipation-dependent irritable bowel syndrome, which has considerable overlap with functional constipation.[36] No specific data exist on hypnotherapy for the treatment of functional constipation, however. Until more evidence is available, it may at times be reasonable to try this noninvasive treatment, especially in patients who have difficulty relaxing the pelvic musculature.

Botanicals

Aloe

Dried latex (aloe latex) from the lining of the inner leaf has been used historically for laxative use. One double-blind RCT of an herbal preparation of aloe, psyllium, and celandin showed a statistically significant advantage of the herbal preparation over placebo.[37] Which part of the preparation was most responsible for the effect was unclear, however, and this preparation is not available in the United States.[37] The anthraquinones in aloe act as a stimulant laxative. A typical dose of aloe is 50 mg aloe extract taken at bedtime.

Traditional Chinese Medicine

Although numerous RCTs have reviewed the approaches of various components of traditional Chinese medicine to constipation, high-level systematic reviews showed that methodologic flaws limit their interpretation.[38–40] Further research is needed to support the potential use of these components: Chinese herbs, moxibustion, and auriculotherapy.

Abdominal Massage

Some evidence indicates that abdominal massage may be a helpful technique in the treatment of constipation. One small 8-week RCT demonstrated an increase in bowel movement frequency but no decrease in laxative use.[41] The study investigators concluded that this approach could be an adjunctive therapy to the treatment of constipation, but because of its delayed effect, which may first be noted after several weeks, abdominal massage is considered a long-term treatment.

Pharmaceuticals

A wide array of laxatives is available to patients. The clinician must understand how to counsel patients on the appropriate use, risks, and optimal dosing of these agents. Dosing and further information on all agents for adults are provided in Table 45-3,[42] and similar information for children is given in Table 45-4.[43]

TABLE 45-4. Agents for Treatment of Constipation in Children

TYPE OF MEDICATION	SELECTED MEDICATIONS	RECOMMENDED DOSAGE FOR MAINTENANCE THERAPY
Bulk-forming laxatives (OTC)	Methylcellulose (Citrucel) powder	Older than 6 yr: 1–1.5 g/dose Older than 12 yr: 4–6 g/dose
Dietary fiber (OTC) supplement (no systemic absorption)	Psyllium (Metamucil, Perdiem, Serutan, Fiberall, Konsyl)	6–11 yr: ½–1 rounded teaspoon in 8 oz liquid one to three times/day Older than 12 yr: 1–2 rounded teaspoons or one to two packets or one to two wafers one to four times/day or five capsules up to three times/day taken with 8 oz liquid
Osmotic laxative (OTC)	Magnesium hydroxide (Milk of Magnesia [MOM]); liquid, tablets	Younger than 2 yr: 0.5 mL/kg/day 2–5 yr: 5–15 mL/day or in divided doses one to two tablets before bedtime 6–12 yr: 15–30 mL/day in divided doses or three to four tablets before bedtime Older than 12 yr: 30–60 mL/day or in divided doses six to eight tablets before bedtime
	Magnesium citrate	Younger than 6 yr: 2–4 mL/kg/day 6–12 yr: 100–150 mL/day Older than 12 yr: 150–300 mL/day, in single or divided doses
	Magnesium citrate	Used only for bowel cleanout
Lubricants	Mineral oil (OTC)	5–11 yr: 5–20 mL every day or in divided doses Older than 12 yr: 15–45 mL/day every day or in divided doses or 1–4 mL/kg/day
Fiber supplement (OTC); powder, chewable tablets, caplets	Benefiber (partially hydrolyzed guar gum): 2 teaspoon = 3 g soluble fiber	7–11 yr: ½–1 tablespoon one to three times/day 12 yr–adult: 1–2 tablespoon one to three times/day
Stool softeners (emollients)	Docusate (Colace); liquid, capsule, gel cap (OTC)	Infants and children younger than 3 yr: 10–40 mg/day in one to four divided doses 3–6 yr: 20–60 mg/day in one to four divided doses 6–12 yr: 40–150 mg/day in one to four divided doses Older than 12 yr: 50–400 mg/day in one to four divided doses
Stimulants	Senna (Senokot, Senna-Gen, Senolax, Ex-Lax); granules, syrup, tablets (OTC)	1–5 yr: 5–10 mL/day 5–15 yr: 10–20 mL/day One tablet = 3 mL/granules = 5 mL/syrup
Osmotic enema	Phosphate enema (OTC)	Younger than 2 yr: not recommended 2–11 yr: 2.25-oz pediatric enema Older than 11 yr: 4.5-oz adult enema
Osmotic laxative	MiraLax (polyethylene glycol); GlycoLax	12 yr or older: 17 g (up to measuring line on cap) in 8 oz of water Older than 2–11 yr: 8.5 g (halfway to measuring line on cap) in 4 oz of water
Stimulant laxative	Bisacodyl (Dulcolax) Dulcolax: 5-mg tablet, 10-mg suppository	Older than 2 yr: one half to one suppository or one to three tablets per dose; no liquid form Adolescents: four tablets maximum
Miscellaneous	Glycerin suppository	Children: one infant suppository one to two times/day Children >6 yr: one adult suppository
	Glycerin enema; Enemeez Mini Enema (ingredients: docusate, polyethylene glycol, glycerin)	5–10 mL glycerin in 500 mL normal saline solution 5-mL tubes: one enema/day
Osmotic laxative	Lactulose (Cephulac, Cholac, Chronulac, Constilac, Duphalac, Enulose, Lactulox); crystals, syrup	Infants: 2.5–10 mL/day individual doses Children: 0.6–0.6 mL/kg/dose three to four times/day or 40–90 mL/day in divided doses or 1–3 mL/kg/day in divided doses (maximum, 3 oz/day) Adults: 15–30 mL/day (maximum, 60 mL/day)
	Sorbitol	1–3 mL/kg/day in divided doses, 70% solution

From Tobias N, Mason D, Lutkenhoff M, et al. Management principles of organic causes of childhood constipation. *J Pediatr Health Care*. 2008;22:12-23; with data from Guandalini S, 2005; *Mosby's Pediatric Drug Consult.* St. Louis: Mosby; 2006; and Pediatric Lexi-Drugs Online. http://lexi.com; 2006 available to subscribers.
OTC, Over the counter.

Bulk-forming Laxatives

Bulk-forming laxatives work naturally to add bulk and water to stools so that stools can pass more easily through the intestines. These laxatives are safe to take every day and include oat bran, psyllium (e.g., Metamucil), polycarbophil (e.g., FiberCon), and methylcellulose (e.g., Citrucel). They are most useful in patients with normal-transit constipation, and one study showed that 80% of this subgroup had resolution of symptoms compared with 35% in the other subgroups.[13]

Stimulant Laxatives

Stimulant laxatives work by stimulating intestinal motility and secretion of water into the bowel. They generally take 6 to 12 hours to take effect, and they may cause abdominal cramping and diarrhea.[5] Products in this class include senna and bisacodyl. Given the poor quality of study design, the lack of placebo-controlled trials, and inconclusive results, the American College of Gastroenterology Chronic Constipation Task Force stated that data were insufficient to make a recommendation about the efficacy of stimulant laxatives for the management of chronic constipation, and available data suggested minimal benefit with these products.[44] These agents can also cause melanosis coli, they may be habit forming, and they have unknown long-term effects on the colon.

Osmotic Laxatives

Saline or osmotic laxatives are hyperosmolar agents that cause secretion of water into the intestinal lumen by osmotic activity. Some of the most commonly used osmotic laxatives are oral magnesium hydroxide (Milk of Magnesia), oral magnesium citrate, sodium biphosphate (Phospho-Soda), PEG, and lactulose.[5]

Data on the commonly used osmotic laxative, magnesium, are sparse.[45] Despite a lack of evidence, patients and physicians find magnesium helpful and use it routinely.[46]

Using magnesium citrate, 150-mg capsules, to help with constipation: Start with two capsules at bedtime and two in the morning. If no stool occurs the next morning after 4 days, add one capsule (three) at bedtime. Add one capsule to the evening dose every 4 days until a soft stool is produced each morning. One of the first side effects of magnesium is diarrhea. This helps prevent toxicity from taking too much magnesium. Stop at eight capsules (total: six at bedtime and two in the morning). Use magnesium-containing laxatives cautiously in patients with congestive heart failure and chronic renal insufficiency because of the potential for electrolyte imbalances.

PEG is superior to lactulose in terms of stool frequency per week, form of stool, relief of abdominal pain, and the need for additional products, both in children and adults.[47] Evidence is sufficient to support PEG as first-line laxative treatment in children, both for efficacy and for palatability.[48]

Stool Softeners

These agents, which include docusate sodium, act by lowering surface tension, thus allowing water to enter the bowel more readily. Although stool softeners are generally well tolerated, their efficacy remains in question.[49]

Emollient Laxatives

Mineral oil, the most common example in this category, works by coating and softening the stool. Scant evidence supports the use of mineral oil, which also may lead to depletion of fat-soluble vitamins and runs the risk of aspiration in older adults and children.[50]

Chloride Channel Activators

Lubiprostone is the first agent in this class that has been approved by the Food and Drug Administration for treatment of chronic constipation. This agent works through chloride channels to increase intestinal fluid secretion. Because nausea is the most common complaint, lubiprostone should be taken orally with food and should be avoided in pregnant women and children. Its safety has been studied for up to 48 weeks of use.

Prevention Prescription

- Eat high amounts of fiber-rich foods, including beans, vegetables, fruits, whole grain cereals, and bran.
- Minimize high-fat, low-fiber foods such as processed foods, dairy products, and meat products.
- Drink an adequate amount of fluid each day to stay hydrated, and increase the amount of water if using higher doses of fiber.
- Engage in regular physical activity to avoid constipation.
- Adopt a good self-care and stress management program to avoid the impact of stress on gut function.
- Stay tuned to the body's natural signals to pass stool.
- Take advantage of the gastrocolic reflex and allow elimination to occur after meals.
- In young children, ensure adequate fiber as they transition to solid foods.

Therapeutic Review

In this summary of therapeutic options for the treatment of constipation, the interventions are presented in a ladder approach from the least to the most invasive options. Although patients with more moderate to severe constipation may travel up the ladder more quickly, the initial approaches are critical for all patients.

Adults

- Removal of exacerbating factors
  - Review the patient's medication list, and eliminate any medications that may be causing or exacerbating the condition.
- Behavioral training
  - If patients experience difficulty in expulsion of stool, they should be advised to place a support approximately 6 inches in height under their feet when they are sitting on a toilet seat, to flex the hips toward a squatting posture.
- Nutrition
  - Include a *gradually* increasing amount of fiber in the diet up to 20 to 25 g a day through fruits, vegetables, whole grain breads and unrefined cereals, flax, or bran. A1
  - Encourage increased fluid intake, especially with the introduction of increased fiber in the diet. C1
- Movement
  - Encourage regular physical activity. B1
- Supplements
  - Consider adding a commercially packaged fiber supplement such as psyllium (Metamucil) or methylcellulose (Citrucel). Be sure to take it with at least 8 to 12 oz of liquid. Using less fluid can worsen constipation (see Table 45-3). B1
- Consider a probiotic strain of *Bifidobacterium* or *Lactobacillus* of at least 10^8 colony-forming units. C1
- Mind-body therapy
  - Address stress management skills.
- Biofeedback
  - In cases of pelvic floor dysfunction, this is a critical component of therapy. B1
- Pharmaceuticals
  - If the foregoing interventions do not resolve symptoms, consider osmotic laxatives with polyethylene glycol (17 to 34 g once or twice daily) as first-line therapy. A2
  - For severe cases, a prescription chloride channel activator (lubiprostone, 8 to 24 mcg twice daily for adults) may be necessary. B2

Children

- Behavioral training
  - Encourage daily sitting on the toilet, preferably after meals, and avoid embarrassing or punishing the child. Using a stool under the feet can also be used for children during toilet training.
- Removal of exacerbating factors
  - Consider a 4- to 6-week trial of elimination of dairy products. B1
- Nutrition
  - Ensure an adequate amount of fiber in the diet. Use the *age + 5 = daily grams of fiber* rule as a general guideline for dosing. B1
  - Increase fluid intake and, in particular, the amount of sorbitol-containing fruit juices (e.g., apple, pear) for osmotic effect. B1
- Movement
  - Encourage regular physical activity. B1
- Supplements
  - Consider adding a commercially packaged fiber supplement if necessary. B1
  - Consider a probiotic strain of *Bifidobacterium* or *Lactobacillus* of at least 10^8 colony-forming units. C1
- Pharmaceuticals
  - If these interventions do not resolve symptoms, consider osmotic laxatives with polyethylene glycol (0.5 to 4 teaspoons a day, depending on age) as first-line medical treatment (see Table 45-4). A2

KEY WEB RESOURCES

The American College of Gastroenterology: http://www.acg.gi.org/
Patient Handout on Constipation: http://www.acg.gi.org/patients/pdfs/CommonGIProblems2.pdf
Mayo Clinic patient information on constipation in children: http://www.mayoclinic.com/health/constipation-in-children/DS01138
American Dietetic Association handout for Nutrition Therapy for Constipation: http://nutritioncaremanual.org/vault/editor/Docs/ConstipationNutritionTherapy_FINAL.pdf

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Chapter 46

Fibromyalgia

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Pathophysiology

Diagnostic criteria for fibromyalgia syndrome (FM) have been reconsidered by Wolfe et al.[1] Chronic widespread pain of at least 3 months' duration remains a hallmark of the disease. However, tender points are no longer relevant. Rather, the number of painful areas reported by the patient in the past week is documented (Widespread Pain Index), and the severity of associated symptoms of fatigue, waking unrefreshed, and cognitive difficulties is assessed and scored (Symptom Severity Scale Score) (Fig. 46-1).[1] The previously noted increased prevalence in women may have been an artifact of using the tender point examination in the diagnostic criteria. When this criterion is eliminated, the difference in prevalence between women and men appears to be reduced.[2] This finding is further supported by previous research showing no impact of the menstrual cycle on symptoms of FM.[3] Increasing evidence supports the hypothesis that the pathophysiology of FM is the result of genetic and biologic factors, environmental triggers, and neurophysiologic abnormalities.[2,4]

Investigators generally agree that the increase in pain sensitivity that is typical of patients with FM is the result of central augmentation of sensory input and diminished central pain inhibitory function.[4,5] Among first-degree relatives of patients with FM, those who do not complain about any pain problems demonstrate increased pain sensitivity compared with healthy controls.[4] Careful history taking often reveals a stressful trigger event or period, such as an accident, a flulike illness, emotional stress, or overwork, preceding the onset of symptoms. Posttraumatic stress disorder often exists as a comorbidity.[6,7] Thus, the role of environment in the pathophysiology of FM cannot be downplayed and may help guide a clinician in creating treatment plans for patients with FM.

Functional magnetic imaging studies provide direct evidence of increased central pain sensitivity. In two similar studies, a nonpainful level of stimulation for control subjects was perceived as painful by patients with FM, and blood flow increased in specific brain areas shown to be associated with pain processing.[5,8]

Autonomic dysfunction is present in patients with FM and likely explains certain patient complaints, including worsening of symptoms with stress.[4] Several neuroendocrine and immune function alterations have been well documented. Cerebrospinal fluid levels of substance P are elevated, and additional abnormalities in the regulation of cortisol and in the adrenergic and serotonin systems have been noted.[9,10] Growth hormone secretion in response to exercise is impaired in patients with FM and appears to be linked to increases in proinflammatory cytokine levels after exercising.[11] The affinity and function of corticosteroid receptors on lymphocytes appear to be altered in FM, which changes the cellular response when lymphocytes are incubated with hormones in the laboratory.[12] Reports have noted decreased numbers of T cells expressing activation markers and a deficiency of interleukin-2 release.[13] Although these immunologic changes in FM do not meet criteria for an immunodeficiency or autoimmune disease, the lymphocyte abnormalities may reflect an altered response to hormone feedback, and altered patterns of cytokine release may contribute to fatigue and inflammatory-type symptoms. Although the foregoing alterations in immune and neuroendocrine function may not play a role in the etiology of FM, they may contribute to sustaining the symptoms.[14]

Alterations in the pituitary-adrenal axis in FM appear to be quite different from those seen in clinical depression; this finding is surprising given the frequent concurrence of the two conditions.[15] That comorbid depression in FM worsens both symptom severity and prognosis for FM sufferers has also become increasingly evident. Patients should be carefully screened for depression, and treatment for the depression should be aggressively pursued for optimum management of FM symptoms.[16]

In our practices, patients with FM often report having sensitive temperaments even before they developed physical symptoms. This quality of temperament is characterized by

FIGURE 46-1
Fibromyalgia clinical diagnostic criteria worksheet. (Data from Wolfe F, Clauw D, Fitzcharles M, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptoms severity. *Arthritis Care Res.* 2010;62:600–610.)

FIBROMYALGIA CLINICAL DIAGNOSTIC CRITERIA

1) Widespread Pain Index (WPI): Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

- ❑ Shoulder girdle, Lt.
- ❑ Shoulder girdle, Rt.
- ❑ Hip (buttock, trochanter), Lt.
- ❑ Hip (buttock, trochanter), Rt.
- ❑ Jaw, Lt.
- ❑ Jaw, Rt.
- ❑ Upper Back
- ❑ Lower Back
- ❑ Upper Arm, Lt.
- ❑ Upper Arm, Rt.
- ❑ Upper Leg, Lt.
- ❑ Upper Leg, Rt.
- ❑ Chest
- ❑ Neck
- ❑ Abdomen
- ❑ Lower Arm, Lt.
- ❑ Lower Arm, Rt
- ❑ Lower Leg, Lt.
- ❑ Lower Leg, Rt.

Total WPI Score from above: __/19

2) Symptoms Severity Score (SS):
For the each of the three symptoms below, indicate the level of severity over the past week using the following scale:

0 = No problem
1 = Slight or mild problems; generally mild or intermittent
2 = Moderate; considerable problems; often present and/or at a moderate level
3 = Severe: pervasive, continuous, life-disturbing problems

Fatigue Score: __/3
Waking Unrefreshed Score: __/3
Cognitive Symptoms Score: __/3
Considering somatic symptoms* in general, indicate whether the patient has:
0 = No symptoms
1 = Few symptoms
2 = A moderate number
3 = A great deal of symptoms
Somatic Symptoms Score: __/3.
Total Symptom Severity Score: __/12 (Total of items under SS)

A patient satisfies clinical diagnostic criteria for fibromyalgia if the following 2 conditions are met:
1) WPU is =>7 and symptom severity score is =>5 OR WPI is between 3–6 and symptom severity score scale =>9.
2) Symptoms have been present for at least 3 months.

*Somatic symptoms for reference purposes: Muscle Pain, Irritable bowel syndrome, Fatigue/Tiredness, Thinking or remembering problem, Muscle Weakness, Headache, Pain/cramps in abdomen, Numbness/Tingling, Dizziness, Insomnia, Depression, Constipation, Pain in upper abdomen, Nausea, Nervousness, Chest pain, Blurred vision, Fever, Diarrhea, Dry mouth, Itching, Wheezing, Raynaud's, Hives/Welts, Ringing in ears, Vomiting, Heartburn, Oral ulcers, Loss/Change in taste, Seizures, Dry eyes, Shortness of breath, Loss of appetite, Rash, Sun sensitivity, Hearing difficulties, Easy bruising, Hair loss, Frequent urination, Painful urination, and Bladder spasms.

high levels of empathy, a tendency to be a caretaker, and a higher than normal sensitivity to environmental factors and emotional cues from others.[17,18] Such sensitivity may prove to be a genetically determined risk factor for FM. Thus, these patients may be the "canaries in the coal mine," by exhibiting FM symptoms not only in response to stressful physical and emotional trigger events but also as a consequence of living in a society that expects high productivity at the expense of self-care. High body mass index and reduced physical activity were found to be independent risk factors for FM.[19]

FM can coexist with and imitate various autoimmune diseases and some chronic infections such as Lyme disease and hepatitis C. Identification of such disorders as the cause of pain is important, to avoid treating these conditions as FM. For coexisting problems, the prudent approach is to pursue the difficult task of determining the contribution of FM to symptoms and thus avoid treating FM with escalating doses of immunosuppressive medications. Hypothyroidism must be ruled out as a treatable cause of similar symptoms. A thorough history should guide a clinician's evaluation. An exhaustive laboratory and imaging workup is seldom indicated.

Integrative Therapy

General Considerations

Patients with FM are often viewed as difficult and burdensome in busy practices. Our observation is that parallel syndromes (e.g., chronic chest wall pain, chronic abdominal pain of undetermined origin, irritable bowel syndrome, interstitial cystitis, chronic pelvic pain, dyspareunia, and vulvodynia) are found in many subspecialties. In our practice, patients with these problems often report experiences of feeling dismissed and disrespected in their encounters with physicians. FM is a syndrome diagnosis, and we have not yet pieced together from a large body of basic science and clinical research a pathophysiologic model to explain the onset and manifestations of FM unequivocally. Consequently,well-meaning physicians often tell patients that they "don't believe in fibromyalgia." We believe this is an error for two reasons. First, evidence of altered neurophysiology and immune function is clear, as previously mentioned, and some evidence indicates that at least one gene polymorphism may play a role.[4] Second, patients experience such statements as harmful and judgmental because they imply that the symptoms are not real or valid. Affirming the patient's experiences of what often appear to be bizarre symptoms, even when we cannot fully understand them, is important. Because allopathic interventions in FM demonstrate limited efficacy, we emphasize the importance of generous listening in the healing relationship. Patients experience this affirmation as therapeutic, and it is something that all of us can provide (see Chapter 3, The Healing Encounter). Until a sensible explanation for their symptoms is presented, many patients remain concerned that something is seriously wrong with them and that a diagnosis has been missed during evaluation. Explaining that current research points to a change in the way that the brain processes sensory information as the reason for physical symptoms can help patients significantly. The therapeutic benefit in this simple practice may be that listening to a patient's worry may help favorably alter the physiology of the stress response and thus help reduce autonomic dysfunction, pain sensitivity, and other symptoms.[20]

Fibromyalgia research suggests that this is a disorder of central nervous system pain sensitization and augmentation associated with neuroendocrine and immune system abnormalities. Explaining this to patients may have some therapeutic benefit.

Nutrition

No specific diet has been shown to be effective for FM. An antiinflammatory diet, based on consumption of whole foods and avoidance of processed foods, may be helpful (see Chapter 86, The Antiinflammatory [Omega-3] Diet) and likely benefits the patient's health in a more general way. We emphasize complete avoidance of trans fats (partially hydrogenated oils, margarine, and shortening) and addressing a few common nutritional deficiencies in the standard U.S. diet. Increasing consumption of foods rich in omega-3 fatty acids, calcium, and antioxidants is strongly encouraged.

Exercise

A 2008 systematic review concluded that aerobic exercise has a beneficial effect on physical function and helps decrease some of the symptoms of FM.[21] Strength training may be helpful, but further study is needed. Adherence and attrition are problematic in many research studies on exercise in FM.

Many studies report a significant increase in symptoms of FM with exercise interventions.[21] In our experience, patients often report increased symptoms when they try to exercise. These symptoms are frequently severe and can lead to a cycle of muscle disuse. Not uncommonly, patients report feeling as though they "ran a marathon" after only a few minutes of exercise. Thus, though we support exercise prescriptions for all patients with FM, clinicians must think flexibly about exercise and be willing to revise recommendations based on patients' individual preferences and experiences. Pool exercise appears to provide as much physical fitness and symptom benefit as land exercise and may have additional benefit in improving psychological symptoms.[22] The Arthritis Foundation has information on exercise programs (1-800-283-7800). Tai chi proved beneficial in improving pain and quality of life in a randomized trial,[23] and a yoga intervention was similarly beneficial.[24] Even a cumulative daily 30 minutes of self-selected lifestyle physical activity provided clinically significant improvement in FM symptoms.[25]

Even though activation of the patient through exercise is a most desirable treatment goal, many patients demonstrate resistance. We have found it useful to explore with patients the reasons for resistance by asking, sometimes repeatedly over a long relationship, "What is hard about starting or sticking with an exercise program?" Severe postexercise pain is often cited, but many patients are similar to our usual primary care patients in that they have never embraced an active, exercise-oriented lifestyle. Exploring all the ways that one can move the body rather than selectively focusing on a structured exercise program can be useful. We often tell people to abandon the idea of "working out" and to think more in terms of "playing" or simply "moving." After all, who wants to have more work assigned to them? (See Chapter 90, Prescribing Movement Therapies.)

Evidence suggests that Eastern movement practices such as tai chi, yoga, and qi gong, which contain strong meditative components, appear to be helpful for patients with fibromyalgia in reducing pain and improving function.

Bodywork

Physical therapy can restore muscle balance, and local therapy with stretching, heat, and cold can be beneficial. Massage therapy was shown to be more useful than transcutaneous nerve stimulation (TENS), but TENS was better than sham TENS and may be helpful in some cases.[26] Many patients with FM report that massage therapy is beneficial. Although strong evidence does not yet exist for bodywork as a treatment for FM symptoms, we believe that bodywork is generally safe and can be recommended as a modality to try as part of the self-caring that we wish to promote for our patients with FM.[27]

Mind-Body Therapy

Meditation

Meditation was shown to be helpful in FM in a few trials, although a randomized controlled trial showed dubious benefit.[28–31] Some of the studies documenting FM symptom improvement with Eastern movement therapies had a strong meditation component, which may contribute substantially to the efficacy of this type of exercise.[23,24,32] This training increases the ability to be comfortable in the present and thus can lessen the fear of future pain and, with practice, help transform the sensation of pain. Meditation may have additional, as yet undetermined benefits by favorably altering neurophysiology in patients with FM. Meditation is also useful for personal growth. We recommend training with a nondenominational teacher using a program such as Mindfulness Meditation, pioneered by Dr. Jon Kabat-Zinn.[33] If no teacher is available, tapes can be helpful. The focus on the present moment and the deep levels of personal inquiry cultivated in a meditation practice are actually quite useful to the practitioner working with patients with FM. Therefore, we also endorse this practice for people working with patients with FM.

Psychotherapeutic Interventions

One study found that 10 of 15 subjects responded to a 14-week cognitive-behavioral and relaxation training intervention; however, no patients remained improved on 4-year follow-up evaluation.[34] Electromyographic biofeedback, electroencephalographic biofeedback, and hypnotherapy have been helpful in controlled studies.[35–37] These modalities may be more acceptable for patients who reject meditation training and practice based on religious beliefs. A randomized, controlled study of an Affective Self-Awareness program involving a group intervention of emotional exploration through journaling and meditation demonstrated significant benefit for symptoms and perceived function in patients with FM.[38] Although more research is needed on mind-body interventions, we strongly believe that these generally low-risk and low-harm interventions should be part of every treatment plan for patients with FM. When patients are either not receptive to these interventions, or when patients experience increasing disability, it may be helpful to explore the following "four Rs."[39]

1. Roles: The patient's ability to maintain self-esteem through normal roles as spouse, parent, provider, and so on may be impaired. The work role requires careful evaluation and is often problematic in people who are becoming progressively more symptomatic and disabled. We focus on a simple question as a way of exploring where problems may exist: "In all your roles, are you living for your heart's desire?"
2. Reactions: The emotional reactions to events such as the diagnosis of FM or the events that trigger FM often follow a grieving process, as outlined by Kübler-Ross.[40] These stages are denial, anger, bargaining, depression, and acceptance. Patients are often stuck in anger and depression. In addition, the sensitive temperament of many of these patients is often associated with a greater physiologic reaction to all emotions.[17] Working with reactivity through a meditation practice and journaling can be uniquely helpful.
3. Relationships: The patient may often face seemingly insurmountable problems at home or in relationships at work that create repeated stress triggers for symptoms.
4. Resources: Psychotherapy, ministers, community programs, and self-help groups may each become a key for altering this progressive decrease in ability to function; guided imagery is particularly useful. Isolation and alienation clearly make patients symptomatically worse.

Emotional Awareness

Dr. John Sarno, a physiatrist at New York University, wrote a book that some patients may find useful.[41] Dr. Sarno referred to FM and many other chronic musculoskeletal pain disorders as "tension-myalgia syndromes." The short summary is that the patient may substitute physical pain for emotional pain. He believed that this simple realization can abrogate pain in certain persons. We have seen this happen in patients with FM and in those with chronic low back pain. Our experience suggests that a certain level of self-awareness and acceptance of the power of the mind are required to experience symptomatic improvement just with this insight. Selfridge wrote a book for patients that applied Dr. Sarno's principles to FM by using journaling, meditation, and other workbook format exercises.[42] Dr. Howard Schubiner and Dr. David Schechter produced excellent workbook programs around the same themes that can be very helpful and cost-effective ways for patients to pursue self-exploration (see Key Web Resources and Chapter 100, Emotional Awareness for Pain).

Acupuncture

One high-quality trial of electroacupuncture showed almost complete remission in 20%, satisfactory benefit in 40%, and no effects in 40% of patients with FM in a short-term study.[43] A review of several trials concluded that benefits were reduced over time.[44] A more recent study of acupuncture showed no significant effects compared with three sham acupuncture treatments.[45] However, a limitation of this more recent study was that it used directed acupuncture at fixed points. This study also pointed out the difficulty of blinding that may have affected the outcome of the original high-quality article on electroacupuncture.

Homeopathy

A controversial placebo-controlled trial of a homeopathic treatment (R toxicodendron 6c) decreased tender points.[46] A second study using individualized therapy for 3 months also showed modest positive effects compared with placebo.[47] We recommend referral to a homeopathic physician for evaluation and treatment. Homeopathic remedies are said not to work as well in the presence of certain pharmaceuticals (see Chapter 111, Therapeutic Homeopathy).

Supplements

Little evidence of efficacy exists for supplements and natural medicines in the treatment of FM. Further, some common supplement recommendations, such as the use of calcium

supplements, selenium, and vitamin E, have come under scrutiny as possibly unsafe. Herbal and natural medicines potentially interact with one another and with prescription medication. Thus, we believe that a good peer-reviewed and frequently updated database (e.g., Natural Medicines Comprehensive Database; see Key Web Resources) be used by integrative clinicians to assess available evidence of efficacy and harm before recommending supplement and natural medicine therapy.

Omega-3 Fatty Acids

Use of omega-3 fatty acid supplementation in the form of pharmaceutical grade fish oil, 2 to 4 g daily in a single dose, may have a modest pain modulating effect for some patients and may help depression in some. In general, supplementation with omega-3 fatty acids may also lower cardiovascular risk and help to balance the predominance of proinflammatory omega-6 fatty acids in the typical U.S. diet.

Dosage

Give 2000 to 4000 mg daily in one dose.

Precautions

Omega-3 fatty acids inhibit platelet function and should be discontinued 2 weeks before elective surgical procedures. Use with caution along with anticoagulant therapy. Choose a pharmaceutical grade product to avoid heavy metal contamination.

Vitamin D

Low vitamin D levels appear to be epidemic in northern latitudes. Although the link between low vitamin D and the pain of FM remains unclear, evidence indicates that low vitamin D levels can be associated with widespread pain.[48] We have seen vitamin D–deficient patients eliminate all their FM-like pain when vitamin D levels become repleted. Thus, we recommend checking 25-(OH) vitamin D levels in patients at risk for vitamin D insufficiency and supplementing with vitamin D to keep blood levels optimal (40 to 100 ng/mL) year round. As a general rule, 1000 units of vitamin D will raise serum 25-(OH) vitamin D levels by approximately 10 ng/mL in adults. Although overdosing is unlikely, clinicians recommending vitamin D should be aware that vitamin D levels may be higher in our patients in the summer if they have sufficient skin exposure to sunlight.

Dosage

Cholecalciferol (vitamin D_3) oral supplements in capsule or liquid form are taken to attain a 25-(OH) vitamin D level of 40 to 100 ng/mL year round. Seasonal adjustment of dose may be necessary.

Precautions

Vitamin D is not to be used in patients who have primary hyperparathyroidism or granulomatous disease such as sarcoidosis because of the increased risk of hypercalcemia.

Magnesium

Magnesium may be helpful for some patients with FM, possibly through its muscle-relaxing properties, and it is quite safe.

Dosage

Give 400 to 750 mg of magnesium daily in a single dose.

Precautions

In higher doses, magnesium can cause abdominal cramping and increased frequency of stools.

S-Adenosylmethionine

S-adenosyl methionine (SAMe) was demonstrated to be safe and effective in alleviating depression in patients who failed to respond adequately to monotherapy with a selective serotonin reuptake inhibitor (SSRI), even though SAMe was given with the SSRI.[49] Although SAMe may have only a modest effect on other FM symptoms, this supplement can be helpful in patients who are reticent to use prescription pharmaceuticals to treat their FM and depressive symptoms.[50]

Dosage

The dose is 400 to 800 mg twice daily.

Precautions

SAMe can be activating and should not be taken close to bedtime because it can cause insomnia. It is expensive.

Botanicals

No adequate controlled trials of botanical treatments have been conducted. In anecdotal reports, many treatments lead to a benefit that wanes with time, a finding that may indicate a short-term placebo effect. Individual patients may benefit from trials of botanicals purported to be helpful for common symptoms of FM such as low energy, insomnia, and depressed mood.

Turmeric and Ginger

The use of turmeric and ginger in cooking with culinary doses may provide benefit for some patients. In these doses, these spices are likely safe and can be encouraged. When these agents are used in supplement doses, potential side effects and interactions must be considered.

Dosage

Ginger: As dried root, 1 g total per day, divided into two or three doses to start; increased to up to 4 g daily; as tea, 1 g of dried root steeped in 150 mL of boiling water for 5 to 10 minutes and strained; 1 cup up to four times daily

Turmeric: As powdered root, 0.5 to 1 g two or three times daily

Precautions

Because turmeric and ginger have platelet-inhibiting activities, they must be used with caution in people taking anticoagulant therapy and should be discontinued 2 weeks before elective surgical procedures. Both cause gallbladder contraction and may be problematic in patients with gallstones. Ginger may lower blood glucose levels.

Boswellia

Boswellia is an ayurvedic herb that has some documented antiinflammatory and analgesic effect. Although it has not been studied for FM, this herb may warrant a trial use in selected patients.

Dosage
The dose is 500 mg of standardized product three times daily.

Precautions
Platelet inhibition and increased bleeding risk are possibilities with this plant substance. Discontinue 2 weeks before elective surgical procedures.

St. John's Wort
For patients who need treatment for depression and do not wish to use prescription pharmaceuticals, St. John's wort may be helpful. It also has been shown to help with FM symptoms.

Dosage
As extract standardized to 0.3% hypericin content, use 300 mg up to three times daily; or as tea, steep 2 to 4 g of the dried herb in 150 mL of boiling water for 5 to 10 minutes and strain, and drink 1 cup up to three times daily.

Precautions
Multiple potential interactions with other drugs occur through stimulation of the cytochrome P-450 enzymes of the liver. The result is lower serum levels of drugs that are cleared by this mechanism.

Pharmaceuticals
Medications can be helpful for FM, although improvement in symptoms is seldom dramatic. Overall, 50% of patients will experience a 30% improvement in symptoms. Side effects are common and interfere with adherence.

Antidepressants
As previously stated, treating comorbid depression in patients with FM is in their best interest. Further, antidepressants can help improve sleep. Tricyclic antidepressants (TCAs) have been the gold standard of treatment because, in low doses, they tend to improve the sleep disturbance that is characteristic of FM. Side effects are often prohibitive in higher antidepressant doses. However, the newer dual serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine and milnacipran compared quite favorably with amitriptyline in a meta-analysis, although the studies on amitriptyline were not of high quality.[51] All these drugs were better than placebo for mitigating FM pain and improving function, but the effect size for these improvements was not small. Thus, these newer agents may be good choices for patients with FM and depression because these drugs may help both problems.

Research on SSRIs for the pain of FM has shown mixed results.[52] When depression is present, these medications may be useful. Trazodone is a sedating antidepressant that we prefer when sleep disorder is present and when depressive symptoms are not prominent. One study demonstrated efficacy for FM, and in our practices, trazodone appears to be well tolerated by patients and often works in small doses.[53] Although cyclobenzaprine is not an antidepressant, it is closely related to the TCAs, and meta-analyses have supported its use in FM.[54] The practitioner should develop a familiarity with several different antidepressants to feel comfortable managing the myriad side effects. In addition, patients sometimes add St. John's wort to their regimens, because St. John's wort has been shown to be beneficial for mild to moderate depression. Serotonin syndrome is a distinct risk when this natural medicine is taken with SSRIs or with SNRIs. Be sure to ask specifically about the use of St. John's wort in patients who are taking these prescription antidepressants.

Tricyclic Antidepressant Dosage
Amitriptyline: 5 to 10 mg nightly initially, titrating upward as needed
Nortriptyline: 50 mg nightly initially, titrating upward as needed

Tricyclic Antidepressant Precautions
Excessive sedation, anticholinergic effects, and hypotension may occur.

Selective Serotonin Reuptake Inhibitor Dosage
Fluoxetine: 5 to 20 mg initially, titrating upward as needed
Paroxetine: 10 to 20 mg daily initially, titrating upward as needed

Selective Serotonin Reuptake Inhibitor Precautions
Activation or sedation, induction of mania, hot flushes and sweating, weight gain, sexual dysfunction, and multiple potential drug interactions are possible. Paroxetine has been associated with discontinuation syndrome (withdrawal).

Trazodone Dosage
Give 25 to 50 mg nightly, titrating upward to 300 mg or until patient reports good sleep and no excess morning grogginess.

Trazodone Precautions
Oversedation, orthostatic hypotension, morning grogginess, and vivid dreams may occur.

Cyclobenzaprine Dosage
Give 2.5 to 10 mg initially, up to 40 daily, in divided doses.

Cyclobenzaprine Precautions
Excessive sedation and an increase in "mental fogging" may occur.

Dual Norepinephrine and Serotonin Reuptake Inhibitor Dosage
Duloxetine: 30 mg once daily for 1 week, then increasing to 60 mg daily
Milnacipran: started at 12.5 mg once daily on the first day, and increased by 12.5 to 25 mg daily for the first week until 50 mg twice daily dosing attained (100 mg twice daily may ultimately be necessary for symptom relief)

Dual Norepinephrine and Serotonin Reuptake Inhibitor Precautions
Precautions are potentially the same as for TCAs and SSRIs.

Nonsteroidal Antiinflammatory Drugs
Nonsteroidal antiinflammatory drugs (NSAIDs) had a poor showing in a controlled trial testing their analgesic efficiency in FM.[55] Because of the limited evidence of efficacy and the potential for adverse effects, particularly with long-term use, the wise approach may be to discourage NSAID use in FM

and instead to suggest supplements or botanicals such as omega-3 fatty acids, ginger, turmeric, or Boswellia for their modest analgesic effects.

Anticonvulsants

Gabapentin has been used off-label for FM because of its indication for use in chronic pain. This agent appears safe and efficacious for FM.[56] A similar pharmaceutical, pregabalin, appeared to be effective compared with other newer drugs for FM in a meta-analysis.[57] Both drugs often cause somnolence and dizziness. Significant weight gain with pregabalin is not uncommon and can interfere with adherence. Because significant weight gain may also increase the risk of other chronic diseases such as type 2 diabetes, this side effect cannot be considered trivial.

Dosage

Gabapentin: started 300 mg once daily and increased by one tablet to twice per day, then three times per day as tolerated; maximum dose, 3600 mg daily

Pregabalin: started with 50 mg three times daily, then increased over 7 days to the maximum of 600 mg per day

Precautions

Gabapentin may cause sedation, dizziness, cognitive impairment, and leukopenia, whereas pregabalin may cause sedation, dizziness, weight gain, and thrombocytopenia.

Analgesics: Tramadol

One controlled trial showed a beneficial effect of tramadol.[58] The use of tramadol with antidepressants can cause serotonin syndrome. Tramadol can also cause excessive sedation. Tramadol may be useful in allowing a 4-week drug holiday from antidepressant therapy, to reset neural receptors, and in intermittent therapy for exacerbations. In general, we avoid the long-term use of benzodiazepines and narcotics because of a lack of evidence of efficacy and because of potential safety and addiction issues.

Dosage

Tramadol: 50 to 400 mg daily in divided doses.

Precautions

Sedation, habituation, and serotonin syndrome with antidepressants may occur.

Soft Tissue Injection

The use of subcutaneous tender point injections may be helpful, particularly if these injections are given into palpable areas of muscle spasm. We rarely feel the need to do this procedure, given all the other potential tools that can help patients. These injections are often given as 0.5 to 1 mL of 1% lidocaine per site, although dry needling or saline may work as well. The use of corticosteroids for injection should be avoided.

Therapies to Consider

Adequate studies have not been conducted on the roles of traditional Chinese, Ayurvedic, or spiritual medicine in the management of FM. We counsel our patients to learn about several different modalities and then record in a journal their feelings about these modalities. Then, after discussion, patients can visit practitioners of the selected therapies to explore the approaches further. If the economic burden is not too great, addition of the therapeutic modality may be in order. Another area of potential benefit for patients with FM is emerging from the growing field of energy psychology. Emotional Freedom Techniques (EFT), or tapping, as it is sometimes called, and Eye Movement Desensitization and Reprocessing (EMDR) are showing anecdotal evidence of value in alleviating physical and psychological symptoms in patients with FM (see Chapter 101, Energy Psychology). How these therapies work remains to be determined, but they are simple and quite harmless, and EFT can be taught to the patient to use at home for self-treatment. A good description and several anecdotes about EFT can be reviewed on the Web site www.emofree.com. Patients may similarly benefit from reading about FM, sensitivity, and EFT.[59] Descriptions of EMDR, its history, and evidence of efficacy can be reviewed at www.emdr.com. These therapies may bypass cognitive level processes to diminish or eliminate the central nervous system connection between the neurophysiology of traumatic memory and emotions and the physiology of bodily felt symptoms. We hope the future will bring research directed at examining in depth the efficacy and possible mechanisms of these therapies.

Mainstays of a treatment plan for fibromyalgia include an exercise prescription, mind-body types of interventions, treatment of comorbid depression, and judicious trials of other complementary and alternative medicine modalities and allopathic pharmaceuticals. However, *every* treatment plan should be individualized and flexible.

Prevention Prescription

No proven preventive strategy exists for FM, but the following may help to fortify a susceptible individual against the "slings and arrows of outrageous fortune":

- Exercise and maintain a normal body weight. Combine aerobics, strength training, and stretching. Consider tai chi and yoga. Make exercise a time to play.
- Eat a healthy whole foods diet, rich in plant sources of antioxidants. Avoid trans fats and excess caffeine, alcohol, and sugars.
- Honor your temperament and sensitivity. Learn more about yourself and your unique needs and values in work and relationships.[59,60]
- Journal to stay in touch with your inner feelings and to give voice to negative feelings and stressful events when they arise.
- Put yourself high on the list of things to take care of each day. Consider regular massage therapy or other bodywork to this end.
- Learn to meditate, and practice daily. We recommend a mindfulness-based stress reduction course.
- Allow yourself creative outlets such as art, music, dancing, or creative writing.
- Live for your own heart's desires, and allow yourself time and space to figure out what these are.
- If you get stuck in life, find a good psychotherapist.

Therapeutic Review

This summary provides the most helpful options for treating FM symptoms. FM has no documented "cure." Studies have reported an improvement in 5% to 53% of patients, although 47% to 100% of patients continue to meet criteria for FM 2 to 5 years after diagnosis.[61] Only a few patients experience complete resolution of symptoms. Despite these dismal statistics, we cannot emphasize enough the therapeutic benefit of generous listening and affirming the patient's felt experience. In our practices, approximately 75% of patients will report "some" relief of symptoms with treatment. Better response to treatment is seen in younger patients and in those with continued employment, supportive families, and an absence of litigation or affective disorders.[62]

Nutrition

- Encourage a whole foods antiinflammatory diet with ample plant antioxidants, omega-3 fatty acids, and minerals. C 1
- Counsel avoidance of trans fats and simple sugars. C 1

Exercise

- Write an exercise prescription tailored to the patient's individual preferences and fitness starting point.
- Encourage aerobic exercise, strength training, and stretching. A 1
- Suggest warm-water exercise classes, tai chi, yoga, and qi gong. B 1
- Even 30 minutes of daily cumulative lifestyle activity is beneficial. A 1

Mind-Body Therapy

- Encourage mindfulness meditation training and daily practice. B 1
- Suggest reading *The Mindbody Prescription*[41] and working through one of the available mind-body workbook programs. C 1
- Suggest journaling about emotions and stressors to help increase affective self-awareness. B 1
- Refer for cognitive-behavioral therapy if roles and relationships are problematic or if the patient feels "stuck." B 1
- Consider biofeedback and hypnotherapy as alternatives. B 1

Acupuncture

- If the patient can afford treatments, encourage a five-session trial. B 1

Bodywork

- Suggest regular massage therapy or other bodywork as a way of endorsing self-care. B 1

Supplements

- Omega-3 fatty acids (fish oil): 2000 to 4000 mg daily C 1
- Magnesium: 400 to 750 mg daily C 2
- Vitamin D_3 (cholecalciferol) to maintain 25-(OH) vitamin D levels higher than 40 ng/mL and lower than 100 ng/mL year round C 1
- S-adenosylmethionine: 800 mg twice daily B 2

Botanicals

- Turmeric, ground root: 500 to 1000 mg two to three times daily C 2
- Ginger, ground root: 1 g to 4 g total daily divided into two to three doses C 2
- Boswellia: 250 to 500 mg three times daily C 1
- St. John's wort: 300 mg three times daily B 2

Pharmaceuticals

- Amitriptyline: 5 to 50 mg nightly as tolerated A 2
- Nortriptyline: 25 to 100 mg daily A 2
- Fluoxetine: 10 to 20 mg daily B 2
- Paroxetine: 10 to 30 mg daily B 2
- Duloxetine: 30 mg for 1 week, increasing to 60 mg thereafter A 2
- Milnacipran: 12.5 mg daily to start, increasing to 50 mg twice daily by the end of the first week; 100 mg twice daily may be needed A 2
- Cyclobenzaprine: 2.5 mg daily, titrating to 40 mg daily in divided doses as needed A 2
- Trazodone: 25 to 300 mg nightly as needed B 2
- Gabapentin: 300 mg initially, increasing slowly to a maximum of 3600 mg daily as tolerated B 2
- Pregabalin: 50 mg three times daily, increasing to total of 600 mg per day over 7 days A 2
- Tramadol: 50 to 400 mg daily in divided doses B 2

KEY WEB RESOURCES	
http://www.unlearnyourpain.com	Dr. Howard Schubiner's Mind Body Program (workbook on emotional awareness and mind-body syndrome for patients with fibromyalgia)
http://www.mindbodymedicine.com	Dr. David Schechter's Mind Body Medicine (workbook on emotional awareness and mind-body syndrome for patients with fibromyalgia)
http://www.emofree.com	Emotional Freedom Therapy (tapping) for fibromyalgia
http://www.emdr.com	Eye movement desensitization and deprocessing for fibromyalgia
http://www.med.ufl.edu/rheum/FMSarticles/article25.htm	Diagnostic summary of fibromyalgia from the University of Florida
http://naturaldatabase.therapeuticresearch.com	Natural Medicines Comprehensive Database

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Chapter 47

Chronic Fatigue Spectrum

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Pathophysiology

Chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) are two common names for an overlapping spectrum of disabling syndromes. FMS alone is estimated to affect more than 3 to 6 million people in the United States, and it causes more disability than rheumatoid arthritis.[1] The prevalence of these disorders has also increased dramatically from 2% of the population to 4% to 8% worldwide since 2000.[2–4] Myofascial pain syndrome (MPS) affects many millions more. Although we still have much to learn, effective treatment is now available for most of these patients.[5,6]

CFS, FMS, and MPS represent a syndrome, a spectrum of processes with a common end point. Because the syndromes affect major control systems in the body, myriad symptoms do not seem to be related initially. Research suggests mitochondrial and hypothalamic dysfunction as common denominators in these syndromes.[7–10] Dysfunction of hormonal, sleep, and autonomic control (all centered in the hypothalamus) and energy production centers can explain the many symptoms and the reason that most patients have a similar set of complaints.

To make it easier to explain to patients, I use the model of a circuit breaker in a house: "If the energy demands on the body are more than it can meet, the body trips the circuit breaker. The ensuing fatigue forces the person to use less energy and thus protects him or her from harm. Conversely, although a circuit breaker may protect the circuitry in the home, it does little good if you do not know how to turn it back on or that it even exists."

This analogy actually reflects what occurs. Research in genetic mitochondrial diseases shows not simply myopathic changes, but also marked hypothalamic disruption. Because the hypothalamus controls sleep, the hormonal and autonomic systems, and temperature regulation, it has higher energy needs for its size than other areas. Therefore, as energy stores are depleted, hypothalamic dysfunction occurs early and results in the disordered sleep, autonomic dysfunction, low body temperatures, and hormonal dysfunctions commonly seen in these syndromes. In addition, inadequate energy stores in muscle result in muscle shortening (think of rigor mortis) and pain, which are further accentuated by the loss of deep sleep. Reduction in stages 3 to 4 of deep sleep results in secondary drops in growth hormone and tissue repair. As discussed later, disrupted sleep causes pain. Therefore, restoring adequate energy production through nutritional, hormonal, and sleep support and eliminating the stresses that overuse energy (e.g., infections, situational stresses) restore function in the hypothalamic "circuit breaker" and also allow muscles to release, thus allowing pain to resolve. Our placebo-controlled study showed that when this was done, 91% of patients improved, with an average 90% improvement in quality of life, and most patients no longer qualified as having FMS by the end of 3 months ($P < .0001$ versus placebo).[6]

Chronic fatigue syndrome, fibromyalgia, and to some degree myofascial pain syndrome reflect an energy crisis in the body. It is similar to blowing a fuse in your home. These disorders can have many causes, they protect the body from further harm, but they dramatically reduce function. Causes include infections, disrupted sleep, pregnancy, hormonal deficiencies, toxins, and other physical or situational stresses. The "blown fuse" is the hypothalamus—resulting in poor sleep and in hormonal, autonomic, and temperature dysregulation.

Diagnosis

The criteria for diagnosing CFS are readily available elsewhere. What is important is that these criteria were meant to be used for research and therefore have stringent exclusion criteria to create a "pure" research cohort. These exclusionary criteria eliminate approximately 80% to 90% of patients who clinically

have CFS, and therefore I do not recommend them for clinical use. For example, anyone who was significantly depressed in the past, even 30 years earlier, can technically never develop CFS. The American College of Rheumatology (ACR) criteria for FMS are more useful clinically. According to the ACR, a person can be classified as having FMS if he or she has the following:

- A history of widespread pain. The patient must have been experiencing pain or achiness, steady or intermittent, for at least 3 months. At times, the pain must have been present
  - On both the right and left sides of the body
  - Both above and below the waist
  - At the midbody (e.g., for example, in the neck, midchest, or midback, including a headache)
- Pain on pressing at least 11 of the 18 spots on the body that are known as tender points

The presence of another clinical disorder, such as arthritis, does not rule out a diagnosis of FMS.[11] Although the tender point examination takes time to master, it clinically adds little and is in the process of being eliminated in the newer 2010 ACR diagnostic criteria.[12]

A simpler approach is available that is very effective clinically. If the patient has the paradox of severe fatigue combined with insomnia (someone who is exhausted should sleep all night) and does not have severe primary depression, and if these symptoms do not go away with vacation, he or she will have a CFS-related process. If the patient also has widespread pain, FMS is probably present as well. Both disorders respond well to proper treatment, as discussed later. Alternatively, clinicians may wish to ask the patient whether he or she has the symptoms described in Table 47-1. In addition to strengthening the diagnosis of CFS and FMS, asking about the symptoms summarized in Table 47-1 shows the patient that the health care provider understands this illness.

Although a matter of disagreement in the classical ACR criteria, clinically it is clear that FMS may be secondary to other causes. Secondary causes may be suggested by laboratory findings such as elevations in erythrocyte sedimentation rate, alkaline phosphatase, creatine kinase, rheumatoid factor, antinuclear antibody (1:640 or higher), or thyroid-stimulating hormone (TSH). Depression is less likely to be a secondary cause of FMS and CFS symptoms in patients who express frustration over not having the energy to do the things, as opposed to a lack of interest. These patients likely are simply frustrated by their illness and are not depressed. MPS shares many of the metabolic features seen in FMS and often resolves with the treatments discussed in this chapter, but evaluation for structural problems should also be done for this more localized process.

TABLE 47-1. Symptoms of Chronic Fatigue

- Severe fatigue lasting over 4 months
- Feeling worse the day after exercise
- Diffuse, often migratory, achiness
- Disordered sleep
- Difficulty with word finding and substitution, poor short-term memory, and poor concentration, often described as "brain fog"
- Bowel dysfunction (Many people with irritable bowel syndrome [IBS] or spastic colon have chronic fatigue syndrome or fibromyalgia syndrome, and their IBS also resolves with treatment.)
- Recurrent infections such as sore throats, nasal congestion, or sinusitis

Current research and clinical experience show that these patients have a mix of disordered sleep, hormonal insufficiencies, low body temperature, and autonomic dysfunction with low blood pressure and neurally mediated hypotension. This mix makes sense because the hypothalamus is the major control center for all four of these functions.

Simple diagnostic approach: If the patient has the paradox of severe fatigue combined with insomnia (if someone is exhausted, he or she should sleep all night), and these symptoms do not go away during a vacation, the likely diagnosis is chronic fatigue syndrome–related process. If the patient also has widespread pain, fibromyalgia is probably present as well. Both conditions respond well to proper treatment, as discussed in this chapter.

Anything that results in inadequate energy production or energy needs greater than the body's production ability can trigger hypothalamic dysfunction. This includes infections, disrupted sleep, pregnancy, hormonal deficiencies, and other physical or situational stresses. Although still controversial, a large body of research also strongly suggests mitochondrial dysfunction as a unifying theory in CFS and FMS.[10] Some viral infections have been shown to suppress both mitochondrial function and hypothalamic function. As noted earlier, in several genetic mitochondrial diseases, severe hypothalamic damage is seen. This is likely because the hypothalamus has high energy needs.

Integrative Therapy

Fortunately, two studies (including our recent randomized controlled trial)[5,6] showed an average 90% improvement rate with the SHINE protocol. The acronym SHINE stands for treating Sleep, Hormonal dysfunction, Infections, Nutritional support, and Exercise as able. Patients with fatigue and insomnia coupled with widespread pain can be seen as having a body-wide "energy crisis." Treating with the SHINE approach may help them.

Two studies (including our randomized controlled study) showed an average 90% improvement rate when the SHINE protocol was used to treat chronic fatigue syndrome and fibromyalgia. SHINE stands for Sleep, Hormonal support, Infections, Nutritional support, and Exercise as able.

As discussed earlier, using the acronym SHINE simplifies treatment of these patients. Therefore, the treatment recommendations in this chapter are structured using this model.

Sleep

SHINE has been editorialized as "an excellent and powerfully effective part of the standard of practice for treatment of people who suffer from FMS and MPS."[13] A foundation

of CFS and FMS is sleep disorder.[14] Many patients can sleep solidly only for 3 to 5 hours a night and have multiple awakenings. Even more problematic is the loss of deep stage 3 and 4 "restorative" sleep. Using natural therapies or medications that increase deep restorative sleep, so that the patient has 7 to 9 hours of solid sleep without waking or hangover, is critical. Continue to adjust the treatments each night until the patient is sleeping 8 hours a night without a hangover.

Most addictive sleep remedies, except for clonazepam (Klonopin) and alprazolam (Xanax), actually decrease the time that is spent in deep sleep and can worsen FMS. Therefore, they are not recommended. More than 20 natural and prescription sleep aids can be tried safely and effectively in FMS and CFS. For a more detailed list, see my free "long form" treatment protocol (discussed in the next subsection).

Natural Sleep Remedies

I recommend you begin with the following:

- Valerian: 200 mg
- Passionflower: 90 mg
- L-Theanine: 50 mg
- Hops: 30 mg
- Wild lettuce: 18 mg
- Jamaican dogwood: 12 mg

These are all combined in a product called the Revitalizing Sleep Formula by Integrative Therapeutics (see Key Web Resources). Patients (and anyone with poor sleep) can take one to four capsules at bedtime. These six botanicals can help muscle pain and libido, as well as improving sleep.[15–19] The effectiveness of valerian increases with continued use, but approximately 5% to 10% of patients will actually find it stimulating and not be able to use it for sleep. Although I am discriminating about the products I recommend, I have a policy of not taking money from any natural or pharmaceutical companies, and 100% of the royalties for my products also go to charity.

- The dose of melatonin is 0.5 to 1 mg at bedtime.
- The dose of 5-hydroxytryptophan (5-HTP) is 200 to 400 mg, taken at night. This naturally stimulates serotonin, but it may take 6 to 12 weeks to be fully effective. Do not give more than 200 mg a day if the patient is taking antidepressants, because 5-HTP theoretically could drive serotonin too high. 5-HTP can also help with pain and weight loss, at 300 mg a day for at least 3 months.
- Give calcium and magnesium at bedtime because these help sleep.
- The smell of lavender helps sleep, so place two to three sprays on the pillow at bedtime.

Pharmaceutical Sleep Aids

If natural remedies are not adequate to result in at least 8 hours a night of sleep, consider these medications:

- Zolpidem (Ambien): 5 or 10 mg at bedtime. This medication is very helpful for most patients and is my first choice among the sleep medications. Patients can take an extra 5 to 10 mg in the middle of the night if they wake.
- Gabapentin (Neurontin): 100 to 900 mg at bedtime can help sleep, pain, and restless legs syndrome.
- Cyclobenzaprine (Flexeril): 5 to 10 mg
- Trazodone: 50 mg. Use one half to six tablets at bedtime. Use this medication first if anxiety is a major problem.
- Amitriptyline (Elavil) or doxepin: 10 mg. Use one half to five tablets at bedtime. Amitriptyline can cause weight gain and can exacerbate restless legs syndrome.

Some patients will sleep well with the Revitalizing Sleep Formula herbal preparation or 5 to 10 mg of zolpidem, whereas others will require all the foregoing treatments combined. Because the malfunctioning hypothalamus controls sleep and the muscle pain also interferes with sleep, it is often necessary and appropriate to use multiple sleep aids. Tizanidine (Zanaflex), pregabalin (Lyrica), and many other nonbenzodiazepines can also help sleep. Because of next-day sedation and the independent half-life of each medication, patients with CFS and FMS do better by combining low doses of several medications than by taking a high dose of one.

> These patients must have at least 8 hours of deep sleep a night. Because of the hypothalamic dysfunction, they often need aggressive assistance to treat their insomnia. Begin with herbal mixes such as the Revitalizing Sleep Formula, and then add in magnesium, 5-hydroxytryptophan, and melatonin at bedtime as needed. If additional pharmaceutical support is needed, I recommend beginning with zolpidem, trazodone, or gabapentin.

Although less common, three other sleep disturbances must be considered and, if present, treated. The first is sleep apnea. This condition should especially be suspected if the patient snores and is overweight or hypertensive. If two of these three conditions are present and the patient does not improve with treatment, I would consider a sleep apnea study. Ask the sleep laboratory also to look for upper airway resistance syndrome. Preapproval from the patient's insurance company is recommended because the test usually costs $1500 to $2600. Some patients prefer to do their own inexpensive screening by videotaping themselves for one night during sleep.

Sleep apnea is treated with weight loss and nasal continuous positive airway pressure. A sleep study or a videotape or DVD of the patient while sleeping will also detect restless legs syndrome, which is also fairly common in FMS.[20] It is treated with supplemental magnesium, by keeping ferritin levels higher than 60 ng/mL,[21] and with zolpidem, clonazepam, or gabapentin.

Hormonal Dysfunction

Hormonal imbalance is associated with FMS. Sources of this dysfunction include hypothalamic dysfunction and autoimmune processes such as Hashimoto thyroiditis. When the hypothalamus is not able to regulate hormone balance efficiently, medical management can do so until hypothalamic function is restored. When focusing on achieving hormonal balance, standard laboratory testing aimed at identifying a single hormone deficiency is less effective. For example, increased hormone binding to carrier proteins is often present in CFS and FMS. Therefore, total

hormone levels are often normal, whereas the active hormone levels are low. This situation creates a functional deficiency in the patient. In addition, most blood tests use 2 standard deviations to define blood test norms. By definition, only the lowest or highest 2.5% of the population is in the abnormal (treatment) range. This does not work well if more than 2.5% of the population has a problem. For example, as many as 20% of women older than 60 years are estimated to have antithyroid peroxidase antibodies and may be hypothyroid. Other tests use late signs of deficiency such as anemia for iron or vitamin B_{12} levels to define an abnormal laboratory value.

The goal in the management of CFS and FMS is to restore optimal function while keeping laboratory values in the normal range for safety. One way to convey the difference between the "normal" range based on 2 standard deviations and the optimal range that the patient would maintain if he or she did not have CFS or FMS is as follows:

"Pretend your laboratory test uses 2 standard deviations to diagnose a 'shoe problem.' If you accidentally put on someone else's shoes and had on a size 12 when you wore a size 5, the normal range derived from the standard deviation would indicate you had absolutely no problem. You would insist the shoes did not fit, although your shoe size would be in the normal range. Similarly, if you lost your shoes, the doctor would pick any shoes out of the normal range pile and expect them to fit you."

Thyroid Function

Suboptimal thyroid function is very common and very important. Because thyroid-binding globulin function and conversion of thyroxine (T_4) to triiodothyronine (T_3) may be altered in CFS and FMS, checking a free T_4 level is important. Treating *all* patients with chronic myalgia with thyroid hormone replacement is also important if their T_4 blood levels are lower than even the 50th percentile of normal (Janet Travell, personal communication). Many patients with CFS or FMS also have difficulty in converting T_4, which is fairly inactive, to T_3, the active hormone. Additionally, T_3 receptor resistance may be present, thus requiring higher levels.[22,23]

Synthroid has only inactive T_4, whereas desiccated thyroid (Armour Thyroid), or a compounded combination of T_4 and T_3, has both inactive T_4 and active T_3. Many clinicians give an empirical trial of desiccated thyroid, or T_4 plus T_3, 0.5 to 3 grains every morning, adjusted to the dose that feels best to the patient as long as the free T_4 is not higher than the upper limit of normal. I am likely to recommend an empirical trial of thyroid hormone therapy in most patients with CFS or FMS.

Physicians generally interpret a low-normal TSH (i.e., 0.5 to 0.95) as a confirmation of euthyroidism. The rules are different in CFS and FMS, however. In this setting, hypothalamic hypothyroidism is common, and the patient's TSH can be low, normal, or high.[24] This is why I recommend an empirical therapeutic trial of thyroid hormone treatment in the presence of chronic fatigue or myalgias despite normal laboratory test results. The inadequacy of thyroid testing is further suggested by studies that show the following:

- Most patients with suspected thyroid problems have normal blood study results.[25,26]
- When patients with symptoms of hypothyroidism and normal laboratory values were treated with thyroid (in this study, levothyroxine at an average dose of 120 mcg every day), many improved sigificantly.[25]
- Having a TSH level of 0.5 to 1.4 is associated with a 69% lower risk of myocardial infarction–related death than is having a TSH of 2.5 to 3.5 (to put this in perspective, statins for primary prevention decrease heart attack death by only approximately 1%).[26]

Additional recommendations are as follows:

- Adjust the thyroid dose clinically by using the dose that feels the best to the patient, as long as the free T_4 test does not show hyperthyroidism. Do *not* use TSH or T_3 levels to monitor thyroid replacement.[27] Because of the hypothalamic suppression, TSH levels may be low despite inadequate hormonal dosing. Because T_3 is largely produced and functions intracellularly, we do not have normal ranges for exogenously given T_3. Therefore, I predominantly use clinical signs and symptoms and free T_4 levels to monitor therapy.
- Make sure that the patient does not take any iron supplements within 6 hours or calcium supplements within 2 hours of the morning thyroid dose or the thyroid hormone will not be absorbed. Have the patient take the iron between 2:00 and 6:00 PM on an empty stomach and away from any hormone treatments.
- Thyroid supplementation can increase a patient's cortisol metabolism and unmask a case of subclinical adrenal insufficiency. A patient who feels worse while taking low-dose thyroid replacement may need adrenal support as well.

Because of the hypothalamic dysfunction, hormonal deficiencies are common despite normal blood test results. If symptoms suggest deficiencies, treat hypothyroidism with thyroid replacement (a therapeutic trial is warranted in most of these patients), treat adrenal insufficiency (suggested by low blood pressure, irritability when hungry or hypoglycemic, and recurrent respiratory infections and sore throats) with hydrocortisone and natural adrenal support, and low estrogen or testosterone levels with natural hormones.

Adrenal Insufficiency

The hypothalamic-pituitary-adrenal axis does not function well in CFS and FMS.[7,28,29] This dysfunction and adrenal exhaustion from chronic or severe stress are two key causes of inadequate adrenal function. Because early researchers studying adrenal insufficiency and cortisol were not aware of the physiologic doses for cortisol, they used high doses, and their patients developed severe complications. These side effects are *not* seen with adrenal glandular, herbal, or nutritional support or with physiologic doses of hydrocortisone (Cortef), that is, up to 20 mg a day.[30] A 20-mg dose of hydrocortisone is approximately equivalent in potency to 4 to 5 mg of prednisone. Unfortunately, many hypoadrenal patients are treated only when they are ready to develop an addisonian crisis. Research and clinical experience show that this approach misses many hypoadrenal patients.[5,6,30,31]

Symptoms of an underactive adrenal gland include weakness, hypotension, dizziness, sugar cravings with irritability when hungry, and recurrent infections, all of which are common in CFS and FMS. I recommend natural adrenal support for most patients with CFS or FMS, especially if

they have any of the foregoing symptoms. The needed natural therapies include the following:

- Adrenal glandulars. These contain most of the "building blocks" needed for adrenal repair.
- Licorice extract, which contains glycyrrhizin, a compound that raises adrenal hormone levels. Licorice also protects against stomach irritation, which can occur with hydrocortisone and occasionally even with glandulars.
- Pantothenic acid, vitamin C, vitamin B_6, betaine, and tyrosine: These nutrients are critical for adrenal function and energy, and high doses are often needed.

All these elements are present in a glandular and herbal preparation for adrenal support called Adrenal Stress End (from Integrative Therapeutics; see Key Web Resources), which is very safe and effective. I usually prescribe one to two capsules each morning (or one to two in the morning and one at noon), and the capsules can be taken along with hydrocortisone. This approach helps both symptoms and adrenal repair.

I also consider a therapeutic trial of 5 to 15 mg hydrocortisone in the morning, 2.5 to 10 mg at lunchtime, and 0 to 2.5 mg at 4:00 PM (maximum of 20 mg a day). Most patients find that 5 to 7.5 mg of hydrocortisone each morning plus 2.5 to 5 mg at noon to be optimal (the equivalent of 1.5 to 3 mg prednisone daily). Alternatively, sustained-release compounded hydrocortisone can be used. After keeping the patient on the initial dose for 2 to 4 weeks, adjust the dose up to a maximum of 20 mg daily or, if no benefit has been evident, taper it off. Adjust the hydrocortisone to the lowest dose that feels the best. Give most of the hydrocortisone in the morning and at lunchtime. I often tell my patients to take the last dose, 2.5 to 5 mg, no later than 4:00 PM. Otherwise, the hydrocortisone may keep the patient up at night. After 9 to 18 months, taper the hydrocortisone off over a period of 1 to 4 months. If symptoms recur after the hydrocortisone is stopped, continue treatment with the lowest optimal dose.

Different approaches to treatment are possible, and more is not better. High-dose cortisol taken at night worsens already disrupted sleep patterns. In a study by McKenzie et al,[32] patients received a very high dose of approximately 25 to 35 mg of hydrocortisone daily, which disrupted patients' sleep ($P \leq .02$).[32] Although the investigators did not treat the disrupted sleep, most patients still felt somewhat better while taking the treatment. A small percentage of the patients had significantly suppressed posttreatment cosyntropin (Cortrosyn) test results, without complications, and the investigators therefore, I believe incorrectly, recommended against using any dose of hydrocortisone in CFS and FMS.[33] Our study did not show adrenal suppression with lower hydrocortisone dosing.[6] Dr. Jefferies,[30,31] with thousands of patient-years' experience in using low-dose hydrocortisone, recommended an empirical trial of 20 mg a day in all patients with severe, unexplained fatigue and found this to be quite safe for long-term use. Research and clinical experience suggest that using hydrocortisone at 20 mg a day or less in patients with CFS or FMS is safe and often very helpful.[34] An extensive review of the safety of long-term prednisone in doses lower than 5 mg a day in patients with rheumatoid arthritis patients also supported the safety of this approach.[35]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a major adrenal hormone that has been dubbed a "fountain of youth" hormone.[36] DHEA is stored as DHEA-sulfate (DHEA-S), and levels of free DHEA fluctuate markedly throughout the day. Therefore, I recommend checking DHEA-S levels and not DHEA levels. Many patients with CFS or FMS have suboptimal DHEA-S levels, and the benefit of treatment is sometimes dramatic. Most women need 5 to 25 mg a day, and most men need 25 to 50 mg a day. I use the middle of the normal range for a 29-year-old patient and keep the DHEA-S level at 150 to 180 mcg/dL in women and 350 to 480 mcg/dL in men. Too high a dose in women can cause elevated testosterone and can result in acne, darkening of facial hair, and insulin resistance.

Estrogen Deficiency

Although we are trained to diagnose menopause by cessation of menstrual periods, hot flashes, and elevated follicle-stimulating hormone and luteinizing hormone, these are late findings. Estrogen deficiency often begins many years before and may coincide with the onset of FMS.[37] To compound the problem, research done by Sarrel showed that most women who have a hysterectomy, even with the ovaries left intact, develop estrogen deficiency within 6 months to 2 years after the surgical procedure.[37]

To summarize, the initial symptoms of estrogen deficiency are poor sleep, poor libido, brain fog, achiness, premenstrual syndrome, and decreased neurotransmitter function. If a woman's symptoms of CFS and FMS are worse at ovulation and the 10 days before her period (times when estrogen levels are dropping), then a trial of estrogen is warranted. Although a birth control pill can be used, side effects of bleeding and fluid retention are common for the first 3 to 4 months. Bio-identical hormones are better tolerated and are likely safer. Therefore, natural 17-beta-estradiol as (Estrace, Climara) patches may be preferable. The usual dose of estradiol patch (Climara) is one 0.05- to 0.1-mg patch a week, and the usual dose of oral estradiol (Estrace) is 0.5 to 1 mg a day, adjusted to what feels best to the patient. I prefer to use Biest, a compounded natural estrogen that combines estriol with estradiol, at a dose of 0.1 to 0.5 mg a day.

Unlike estradiol, early data on estriol suggest that it does not raise breast cancer risk and may actually lower it (Jonathan Wright, MD, personal communication). In addition, estriol also has immune-modulating and other properties that can be beneficial in FMS. In the absence of a hysterectomy, progesterone should be added to prevent uterine cancer. If you are prescribing the Biest cream, have the pharmacist make a combination of Biest plus progesterone 30 to 50 mg, in addition to testosterone 0.5 to 1 mg all in 0.2 mL of cream (which can be applied to the mucosal surface of the labia each evening). When the creams are applied to the skin instead of to the mucosal surfaces, patients often stop absorbing the cream after a few years of use. Clinical experience is suggesting that the lower doses of testosterone and Biest recommended here may be preferable to the higher doses used in the past.

Testosterone Deficiency

Testosterone deficiency is important in both men and women. Clinicians should check a free testosterone level rather than total testosterone, because free testosterone is a better measure of testosterone function. If the age-adjusted free testosterone is low or low normal (lowest quartile), a trial of treatment is often very helpful. Among my patients with CFS or FMS, 70% of men and many women have free testosterone levels in the lowest quartile, whereas their total testosterone levels are usually normal. One study found that treating low testosterone in women decreased FMS pain. Only natural testosterone should be used for treatment. In men, topical testosterone (AndroGel) works fairly well. Applying 25 to 50 mg once daily is a good dose in men, and 0.5 to 1 mg is recommended in women.

Despite the concerns about athletes who use very high levels of synthetic testosterone, research shows that raising low testosterone levels in men by using natural testosterone actually results in lower cholesterol, decreased angina and depression, and improved diabetes.[38]

Immune Dysfunction and Infections

Immune dysfunction is part of the process. In fact, the other name for CFS is chronic fatigue and *immune dysfunction* syndrome (CFIDS). Literally dozens of infections are present in CFIDS and FMS, including viral, parasitic, *Candida,* and antibiotic-sensitive infections. Most of these infections seem to resolve on their own as the immune system recovers with the SHINE protocol.

Some infections do require treatment. I treat all patients with CFS for *Candida* and treat all parasites based on testing stool for ova and parasites. Dysbiosis may also need to be treated.

Chronic sinusitis responds poorly to antibiotics but responds well to antifungals. Conservative measures such as saline nasal rinsing and avoiding refined carbohydrates are more appropriate than are long-term antibiotics.[39] Our experience has shown, and research at the Mayo Clinic in Rochester, Minnesota also suggests, that chronic sinusitis is predominantly caused by a sensitivity reaction to yeast, with secondary bacterial infections resulting from swelling and obstruction. Most of our patients find that their chronic sinusitis goes away on the yeast protocol discussed here. Avoiding antibiotics also decreases the risk of secondary fungal overgrowth in the sinuses and gastrointestinal tract.

When initially treating sinusitis and for acute flares, our patients find that a compounded nose spray containing a combination of itraconazole, xylitol, mupirocin, very-low-dose bismuth, and cortisone can be very helpful. This nose spray is available from the ITC Compounding and Natural Wellness Pharmacy (888-349-5453). Ask for the Sinusitis Spray, which ITC can mail to the patient after the prescription is called into the pharmacy. The dose is one to two sprays in each nostril twice a day for 2 to 6 weeks. Ordering the one bottle is adequate for most patients. Although the chronic sinusitis often resolves after 6 weeks of fluconazole (Diflucan) and the sinus spray, the patient can use the spray as needed if symptoms recur. If sinusitis or spastic colon symptoms recur, however, the patient likely is also having regrowth of *Candida* in the gut, and if other CFS symptoms are recurring, I consider a 6-week retreatment with fluconazole. I treat all patients with CFS or FMS for *Candida* and do not find additional *Candida* testing to be necessary, reliable, or helpful.

Yeast Infection

Treatment of yeast infection in patients with CFS or FMS consists of the following:

1. *Acidophilus* bacteria, 4 to 8 billion colony-forming units per day, can help to restore normal bowel flora. In addition, patients must avoid sugar because yeast grows by fermenting sugar. This includes food juices, which have as much sugar as sodas. To improve compliance (and show compassion), I do allow patients to have chocolate.
2. Anti-Yeast (a mix of natural antifungals by Nutri Elements) is taken for 5 months. This contains coconut oil powder (50% caprylic acid), 240 mg; oregano powder extract, 200 mg; *Uva ursi* extract, 120 mg; garlic powder (deodorized), 240 mg; grapefruit seed extract, 160 mg; berberine sulfate, 80 mg; and olive leaf extract, 200 mg.
3. After 4 weeks on the Anti-Yeast, add 200 mg of fluconazole (Diflucan) each day for 6 weeks, and repeat the 200 mg per day for another 6 weeks if needed.

Because of the immune suppression, most of these patients must be treated empirically for yeast/fungal/*Candida* overgrowth. Nasal congestion or sinusitis and spastic colon are often caused by *Candida* and resolve with the treatments discussed earlier.

In patients with low-grade fevers or chronic lung congestion, occult infections such as with *Chlamydia* and *Mycoplasma fermentans* incognitus are being found. Empirical therapy with doxycycline 100 mg twice daily for 6 months to 2 years, during nystatin therapy, can be helpful in unique cases. Research is showing that human herpesvirus 6, cytomegalovirus, and Epstein-Barr virus are also sometimes active in CFS and FMS.

Nutritional Support

Patients with CFS or FMS are often nutritionally deficient. This occurs because of (1) malabsorption from bowel infections, (2) increased needs because of the illness, and (3) inadequate diet. B-complex vitamins, ribose, magnesium, iron, coenzyme Q10, malic acid, and carnitine are essential for mitochondrial function.[10,40] These nutrients are also critical for many other processes. Although blood testing is not reliable or necessary for most nutrients, I do recommend checking vitamin B_{12}, iron, total iron-binding capacity, and ferritin levels.

I begin patients with CFS or FMS on the nutritional regimen described next.

Multivitamin

A high-quality multivitamin suited for their needs should contain at least 50 mg of B-complex vitamins, 150 mg of magnesium glycinate, 900 mg of malic acid, 600 units of vitamin

D, 500 mg of vitamin C, 15 mg of zinc, 50 mcg of selenium, 200 mcg of chromium, and amino acids. A powdered vitamin is generally better tolerated, better absorbed, and less expensive than tablets.

D-Ribose

Because CFS and FMS represent an energy crisis, patients must have what is needed for optimal mitochondrial function. If you remember your biochemistry training on the Krebs citric acid cycle, the key energy molecules are adenosine triphosphate, reduced flavin adenine dinucleotide, and reduced nicotinamide-adenine dinucleotide. These molecules are made up predominantly of ribose in addition to B-complex vitamins and adenosine. Some of my patients improved markedly with improved energy and decreased pain when they were given one scoop (5 g) of ribose three times a day for 3 weeks, followed by one scoop twice a day (Corvalen, Bioenergy Life Science; see Key Web Resources). Two studies with a total of 298 patients with CFS or FMS that were conducted by 53 health practitioners showed an average 61% increase in energy at 3 weeks.[41,42] If ribose is going to help, improvement is usually seen within 1 month (a 280-g container is a fair therapeutic trial). Ribose is a very powerful new addition to our therapeutic armamentarium for treating fatigue, pain, and cardiac dysfunction.

Dosage

Give 5 g (one scoop of Corvalen) of ribose three times a day for 3 weeks, followed by 5 g twice a day.

Precautions

D-Ribose is natural, quite safe, tastes good (sweet like sugar), and is very low in side effects. Rarely, it can cause a mild drop in blood glucose as it stimulates energy production. If patients feel overenergized or hyperactive when they take ribose, simply have them take it with a meal or lower the dose. This response also suggests the need for adrenal support.

> Widespread nutritional deficiencies are common, and no single tablet will address them all. Patients should consider a good multiple vitamin, with the addition of ribose at 5 g two to three times daily, coenzyme Q10 at 200 mg daily, and acetyl-L-carnitine at 1000 mg daily for approximately 4 to 9 months, then PRN.

Iron

If the patient's iron percent saturation is less than 22% or the ferritin is less than 60 mg/mL, supplement with iron (taken on an empty stomach because food markedly decreases iron absorption). Iron should not be taken within 6 hours of thyroid hormone because iron blocks thyroid absorption. Continue treatment until the ferritin level is greater than 60 mg/mL and the iron percent saturation is higher than 22%.

Vitamin B_{12}

If the vitamin B_{12} level is less than 540 pg/mL, I recommend vitamin B_{12} injections, 3000 mcg intramuscularly three times a week for 15 weeks, then as needed based on the patient's clinical response. Studies of CFS are showing absent or near-absent cerebrospinal fluid vitamin B_{12} levels despite normal serum vitamin B_{12} levels.[43] Metabolic evidence of vitamin B_{12} deficiency is seen even at levels of 540 pg/mL or more.[44] Severe neuropsychiatric changes are also seen in vitamin B_{12} deficiency even at levels of 300 pg/mL (a level higher than 209 is technically normal).[45] As an editorial in the *New England Journal of Medicine* suggested, the old-time doctors may have been right about giving vitamin B_{12} shots.[46] Compounding pharmacies can make vitamin B_{12} at 3000 mcg/mL concentrations. I use hydroxycobalamin, although methylcobalamin may be more effective, albeit more expensive.

Coenzyme Q10

The dose of coenzyme Q10 is 200 mg a day. This conditionally essential nutrient improves energy production in patients with CFS or FMS. It is especially critical in patients taking statin-family cholesterol treatments (which can actually cause FMS pain and which I avoid using in patients with FMS).

Acetyl-L-Carnitine

Treating with acetyl-L-carnitine, at 500 mg twice daily for 4 months, is strongly recommended. Biopsies show that intracellular levels are routinely low in patients with CFS. This not only causes weakness, but also contributes to the average 32-lb weight gain seen in CFS or FMS.

Diet

No one diet is best for everyone. I recommend that patients eat those things that leave them feeling the best (which is not always the same as what they crave). Having said this, however, most patients with CFS find that they do best with a high-protein, low-carbohydrate diet. They should avoid sugar, as well as excessive caffeine (which is a loan shark for energy) and excess alcohol. Warn the patient about a possible 7- to 10-day withdrawal period when eliminating sugar and caffeine. If patients have low blood pressure or orthostatic dizziness, increasing salt intake markedly should also be considered.

Exercise as Able

Patients must prevent deconditioning. Conversely, because of decreased energy production, too much exercise will result in postexertional fatigue, often leaving patients bedridden for a day or so afterward. Therefore, I recommend that patients see how far they can comfortably walk each day and initially walk that amount. After 2 to 3 months on the SHINE protocol, patients will find they can usually begin conditioning and increase the walk by a minute every 1 to 2 days, as able. Using a pedometer is helpful, and the goal is reaching 10,000 steps a day. Patients should increase the exercise level only as is comfortable to them.

Mind-Body Therapy

Psychological Well-Being

Many illnesses are associated with various psychological profiles. In CFS and FMS, a common profile is a "mega-type-A" overachiever who, because of childhood low self-esteem, overachieves to gain approval. These patients tend to be perfectionists and have difficulties protecting their boundaries—that is, they say yes to requests when they feel like saying no. Instead of responding to their bodies' signal of fatigue by resting, they redouble their efforts. Taking time to rest and getting and staying out of abusive personal and work environments are critical. As they start to feel better, these patients need to be instructed to take it slowly and not go back to the toxic environment or level of overfunctioning that made them sick in the first place. A simplified approach is for patients to learn to say no to things that feel bad.

Although the metabolic problems require treatment, most chronic illnesses will not fully resolve unless mind-body issues are also treated. In chronic fatigue syndrome and fibromyalgia, this means that the patients must stop seeking approval and must learn to say no when they feel like it. Teach patients to do and keep their attention on what feels good from a centered place. In summary, follow your bliss!

Prevention Prescription

- Nutrition: Avoid excess sugar and receive optimal nutritional support. Patients usually feel best with a high-protein, low-carbohydrate diet.
- Sleep: Encourage 8 hours of sleep a night.
- Exercise by doing things that are fun and feel good.
- Follow your bliss! If you are chronically doing things that feel bad to you, your body is unlikely to support you in the long term. Develop the habit of only doing, and keep your attention on, things that feel good from a centered place (e.g., the heart or solar plexus center).

Therapeutic Review

Treat chronic fatigue syndrome, fibromyalgia syndrome, and myofascial pain by restoring energy levels metabolically. Do this by using the SHINE protocol summarized here:

Sleep

- Adjust the dose of sleeping aids as needed to obtain 8 to 9 hours of solid sleep without waking or hangover.
- Supplements
  - Consider the following botanicals to help with sleep: valerian, 200 mg; passionflower, 90 mg; L-theanine, 50 mg; hops, 30 mg; piscidia, 12 mg; and wild lettuce, 28 mg. A product that contains these ingredients is the Revitalizing Sleep Formula (by Integrative Therapeutics): Take two to four capsules each night 30 to 90 minutes before bedtime. This formula can also be used during the day for anxiety. B2
  - 5-Hydroxytryptophan: 200 to 400 mg at night A2
  - Melatonin: 0.5 mg at bedtime B2
- Pharmaceuticals
  - Zolpidem: 10 mg, one half to one at bedtime A2
  - Trazodone: 50 mg, one half to six at bedtime B2
  - Clonazepam: 0.5 to 1 mg B3
  - Gabapentin: 300 mg, one to two capsules at bedtime. It also helps relieve pain and restless legs syndrome. B2

Hormonal Treatments

- Desiccated thyroid (triiodothyronine [T_3] plus thyroxine [T_4]): Follow free T_4 to make sure of appropriate dosing and be careful not to overtreat. Otherwise, dose for clinical effect. For Armour Thyroid, 30 mg = 0.5 grains. Adjust dose based on clinical signs and symptoms. A2
- Hydrocortisone, 5-mg tablets: one half to two and one half tablet(s) at breakfast, one half to one tablet at lunch, and 0 to one half tablet at 4 PM. Use the lowest dose that feels the best to the patient. B2
- Dehydroepiandrosterone (DHEA): Keep DHEA-sulfate levels between 140 and 180 mcg/dL for female patients and between 300 and 500 mcg/dL for male patients. A common dose for women is 5 to 25 mg, and a common dose for men is 25 to 50 mg daily. B2
- Biest (female patients), 0.1 to 0.5 mg; plus progesterone, 30 to 50 mg; plus testosterone, 0.5 to 1.0 mg, all in 0.2 mL of cream. Apply 0.2 mL of cream to inner labia at bedtime. B2
- Testosterone (male patients): topical patch or compounded, 25 to 50 mg every morning B2

Infections: Anti-Yeast Treatments

- Avoidance of sweets: This includes sucrose, glucose, fructose, and corn syrup. Encourage whole fruits with fiber and avoid sweetened fruit juices. Consider stevia as a sugar substitute.
- Probiotics: Consider a *Lactobacillus acidophilus*–containing probiotic twice daily for 5 months and then consider taking one daily to maintain a healthy bowel. 
- Anti-Yeast (by Nutri Elements, an excellent natural antifungal mix), for 3 to 5 months 
- Fluconazole: 200 mg a day for 6 to 12 weeks 

Nutritional Treatments

- Encourage a high-protein, low-carbohydrate diet rich in fruits and vegetables. 
- Recommend a high-quality multiple vitamin that contains at least: 
  - B-complex vitamin: 50 mg
  - Magnesium: 150 mg combined with malic acid, 900 mg
  - Vitamin D: 600 units
  - Vitamin C: 500 mg
  - Zinc: 15 mg
  - Selenium, 50 mcg
  - One product that contains these ingredients is Energy Revitalization System Powder, made by Integrative Therapeutics: one half to one scoop a day (as feels best). If diarrhea occurs, mix the powder with milk or start with a lower dose and work your way up to the dose that feels best, or divide the daily dose into smaller doses and take two to three times a day.
  - Mitochondrial energy treatments: Use these for 3 to 9 months.
- D-Ribose (Corvalen, from 1-866-267-8253; www.Corvalen.com): one scoop of powder three times a day for 3 weeks, then twice a day 
- Coenzyme Q10: 200 mg a day 
- Acetyl-L-carnitine: 500 mg twice a day for 3 months 

Exercise

- Encourage the use of a pedometer, with a goal of 10,000 steps a day. The patient should increase the exercise level only as is comfortable, and increasing it too quickly can cause a flare of fatigue. 

KEY WEB RESOURCES

Integrative Therapeutics, Inc.: http://www.integrativeinc.com/Home.aspx.	This is the company that I respect most in the natural supplements industry. They carry the Energy Revitalization System vitamin powder and B-complex vitamins and the Revitalizing Sleep Formula.*
Bioenergy Life Science: http://www.douglaslabs.com/corvalen	This is a good resource for Corvalen D-ribose. ITC Compounding and Natural Wellness Pharmacy: http://www.itcpharmacy.com/. This company (888-663-4224) is an excellent compounding pharmacy that ships worldwide and is a good source for natural hormones, pain creams, and the sinusitis nose spray.
Vitality 101!: www.endfatigue.com	This is my Web site, and I invite you to use the free "Symptom and Lab Analysis" program. E-mail me at endfatigue@aol.com for the free "Treatment Tools" file. These will dramatically simplify patient care.

*Editor's Note: Dr. Teitelbaum is an unpaid member of medical board of Integrative Therapeutics. Although he promotes a number of products in this chapter that can be obtained on his Web site, he claims to donate all proceeds to charity.

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Chapter 48

Rheumatoid Arthritis

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Pathophysiology

Rheumatoid arthritis (RA) is likely caused by a pathologic immune response in a genetically predisposed person to an environmental insult, probably a viral or bacterial infection.[1] Epidemiologic studies show that genes encoding the class II major histocompatibility antigens are linked to clinical features of RA. The HLA-DR4 and DR1 proteins present foreign and self-antigens to T cells. These molecules are presumed to play a direct role in the etiology of this autoimmune disease by presenting an "arthritogenic" viral or bacterial antigen to T cells. However, no organism has been definitively linked to the etiology of RA. Antibiotic therapy with minocycline is helpful in mild disease, although minocycline may act through direct immunomodulatory or antiinflammatory effects rather than through antibacterial activity. Other genes of the immune, endocrine, and neural systems may contribute to the pathogenesis of RA. The precise pathophysiologic cascade is not yet defined. RA is an autoimmune inflammatory disease in which immunosuppressive drugs constitute the mainstay of therapy. Certain cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6, appear to play important roles because inhibitors of these molecules decrease disease activity.[2–5] Similarly, the importance of the roles of cell surface molecules on B and T cells can be shown when these molecules are used as targets for immunomodulatory therapy.[6,7]

Nonsteroidal antiinflammatory drugs (NSAIDs) act to inhibit the enzymes that produce inflammatory prostaglandins, particularly thromboxanes and leukotrienes. The newer NSAIDs preferentially inhibit the cyclooxygenase (COX)-2 enzyme that produces certain of these inflammatory molecules. Unfortunately, these COX-2 inhibitors may have increased thrombotic and hence cardiovascular risks, and they may not offer any increased gastroprotection.[8,9] Celecoxib (Celebrex) is still on the market, albeit with increased warnings; other COX-2 inhibitors have been withdrawn from the market. Omega-3 fatty acids and certain botanicals such as ginger and turmeric also may act through decreasing the production or activity of inflammatory prostaglandins.[10–14]

The neural, endocrine, and immune systems all share communication molecules that interact extensively. Molecules from the hypothalamic-pituitary-adrenal axis, particularly cortisol and corticotropin-releasing factor, and from the sympathetic-adrenal-medullary system are linked to disease activity in RA.[15] Corticosteroid drugs have powerful disease-suppressing activity, with equally powerful adverse side effects such as osteoporosis.[16,17] Prolactin and the estrogenic and androgenic sex hormones have been postulated to play roles as well. Other environmental factors such as nutrition, coffee, and tobacco also may contribute to the increased risk of RA.[18,19]

Stress and psychological factors have been linked to the etiology of RA and to disease exacerbations.[20] In one study, psychological factors and depression accounted for at least 20% of disability in patients with RA, greater than the 14% attributable to articular signs and symptoms.[21] In another study, helplessness had a direct effect on disease activity.[22]

Data point to an increased risk for cardiovascular disease in patients with inflammatory and autoimmune diseases. Current recommendations include controlling underlying disease, monitoring the ratio of total cholesterol to high-density lipoprotein, use of statins and angiotensin-converting enzyme inhibitors for antiinflammatory activity, and caution with the use of COX-2 inhibitors and steroids.[23]

Diagnosis

In 2010, new criteria for diagnosing RA were approved by the American College of Rheumatology and the European League against Rheumatism (ACR/EULAR) (Fig 48-1).[24] Definite RA is confirmed by the presence of synovitis in at least one joint, the absence of a better alternative diagnosis, and a score of 6 or greater (out of a possible 10) from four domains: number and site of involved joints (0 to 5), rheumatoid factor or anticyclic citrullinated peptide (0 to 3), elevated sedimentation rate or C-reactive protein (0 to 1), and duration greater than 6 weeks (0 to 1). Prior criteria had been

FIGURE 48-1
American College of Rheumatology and European League against Rheumatism (ACR/EULAR) diagnostic criteria for rheumatoid arthritis (RA): 6 out of 10 points or more suggest the diagnosis of RA. ACPA, anticyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Rf, rheumatoid factor. From Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62:2569–2581.

Joint involvement (0–5)	
1 med/large joint	0
2–10 med/large joints	1
1–3 small joints	2
4–10 small joints	3
>10 joints (at least 1 small)	5
Serology (0–3)	
Neither Rf nor ACPA positive	0
At least one test low positive	2
At least one test high positive	3
Duration of synovitis (0–1)	
<6 weeks	0
>6 weeks	1
Accute phase reactants (0–1)	
Neither CRP nor ESR abnormal	0
Abnormal CRP or abnormal ESR	1

criticized for insensitivity to early RA disease. The newer criteria are directed toward instituting more aggressive therapy sooner. Official diagnostic criteria are used for inclusion into studies and do not always reflect diagnoses made in the clinic. In practice, a diagnosis of RA may include findings included in earlier diagnostic criteria, such as duration of morning stiffness greater than 1 hour, subcutaneous nodules, x-ray changes, and histologic changes in biopsies of synovial tissue. Further, these ACR/EULAR diagnostic criteria do not include newer methods of diagnosis such as ultrasound and magnetic resonance imaging. Earlier treatment of RA results in better long-term outcomes. These criteria will be used to test whether more aggressive treatment will be helpful in disease in which joint damage has not yet taken place.

Integrative Therapy

Exercise

Joint pain can inhibit activity and lead to muscle disuse and atrophy. In turn, muscle atrophy can lead to decreased stability of joints. Light weight training can maintain or even increase muscle strength around joints and can lead to increased joint stability. Stretching muscles can help decrease flexion contractures. Aerobic exercise improves mood, decreases fatigue, and helps control weight gain. Water exercise can be helpful because it is less stressful on joints, but weight training and walking work better to decrease bone loss (osteoporosis). The Arthritis Foundation has information on programs (see Key Web Resources). Asian exercise disciplines such as tai chi and yoga can also be beneficial. A form of tai chi called the range of motion (ROM) dance is particularly suited to persons with disabilities (see Key Web Resources).

Physical and Occupational Therapy

Physical therapy and occupational therapy programs can be invaluable in the treatment of RA. Goals are to improve range of motion and strengthen muscles. Joint protection from deformities can be aided by education and use of splints, orthotics, ambulatory aids, and other devices. Massage and local heat and cold applications can decrease inflammation, increase circulation, and relax muscles.

Mind-Body Therapy

Self-help courses given through the Arthritis Foundation provide information about diseases and medication and can help in developing coping skills. Simply writing in a journal about positive and negative emotions for 15 minutes a day can be powerful medicine that relieves symptoms by 25% or more (see Chapter 96, Journaling for Health).[25]

The benefit of psychological interventions for RA was reviewed in a meta-analysis of 27 studies. Comparisons showed benefit in increasing physical activity and in decreasing pain, disability, depression, and anxiety. Self-regulation techniques, such as goal setting, planning, self-monitoring, feedback, and relapse prevention, were particularly helpful in reducing depression and anxiety.[26]

Meditation has been shown to be helpful for chronic pain.[27] A study of meditation in psoriasis, an autoimmune inflammatory skin disease, showed decreased time to clearing the skin disease.[28] Two studies investigated the role of meditation in RA. Pradhan et al[29] found reductions in psychological stress and increases in measures of well-being at 6 months, but no effects on the progression or activity of RA disease. Zatura et al[30] reported that both cognitive therapy and meditation were helpful in RA, with better responses in subjects with depression. I continue to recommend this modality for RA (see Chapter 98, Recommending Meditation). The effects of mind-body therapies on depression are important because depression is correlated with pain levels and measures of inflammatory markers.[31]

Nutrition

Food Triggers

Fasting clearly decreases symptoms in RA; however, symptoms rapidly recur with the resumption of food intake.[32] A few people with RA appear to have a food intolerance that exacerbates their disease. Many more people believe that certain foods exacerbate symptoms, but this effect was not shown in blind trials of food exposure. The offending foods are usually dairy products, wheat, citrus, or nuts. An elimination diet for 2 weeks with the reintroduction of the suspected food can be done with or without the supervision of a physician or a nutritionist (see Chapter 84, Food Intolerance and Elimination Diet).

Omega-3 and Omega-9 Fatty Acids

Increased intake of omega-3 fatty acids from cold-water fish, such as salmon, and from nuts, such as walnuts, as well as from flaxseed or hempseed, can provide modest

improvement in the control of RA.[10,11,32] The role of saturated fatty acids and trans fats in increasing symptoms is unproved. In view of the association of these saturated and trans fats with cardiovascular disease, however, reduction in intake is worthwhile (see Chapter 86, The Antiinflammatory Diet).

Cooked vegetables and olive oil have been found to be independently protective for the development of RA. Omega-9 fatty acids in olive oil may confer anti-RA activity.[33]

Coffee

A high intake of coffee (4 or more cups a day) has been linked to an increased risk of RA.[18,19] Intake should be decreased to less than this level, or the patient can switch to green tea, for the possible benefit from its antioxidant polyphenols.

Elimination of Tobacco Use

Smoking causes oxidant stress on connective tissue, as evident from the increased wrinkles seen in long-term smokers. One study showed a clear association between smoking and increased risk of RA. In this Swedish population, more than 50% of RA cases could be attributable to smoking in association with certain HLA-DR genes.[34] Patients with RA should be counseled to avoid tobacco.

Supplements

Essential Fatty Acids

Omega-3 fatty acids can be increased by dietary means or through supplementation. Approximate doses for supplementation are eicosapentaenoic acid, 30 mg/kg/day, and docosahexaenoic acid, 50 mg/kg/day.[10,32]

Gamma-linolenic acid, 1.4 to 2.8 g/day, the equivalent of 6 to 11 g of borage oil daily, also has been shown to be helpful.[11] Effects may not be felt for 6 weeks or more, and continued improvement may occur after many months.

Conjugated Linoleic Acids

One study showed that 3-month supplementation with conjugated linoleic acids (CLAs) showed reductions in standard measures of RA activity (DAS28), morning stiffness, and erythrocyte sedimentation rate. This study provided 2.5 g CLA daily in two capsules containing equal amounts of *cis*-9, *trans*-11 CLA and *cis*-12, *trans*-10 CLA.[35]

Antioxidants

Antioxidant vitamins may be helpful in RA, as they seem to be in osteoarthritis. Additionally, vitamin E has some analgesic effects.[12] Vitamin E should be taken at 800 units daily as mixed tocopherols, and vitamin C at 250 mg twice per day. Selenium can be found in many foods, including nuts; intake should be at least 100 mcg daily, not to exceed 400 mcg daily.

The recommended intake of calcium to prevent osteoporosis is 1000 to 1200 mg daily. Adding magnesium, at 400 to 750 mg daily, and a vitamin D supplement, at 2000 units per day, is probably a prudent approach.[36]

Echinacea should be avoided by patients with rheumatoid arthritis because of anecdotal reports of increased symptoms in persons with autoimmune disease.

Botanicals

Ginger

Ginger *(Zingiber officinale)* may have efficacy in RA by inhibiting inflammatory prostaglandins.[13]

Dosage

As the dried root, 1 g two or three times per day to start, increase up to 4 g daily. As a tea, 1 g of dried root steeped in 150 mL of boiling water for 5 to 10 minutes and strained, 1 cup up to four times daily. It can also be taken in 500-mg capsules for a dose of 1 g two or three times a day.

Precautions

The stimulation of increased bile flow can cause pain in the presence of cholelithiasis. Other risks include bleeding, hypertension or hypotension, and hypoglycemia.

Turmeric

Turmeric (curcumin) in an open trial was shown to be similar to NSAIDs in efficacy.[13]

Dosage

As powdered root, 0.5 to 1 g two or three times daily.

Precautions

Risks include bleeding, gastrointestinal intolerance, and impaired fertility.

Pharmaceuticals

Nonsteroidal Antiinflammatory Drugs

NSAIDs can be used on a short-term basis with minor risk of gastrointestinal toxicity. The long-term use of NSAIDs, particularly in older adults, poses significant risks for gastrointestinal bleeding. Many NSAIDs are available, and many of the newer ones are restricted on some formularies. The classic NSAIDs are ibuprofen (Motrin), in a dose of 800 mg three times daily, and naproxen (Naprosyn), in a dose of 500 mg twice daily. Both have antiplatelet activity. The advantage of using the COX-2 inhibitor celecoxib for possible decreased gastrointestinal toxicity has been called into question.[9] Celecoxib shares a lack of antiplatelet effects with other newer NSAIDs. These drugs also have the potential for renal toxicity and are no more effective than older NSAIDs. Data point to the risk of increased thrombosis in patients taking COX-2 inhibitors who have a preexisting increased risk of thrombosis or cardiovascular disease.[8] Two other COX-2 inhibitors have been withdrawn from the market. Celecoxib is used in a dose of 200 mg twice daily.

Corticosteroids

Corticosteroids can rapidly decrease RA symptoms, often within a few hours at high doses. However, both short-term and long-term toxic effects are well known. High and even moderate doses can lead to avascular necrosis of joints such as the hip, knee, or shoulder; fortunately, this is a rare occurrence. With proper care and early diagnosis of avascular necrosis, disability and joint replacement may be avoided. With long-term corticosteroid use, osteoporosis is a significant risk when doses of prednisone or equivalent are higher 7.5 mg daily. Other risks include atherosclerosis, diabetes

mellitus, cushingoid features, acne, and infection. Often a minor disease flare can be treated with a moderately high dose such as 30 to 40 mg of prednisone orally and a rapid taper over the course of 1 to 2 weeks. In some patients, a low dose of corticosteroids appears necessary for optional function; prednisone, 5 to 7.5 mg daily, is often used for this purpose.[16,17] A common method of treating a flare is to give a long-acting depot preparation such as triamcinolone acetonide (Kenalog), 80 mg intramuscularly. This approach can often control disease for 1 to 2 months, long enough for the slower-acting disease-modifying antirheumatic drugs (DMARDs) to start working. For disease flares in isolated joints, once infection is ruled out, an intra-articular injection of triamcinolone, 2.5 to 40 mg, can be given to control local disease.

A single joint with severely decreased range of motion and increased pain is presumed to be infected until proven otherwise. The patient should be hospitalized overnight for joint aspiration to obtain culture specimens. Blood should also be drawn for cultures, followed by administration of intravenous antibiotics until results of culture are known.

Antibiotics

Antibiotics, particularly minocycline (Minocin) in a twice-daily dose of 100 mg, may be useful in patients with less severe disease.[37] Side effects include gastrointestinal intolerance, dizziness, photosensitivity rash, vaginitis, skin and gingival discoloration, and, rarely, hepatic, lung, and kidney injury. The salutary effects of these agents may not be caused by their antibacterial activity, because the tetracyclines also show immunomodulatory and antiinflammatory activities.

Disease-Modifying Antirheumatic Drugs: Overview

DMARDs are also referred to as slow-acting antirheumatic drugs (SAARDs) because they usually take 6 weeks to 3 months to show activity. The use of most U.S. Food and Drug Administration (FDA)–approved DMARDs is supported by Cochrane Reviews, including low-dose steroids, hydroxychloroquine, sulfasalazine, methotrexate (with folic acid), azathioprine, leflunomide, cyclophosphamide, etanercept, adalimumab, and infliximab (Fig. 48-2).

Hydroxychloroquine and Sulfasalazine

Hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine-EN) are used early in disease when a diagnosis may not be clear or in patients with no characteristic erosive disease. Both drugs have little short-term and long-term toxicity.

Dosage

The current accepted dose of hydroxychloroquine is 200 mg twice daily, which carries little risk of toxicity; nevertheless, an ophthalmologic examination to test for retinal toxicity is recommended every 6 to 12 months. To reduce gastrointestinal intolerance, sulfasalazine is usually used in an enteric-coated form; dosing is started at 500 mg a day and raised by one tablet every few days until a dose of 1 g twice daily is reached.

Precautions

When used in high doses, hydroxychloroquine carries a risk of retinal toxicity resulting from deposition of the drug into the retina. Sulfasalazine can uncommonly cause rash, hepatotoxicity, and leukopenia.

Methotrexate

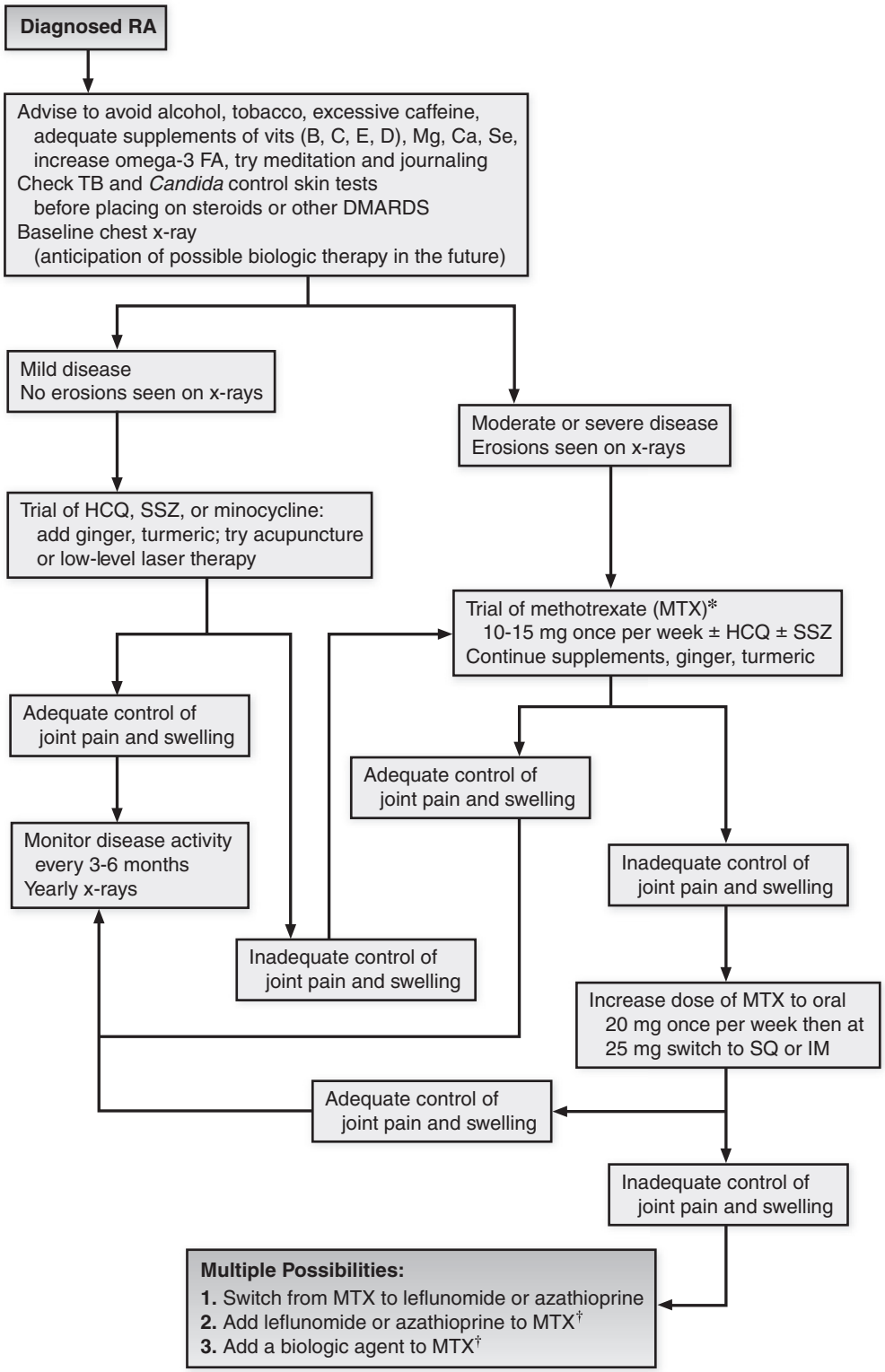
Of all of the DMARDs, methotrexate (Rheumatrex) has been shown to be tolerated for longer periods of treatment than any other drug.[3,38] Methotrexate is a folate antagonist and has a multitude of immunomodulatory activities, but its exact mechanism of action in RA is unknown. Doses of methotrexate for RA are usually between 5 and 25 mg given once a week. The dose is usually given orally in tablet form; however, the liquid form can be used orally and is sometimes less expensive. A common practice is to start with 7.5 mg orally once per week, although many practitioners, including myself, recommend starting higher doses such as 15 mg/week. With use of higher doses of 20 mg and more, patients are often taught to self-administer the dose subcutaneously once per week to avoid possible problems with gastrointestinal absorption. To decrease side effects, I always prescribe folic acid, 1 to 2 mg, to be taken each day. A decision to start methotrexate therapy or to raise or decrease the dose should be placed in the hands of a practitioner with extensive experience. Methotrexate is the standard by which all other drugs are judged, yet few patients achieve remission, and less than a majority will achieve a 50% improvement on composite scores.

Contraindications to use of methotrexate include the following: preexisting hepatic, renal, or pulmonary disease; unwillingness to discontinue alcoholic beverages; and recent malignant disease. Methotrexate has many side effects, the most prominent being hepatitis, bone marrow suppression, pneumonitis, mouth sores, nausea, and headache. A complete blood count, platelet count, and determination of aspartate transaminase, albumin, and creatinine levels are done initially and then every 2 weeks for 6 weeks after methotrexate therapy is begun. Thereafter, monitoring can be done every 4 to 8 weeks. A baseline hepatitis screen and chest radiography are recommended. Tuberculosis skin testing is reserved for patients with strong risk factors or an abnormal appearance on chest radiograph.

Other Immunosuppressive Drugs

Many other immunosuppressive drugs are used in RA. Leflunomide (Arava) is a newer drug that is similar in efficacy to methotrexate.[39] Leflunomide interferes with pyrimidine synthesis, whereas methotrexate interferes with purine synthesis. Leflunomide has fewer hepatotoxic effects and possibly little bone marrow toxicity but is much more likely to cause diarrhea. Azathioprine (Imuran) is metabolized to 6-mercaptopurine and interferes with inosinic acid synthesis. It is often substituted for methotrexate; however, its use is associated with gastrointestinal and bone marrow toxicity. Other immunosuppressive drugs less commonly used are mycophenolate mofetil (CellCept), cyclosporine (Neoral), tacrolimus (Prograf), and chlorambucil (Leukeran). Cyclophosphamide (Cytoxan) is often used to treat rheumatoid vasculitis.

FIGURE 48-2
Treatment algorithm for rheumatoid arthritis (RA) in adults.
*When starting methotrexate (MTX), add 1 mg of folic acid by mouth daily to decrease side effects, warn patients to avoid alcohol, and schedule laboratory studies (complete blood count, differential, platelets, aspartate aminotransaminase, albumin, creatinine) before starting, then every 2 weeks for 6 weeks, then every 2 months if results are normal.
†When adding another disease-modifying antirheumatic drug (DMARD) to MTX, decrease the dose of MTX to 10 to 15 mg once per week.
Ca, calcium; FA, fatty acid; HCQ, hydroxychloroquine; IM, intramuscular; Mg, magnesium; Se, selenium; SQ, subcutaneous; SSZ, sulfasalazine; TB, tuberculosis; vits, vitamins.



Recombinant Biologics

Advances in the therapy of RA have targeted cytokines and cell surface molecules used to communicate between cells of the immune system.[3–7] Etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade) are TNF inhibitors.[40–42] Etanercept is given subcutaneously once or twice per week, adalimumab is given subcutaneously once every 2 weeks, whereas infliximab is usually given intravenously once every 2 months. Two newer TNF inhibitors, certolizumab (Cimzia) and golimumab (Simponi), have been approved for use and can be given subcutaneously once per month.[43] These drugs are most often used with another DMARD, usually methotrexate, to reduce the development of autoantibodies. Short-term safety is very high, with little toxicity. As many as 30% of patients may show almost complete remission of symptoms with the combination of methotrexate and an anti-TNF agent. Currently, approximately 10 years of data are available on long-term safety and efficacy.[3] Use of these agents carries a risk of life-threatening exacerbations of severe infections, especially sepsis. Patients should temporarily discontinue the anti-TNF therapy during presumed infections and restart the therapy when the infection has resolved. All patients must be tested for latent tuberculosis with the purified protein derivative (PPD) skin test before they begin therapy. These drugs also may exacerbate demyelinating disorders; therefore, they should be avoided in patients with suspected or proven multiple sclerosis or optic neuritis.

An IL-1 receptor antagonist, anakinra (Kineret), is approved for the treatment of RA. It is given subcutaneously daily and also increases the risk of serious infection. Anakinra is generally thought to have lower efficacy in RA than other biologics. Agents directed toward a cell surface molecule on B cells (rituximab [Rituxan]),[6] and a costimulatory molecule on T cells (abatacept [Orencia]),[7] have been approved for use in RA. The latest biologic (tocilizumab [Actemra]) is directed toward another cytokine, IL-6, and has been approved for use in RA, but it has risks of neutropenia and increased cholesterol and liver function values. Thus, tocilizumab will require additional laboratory monitoring compared with the other biologics.[5]

Acupuncture

Several small controlled trials of acupuncture in RA showed decreased knee pain for an average of 1 to 3 months.[44]

Low-Level Laser Therapy

Low-level laser therapy uses a single-wavelength laser source that likely has photochemical, not thermal, effects on cells. A Cochrane Review suggests that this therapy may be considered for short-term relief of pain and morning stiffness for patients with RA, particularly because it has few side effects.[45]

Surgery

Loss of joint function and intractable pain may be indications for surgical intervention. Synovectomy can be helpful when systemic therapy and intra-articular corticosteroids are ineffective. Joint replacement can help restore function and increase independent activity. Patients with RA have an increased risk of surgical and postoperative complications. Cervical spine disease can lead to spinal instability and risk of neurologic injury. Replacement of one joint can result in increased stress on other joints during recovery and rehabilitation. Long-term corticosteroid use can cause fragility of vessels and connective tissue and thus increase the risks of surgery.

Therapies to Consider

The roles of traditional Chinese medicine or Ayurvedic, homeopathy, or spiritual therapies in the management of RA have not been adequately studied. Patients should learn about several different modalities and then record their feelings about these approaches in a journal. They may then choose to visit a practitioner of a selected modality for a trial of the techniques. If the economic burden is not too great, further exploration of that therapeutic technique may be appropriate.

Prevention Prescription

No proven methods of preventing rheumatoid arthritis exist. However, the following can be recommended:

- Laugh as much as possible. Watch funny movies, read funny books, get up every morning and force yourself to laugh. You'll find it is awkward at first, but it works anyway!
- Journal about stressful events. Make a list of 25 things for which you are grateful.
- Be creative. Do art, dance, play an instrument, beat a drum, write poetry or prose.
- Meditate; I recommend mindfulness meditation.
- Find meaning in life. Ask what gives you the energy to get up in the morning.
- Investigate your personality.[46] Try new things that you are afraid to do.
- If you feel stuck, find a good psychotherapist.
- Exercise. Combine aerobics, strength training, and stretching. Make it a time to play!
- Love people. Hang out with "positive people," make sure they outweigh the "negative" people in your life. Find "positive" support groups.
- Eat well. Try a vegetarian diet. Make sure to balance your protein intake, and make sure you have adequate vitamin intake.
- Eliminate coffee, smoking, and alcohol. Make high-sugar desserts a small, rare treat.

Therapeutic Review

Evidence is accumulating that current allopathic treatments are successful in slowing joint destruction and in decreasing the mortality associated with rheumatoid arthritis (RA).[38,40–42,47] In addition, the rates of extra-articular manifestations of RA, such as Felty syndrome and rheumatoid vasculitis, seem to be decreasing. Therefore, in any but the mildest cases of RA, an integrated approach should include the disease-modifying antirheumatic drugs (DMARDs), usually starting with methotrexate.

Exercise

- Muscle strengthening and stretching can be invaluable for maintaining function. Physical therapy can be used initially for instruction; tai chi in the form of the range-of-motion dance can be helpful. A1

Mind-Body Techniques

B1

- Meditation is highly recommended for patients with RA who are willing to devote the daily time to looking more closely at the connections among body, mind, and spirit. Also recommended are relaxation exercises and the development of methods to cope with stress. Tai chi and yoga also may include a meditative component to the training.
- Journaling should be encouraged (see Chapter 96, Journaling for Health).

Removal of Exacerbating Factors

- Use of coffee, tobacco, and alcohol should be eliminated. A1
- If intolerance to dairy products, wheat, citrus, or nuts is suspected, a trial of an elimination diet for 2 weeks with the reintroduction of the suspected food can be undertaken (see Chapter 84, Food Intolerance and Elimination Diet). B1

Nutrition

- A diet rich in omega-3 fatty acids is achieved by increasing intake of cold-water fish or adding flaxseed meal or flaxseed oil. Olive oil should be increased in the diet as well. An antiinflammatory diet is also recommended (see Chapter 86, The Antiinflammatory Diet). B1

Supplements

- Omega-3 fatty acids are recommended; doses for supplementation are eicosapentaenoic acid, 30 mg/kg/day, and docosahexaenoic acid, 50 mg/kg/day, along with gamma-linolenic acid, 1.4 to 2.8 g/day, the equivalent of 6 to 11 g of borage oil daily. A1
- Conjugated linoleic acid (borage oil, evening primrose oil) can be tried, at 2.5 g/day. B1
- Vitamin E should be taken in a dose of 800 units daily as mixed tocopherols, and vitamin C can be taken in a dose of 250 mg twice daily. Selenium intake, as nuts or supplements, should be at least 100 mcg daily, not to exceed 400 mcg daily. Recommended intake of calcium is 1.5 g daily; magnesium, 400 to 750 mg daily, and a vitamin D supplement of 2000 units/day are also recommended. B2

Botanicals

- Start with ginger, at 1 g twice daily to a maximum of 4 g daily. B1
- If no effect is seen after 6 to 8 weeks, turmeric 0.5 to 1 g two to three times daily can be tried. B1

Pharmaceuticals

- NSAIDs are used as little as possible owing to gastrointestinal toxicity. The classic NSAIDs are ibuprofen, 800 mg three times daily, and naproxen, 500 mg twice daily. A3
- The COX-2 inhibitors decrease but do not eliminate the risk of gastrointestinal bleeding. The dose of celecoxib is 200 mg twice daily. A3
- Most patients with RA are receiving combinations of drugs. Most patients are given methotrexate therapy unless they have contraindications or side effects. A3
- A common combination is methotrexate and hydroxychloroquine. Corticosteroids in moderately high doses with a rapid taper are often used for exacerbations. A3
- Commonly, a TNF inhibitor such as etanercept, adalimumab, infliximab, certolizumab, or golimumab is added if methotrexate is only partially effective. If one to two TNF inhibitors are unsuccessful, try rituximab, abatacept, or tocilizumab. A3
- Leflunomide or azathioprine is often substituted for methotrexate if side effects of methotrexate are intolerable. A3
- Methotrexate and leflunomide can be used together with only a modest increase in risk of side effects. The DMARDs and the recombinant biologics have many varied side effects, some of which are only now being defined. New biologics are being developed, including oral formulations. The immunosuppressive pharmaceuticals should be used only with input from a subspecialist rheumatologist.

Acupuncture

- Acupuncture can be tried for any patient with RA. This modality may be less effective in patients taking corticosteroids. B1

Low-Level Laser Therapy

- Low-level laser therapy can be tried with little risk of side effects.

Surgery

- Loss of joint function and intractable pain may be indications for surgical intervention. Synovectomy can be helpful when systemic therapy and intra-articular corticosteroids are ineffective. Joint replacement can help restore function and increase independent activity.

Caution

Studies have not been done on the possible additive effects of ginger, turmeric, vitamin E, and an NSAID for increased risk of hemorrhage. Other commonly used supplements or botanicals such as ginkgo may add further risk. Particular care must be used in patients taking other antiplatelet agents or warfarin sodium (Coumadin). In addition, the interactions of supplements and botanicals with allopathic pharmaceuticals are not fully understood. All health care professionals involved in the patient's care must be aware of all therapies being used. The addition of any new treatment should prompt increased laboratory monitoring for patients receiving immunosuppressive pharmaceuticals.

KEY WEB RESOURCES

Arthritis Foundation. www.arthritis.org.	Information on all aspects of rheumatoid arthritis, treatment, self-help, and other resources from the Arthritis Foundation (800-283-7800)
National Center for Complementary and Alternative Medicine. www.nccam.nih.gov/health/RA	Information on integrative therapies
Tai Chi Health. www.taichihealth.com; http://www.taichihealth.com/indexrom.html	A range-of-motion dance from Tai Chi Health (800-488-4940) that is particularly suited to persons with disabilities

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References are available online at expertconsult.com.

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Chapter 49

Inflammatory Bowel Disease

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Pathophysiology

Crohn's disease (CD) and ulcerative colitis (UC) are thought to result from inappropriate activation of the mucosal immune system, facilitated by regulatory defects in the mucosal immune response and failure of the mucosal barrier that separates immune response cells from the contents of the intestinal lumen. The normal gut flora act as a trigger for the inflammatory response and appear to play a central role in pathogenesis.[1] In both diseases, increased numbers of surface-adherent and intracellular bacteria have been observed in mucosal biopsies.[2,3] Patients with UC and CD share immunologic abnormalities that are common among patients with other types of autoimmune disorders, including up-regulation of subtype 17 helper T-cell (Th17)–positive lymphocytes and the proinflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1), IL-6, and IL-23, accompanied by down-regulation of regulatory T cells and the antiinflammatory cytokine IL-1 receptor antagonist (IL1ra).[4-7]

Despite these similarities, CD and UC have distinct differences in pathophysiology. The immune response underlying the pathologic features of CD, as in other granulomatous diseases, is driven by lymphocytes with a Th1 phenotype and their cytokines: IL-2 and interferon-gamma (IFN-gamma). The lymphocytes that organize the inflammatory response in UC demonstrate an atypical type 2 helper T-cell (Th2) phenotype, with IL-5 as a distinctive cytokine mediator.[8] Another interesting but unexplained difference between CD and UC is the effect of cigarette smoking, which increases the risk and decreases therapeutic responsiveness of patients with CD but has the opposite effect in patients with UC.[9] Response to diet and probiotics is often different for the two disorders, as discussed later.

The current consensus is that the development of inflammatory bowel disease (IBD) requires the combined effects of four basic components: (1) the input of multiple genetic variations that govern intestinal barrier function, repair, and immunity; (2) alterations in the intestinal microflora; (3) acquired aberrations of innate and adaptive immune responses; and (4) global changes in environment and hygiene. Most researchers believe that none of these four components can by itself trigger or maintain IBD, but that a combination of various factors is probably needed to bring about CD or UC in individual patients. This model implies that different and diverse mechanisms underlie IBD in different patients and that each patient may have a distinctive illness with his or her own clinical manifestations and a personalized response to therapy.[10] This model is well suited to the patient-centered diagnostic and therapeutic perspective of integrative medicine, in which the specific antecedents, triggers, and mediators of disease in each patient, rather than the disease entity, form the basis for therapy.[11]

Malnutrition is a major reversible complication of IBD. The mechanisms of malnutrition include anorexia resulting from the systemic effects of IL-1, a catabolic state induced by TNF-alpha, malabsorption secondary to disease or surgical resection, nutrient losses through the inflamed and ulcerated gut, small bowel bacterial overgrowth resulting from strictures or fistulas, and the side effects of drug therapy.[12] Inflammation increases oxidative stress in the bowel mucosa and decreases levels of antioxidants.[13] Nutritional deficiencies described in mucosal biopsies of patients with IBD include vitamin C,[14] zinc, copper, and the zinc- and copper-dependent enzyme superoxide dismutase (Cu-Zn SOD).[15] Plasma levels of vitamins A and E are lower and plasma levels of the oxidative stress marker 8-hydroxy-deoxy-guanosine (8-OHdG) are higher in patients with IBD than in controls.[16] Compared with controls, children and adults with IBD have lower blood levels of zinc and selenium, mineral cofactors of antioxidant enzymes,[17-19] and adults with UC may show lower levels of beta-carotene, magnesium, selenium, and zinc.[20] Micronutrient deficits may favor self-perpetuation of IBD by causing defects in the mechanisms of tissue repair.[21] Micronutrient deficiencies may also contribute to some complications of IBD, such as growth retardation, osteopenia, urolithiasis, and thromboembolic phenomena.[12]

In CD, abnormal mucosal barrier function may play a primary role in pathogenesis. Small intestinal permeability is increased among healthy first-degree relatives of patients with CD[22] and is increased in noninflamed enteric tissue obtained from patients.[23] Aspirin, a drug that increases intestinal permeability of healthy controls, causes an exaggerated increase in intestinal permeability of first-degree relatives of patients with CD.[24] The rate of relapse among patients who have entered remission is directly proportional to the degree of small intestinal hyperpermeability measured with chemical probes.[25] Hyperpermeability is associated with polymorphism of genes associated with regulation of epithelial barrier function,[4] and it increases exposure of the intestinal immune system to luminal antigens. Intestinal epithelial lymphocytes of patients with CD are abnormally sensitive to antigens derived from Enterobacteriaceae and *Candida albicans,* both normally present in the small intestine.[26]

Integrative Therapy

General Principles

No single diet or set of supplements is right for every patient with CD or UC. Any intervention, even if supported by clinical trial data, may cause exacerbation of IBD in an individual patient. Each patient should serve as his or her own control, with symptoms, signs, and laboratory parameters followed closely. The evidence-based information presented in this chapter is at best a guide to help practitioners apply therapeutic options to individual patients. The only thing that matters is what works for this patient.

Enteral Feeding

Defined formula diets, either elemental or polymeric, are successful in improving the nutritional status of patients with IBD and preventing complications of surgery.[11] In CD, but not in UC, enteral feeding of defined formula diets as primary therapy has been shown to induce remission of active disease in 30% to 80% of patients.[11] Although enteral feeding is most commonly used in pediatric patients because of growth-enhancing and steroid-sparing effects,[27] it is equally effective in adults,[28] and it appears to have a direct antiinflammatory effect on the bowel mucosa.[29] Theories to explain the antiinflammatory effect of enteral feeding in CD include alteration in intestinal microbial flora,[30] diminution of intestinal synthesis of inflammatory mediators, and nonspecific nutritional repletion or provision of important micronutrients to heal the diseased intestine.[11] Decreased dietary antigen uptake, an early concept, is not a likely mechanism; polymeric diets, composed of whole protein, are as effective as elemental diets, in which nitrogen is supplied as free amino acids.[31,32] Results are conflicting concerning the effect of supplemental food on the response to enteral feedings.[33,34]

Part of the benefit derived from enteral feeding may reflect dietary fat content.[11] Those liquid diets that are most effective in inducing remission of active CD are either very low in fat or supply one third of their dietary fat in the form of medium-chain triglycerides (MCTs) from coconut oil.[35,36] The addition of long-chain triglycerides derived from vegetable oils attenuates benefit,[37] whereas diets enriched with MCT oil are as effective as very-low-fat diets.[38] MCT oil may have a direct antiinflammatory effect, by modulating expression of adhesion molecules and cytokines.[11] The potential role of omega-3 fatty acids in treatment of IBD is discussed later in the section on supplements.

The main advantage of enteral feeding as primary therapy for CD is avoidance of medication side effects, especially in children.[39] Although no clear clinical predictors of response have been established, clinicians believe that patients treated early in the course of CD are more likely to respond than are patients with long-standing disease.[11] Small studies have indicated that remission may be more likely in patients with ileal involvement than colonic involvement only[40] and with perforating or fistulating disease than with more superficial disease.[41] The main disadvantages of enteral feedings is poor compliance because of the lack of palatability and the high rate of relapse (more than 60%) following the discontinuation of these feedings. The use of exclusion diets (discussed later) may significantly extend the benefit of enteral feeding regimens.

Specific Carbohydrate Diet

The Specific Carbohydrate Diet (see Key Web Resources) is a food-based approach to enteral nutrition for patients with IBD and many anecdotal reports have noted long-term remission without medication.[42] The alleged mechanisms of action of this diet are improvement of nutritional status and alteration in ileocecal flora by the proper choice of nutritious carbohydrate sources.[43] The diet is far more effective for patients with CD than UC (Elaine Gottschall, personal communication, 1994). In practice, the diet consists of meat, poultry, fish, eggs, most vegetables and fruits, nut flours, aged cheese, homemade yogurt, and honey. Forbidden foods include all cereal grains and their derivatives (including sweeteners other than honey), legumes, potatoes, lactose-containing dairy products, and sucrose. Early studies found that high sucrose intake predisposed to CD[44-47] and that control of disease was enhanced by its avoidance.[48]

I have used the Specific Carbohydrate Diet as primary treatment for patients with CD since the 1990s and have observed an overall response rate of 55%, unrelated to duration of illness but most pronounced in patients with ileitis or perianal fistula.[49] Improvement occurred in symptoms and laboratory parameters, such as serum albumin and erythrocyte sedimentation rate (ESR), and permitted decreased use of glucocorticoids.

Diets that induce remission of CD do not usually induce remission of UC, although they improve patients' nutritional status and prevent complications related to surgery.[11] Although I have occasionally seen a patient with UC who responded very well to the Specific Carbohydrate Diet, research suggests that modification in dietary sources of fat and protein, rather than carbohydrates, may be therapeutic for patients with UC. A role for dietary fat in the pathogenesis of UC is suggested by the association between incident UC and high consumption of vegetable oils rich in linoleic acid (18:2n6).[50] These individuals also show increased levels of arachidonic acid (20:4n6), a metabolite of linoleic acid, in fat biopsies, before development of UC.[51] In contrast, dietary omega-3 fatty acids, especially docosahexaenoic acid (DHA, 22:6n3) may exert a preventive effect on development of UC.[52]

Nutritional approaches to treatment of UC have examined the therapeutic potential of short-chain fatty acids, in particular butyric acid.[11] Not only do short-chain fatty acids nourish the colonic epithelium, but also they lower intraluminal pH, thus favoring growth of *Lactobacillus* and *Bifidobacterium* (considered to be beneficial organisms, or probiotics) and inhibiting the growth of *Clostridium, Bacteroides,* and *Escherichia coli,* which are potential pathogens. In addition to serving as the preferred energy substrate for colonic epithelial cells, butyrate has a true antiinflammatory effect, preventing activation of the proinflammatory nuclear transcription factor NF-kappaB.[53] When added to 5-aminosalicylic acid (5-ASA) enemas, butyrate (80 mmol/L) induces remission in ulcerative proctitis that is resistant to combined 5-ASA–hydrocortisone enemas.[54] Because butyrate is normally produced by bacterial fermentation of indigestible carbohydrate in the colon, studies have examined the effect of fiber supplementation on the course of UC. These studies are described later in the section on prebiotics.

Patients with UC are not deficient in butyrate, but they appear unable to use it, perhaps because organic sulfides produced by their enteric flora inhibit the epithelial effects of butyrate.[55,56] Protein consumption is a major determinant of sulfide production in the human colon.[57] Higher intake of protein, especially from animal sources, is associated with an increased risk of developing UC.[58]

For patients with UC in remission, the risk of relapse is directly influenced by higher consumption of protein, especially meat protein, and by total dietary sulfur and sulfates.[59] An interesting effect of 5-ASA derivatives, drugs proven to help prevent relapse of UC, is inhibition of sulfide production by gut bacteria, with sulfasalazine having the strongest effect.[60] Levels of sulfate-reducing bacteria, required for production of sulfides from dietary sulfate, are higher in fresh fecal samples of patients with UC and active pouchitis than in patients with UC and normal ileoanal pouches or in postcolectomy patients with familial polyposis who have ileoanal pouches.[61] Based on these findings, a reasonable if unproven dietary approach to help patients with UC maintain remission would be one high in fiber and omega-3 fatty acids and low in meat, eggs, dairy fat, and vegetable oils.

Exclusion Diets

Exclusion diets eliminate specific symptom-producing foods and have been used to maintain remission of IBD. Although self-reported food intolerance is common among patients with IBD,[62] most of the data from controlled studies have been gathered from patients with CD. In the East Anglia Multicentre Controlled Trial, 84% of patients with active CD entered clinical remission after 2 weeks of a liquid elemental diet,[63] which produced a significant decrease in ESR and C-reactive protein (CRP) and an increase in serum albumin. Patients were then randomized to receive treatment either with prednisolone or with a specific food exclusion diet. To determine which foods each patient needed to avoid, a structured series of dietary challenges was conducted. Patients would introduce foods of their choice, one at a time. Any food that appeared to provoke symptoms was excluded from further consumption; foods that did not provoke symptoms were included in a maintenance diet. At 6 months, 70% of patients treated with diet were still in remission, compared with 34% of patients treated with prednisolone. After 2 years, 38% of patients treated with specific food exclusion were still in remission, compared with 21% of steroid-treated patients. In previous uncontrolled studies, some of the same investigators had used a diet consisting of one or two meats (usually lamb or chicken), one starch (usually rice or potatoes), one fruit, and one vegetable, instead of the elemental diet, to induce remission. Structured food challenges were then used to construct a maintenance diet free of symptom-provoking foods. Compliance with the specific food elimination diet was associated with a rate of relapse that was less than 10% per year.[64] Individual foods found most likely to provoke symptoms in this study were wheat, cow's milk and its derivatives, cruciferous vegetables, corn, yeast, tomatoes, citrus fruit, and eggs.

Many patients with CD develop antibodies to baker's and brewer's yeast, *Saccharomyces cerevisiae* (ASCA).[65] Lymphocytes of ASCA-positive patients proliferate after stimulation with mannan, a lectin common to most types of yeast. For these patients, lymphocyte proliferation is associated with increased production of TNF-alpha.[66] A small placebo-controlled study found that patients with stable, chronic CD experienced a significant reduction in the CD activity index (CDAI) during 30 days of dietary yeast elimination and a return to baseline disease activity when capsules of *S.cerevisiae* were added to their diets.[67]

An observational study of patients with UC suggested that dietary practices based on food avoidance did not appear to modify the risk of relapse,[68] but a small experimental study from South Africa found that diarrhea, rectal bleeding, and the appearance of the colon on sigmoidoscopy improved significantly more for patients receiving a diet that systematically eliminated symptom-provoking foods than for those assigned only to monitor their diets.[69] The potential value of this study is reduced by the small number of patients and the maintenance of remission despite a return to an unrestricted diet after 6 months. Earlier reports from dietary trials led to an estimate that 15% to 20% of patients with UC have specific food intolerance that affects severity of illness, with cow's milk protein the leading offender.[70] This estimate is consistent with my clinical experience (see Chapter 84, Food Intolerance and Elimination Diet).

Supplements

Nutritional supplements may be used to correct or prevent the deficiencies that are common among patients with IBD or to achieve an antiinflammatory effect.

Folates

5-ASA derivatives, sulfasalazine in particular, impair folic acid transport.[71] Reduced folic acid in patients with IBD is associated with hyperhomocysteinemia,[72] a risk factor for deep vein thrombosis,[73] which is an extraintestinal complication of IBD. Concurrent administration of folic acid with 5-ASA derivatives prevents folic acid depletion and has been shown to reduce the incidence of colon cancer in patients with UC.[74,75] One study found that a high dose of folic acid (15 mg/day) reversed sulfasalazine-induced pancytopenia in two patients.[76]

Vitamin B_{12}

Because vitamin B_{12} absorption may be impaired by ileal inflammation and by small bowel bacterial overgrowth, deficiency of vitamin B_{12} has long been described as a potential complication of CD.[77] Although frank vitamin B_{12} deficiency is unusual, lower vitamin B_{12} levels are associated with increased serum homocysteine in patients with CD.[78] Ischemic strokes in a woman with CD were associated with vitamin B_{12}–reversible hyperhomocysteinemia.[79] A single dose of 1000 mcg of cobalamin by injection corrects the megaloblastic anemia associated with CD.[80]

Vitamin B_6

Median vitamin B_6 levels are significantly lower in patients with IBD than in controls; low levels are associated with active inflammation and hyperhomocysteinemia.[81] Although some homocysteine is removed by folate-vitamin B_{12}–dependent remethylation, the bulk of homocysteine is converted to cystathionine in a reaction catalyzed by vitamin B_6. Ischemic stroke and high-grade carotid obstruction in a young woman with CD were attributed to hyperhomocysteinemia, vitamin B_6 deficiency, and a heterozygous methylene-tetrahydrofolate reductase gene mutation. The investigators believed that vitamin B_6 deficiency was the principal cause of hyperhomocysteinemia in this patient.[82]

Vitamins E and C

Blood levels of vitamins E and C are often reduced in patients with IBD.[83] Administration of alpha-tocopherol, 800 units per day, and vitamin C, 1000 mg per day, to patients with stable, active CD decreased markers of oxidative stress but had no effect on the CDAI.[84] A small study of patients with ulcerative proctitis demonstrated significant improvement after 2 weeks of vitamin E administered as a rectal suppository.[85]

Vitamin A

Although levels of carotenoids[86] and retinol[87] are diminished in patients with active CD, low levels appear to be related not to malabsorption but to inflammation,[88,89] as well as a reduction in circulating retinol binding protein.[90] Supplementation with vitamin A at doses of 100,000 to 150,000 units per day had no effect on symptoms or CDAI.[91,92]

Vitamin D

Reduced blood levels of 25-OH cholecalciferol, the major vitamin D metabolite, are common in patients with CD and are related to malnutrition and lack of sun exposure.[93,94] One study found that patients with CD who received 1200 units of vitamin D_3 daily for 12 months had less than half the risk of relapse than those treated with placebo.[95] Administration of vitamin D, 1000 units per day for 1 year, prevented bone loss in patients with active disease.[96] The major causes of bone loss in IBD, however, are the effects of inflammatory cytokines and glucocorticoid therapy,[97] not vitamin D status. Calcitriol (1,25-dihydroxycholecalciferol), the most active metabolite of vitamin D, may actually be increased in patients with IBD because activated intestinal macrophages increase calcitriol synthesis; elevated calcitriol is associated with increased risk of osteoporosis and may serve as a marker of disease activity.[98] Hypercalcemia is a rare complication of excess calcitriol, and serum calcium should be monitored in patients with IBD receiving vitamin D supplements.[99]

Vitamin K

Biochemical evidence of vitamin K deficiency has been found in patients with ileitis and in patients with colitis who were treated with sulfasalazine or antibiotics.[100] Serum vitamin K levels in CD are significantly decreased compared with normal controls and are associated with increased levels of undercarboxylated osteocalcin, a finding indicating low vitamin K status in bone. In patients with CD, undercarboxylated osteocalcin is inversely related to lumbar spine bone density.[101] Furthermore, the rate of bone resorption in CD is inversely correlated with vitamin K status, a finding suggesting that vitamin K deficiency may be another etiologic factor in osteopenia of IBD.[102] The optimal dose of vitamin K for correction of deficiency is not known. Patients with active disease may not absorb oral vitamin K, even at high dosage.[103]

Calcium

Although calcium supplementation is recommended for maintaining bone density in patients with IBD, especially those receiving glucocorticoids, calcium supplementation (1000 mg per day) with 250 units of vitamin D per day, conferred no significant benefit to bone density at 1 year in patients with corticosteroid-dependent IBD and osteoporosis.[104] Nonetheless, calcium supplementation should be given to patients with low dietary calcium intake. In experimental animals, low dietary calcium increases severity of IBD.[105]

Zinc

Low plasma zinc is common in patients with CD and may be associated with clinical manifestations such as acrodermatitis, decreased activity of zinc-dependent enzymes such as thymulin and metallothionein, reduction in muscle zinc concentration, and poor taste acuity.[11] Zinc absorption is impaired and fecal zinc losses are inappropriately high.[18] Zinc-deficient adolescents with CD grow and mature more normally when zinc deficiency is treated. Anecdotally, correction of zinc deficiency as a specific intervention has been associated with global clinical improvement, a finding suggesting that zinc replacement may have beneficial effects on disease activity.[106] A small study of patients in remission from CD found that high-dose supplementation with zinc sulfate, 110 mg three times a day for 8 weeks, significantly decreased small intestinal permeability for a period of 12 months.[107] In patients with active disease, zinc sulfate, 200 mg per day (but not 60 mg per day) significantly increased plasma zinc and thymulin activity.[108]

> Zinc competes with copper, iron, calcium, and magnesium for absorption. When administering high doses of zinc, consider administering a multimineral at a separate time of day. Zinc is absorbed best if not taken at the same time as copper, magnesium, or iron.

Selenium

Low selenium levels in patients with CD are associated with increased levels of TNF-alpha and decreased levels of the antioxidant enzyme glutathione peroxidase (GSHPx).[109] In one study, although selenium supplementation raised plasma selenium to the level of a control population, it did not significantly increase activity of GSHPx.[110] Patients with small bowel resection are at risk for severe selenium deficiency; monitoring of selenium status and selenium supplementation

has been recommended for this group in particular.[111] Patients receiving enteral feeding with liquid formula diets experience decreased selenium concentrations proportional to the duration of feeding, a finding suggesting that additional selenium supplementation is also needed by these patients.[112]

Magnesium

Magnesium deficiency is a potential complication of IBD, a result of decreased oral intake, malabsorption, and increased intestinal losses from diarrhea. Urinary magnesium is a better predictor of magnesium status than is serum magnesium in this setting.[113] Reduced urinary magnesium excretion is a significant risk factor for urolithiasis, one of the extraintestinal manifestations of IBD.[114] For patients with IBD, the urinary ratio of magnesium and citrate to calcium is a better predictor of lithogenic potential than is urinary oxalate excretion.[115] Supplementation with magnesium and citrate may decrease urinary stone formation, but diarrhea is a dose-related, limiting side effect.

Chromium

Glucocorticoid therapy increases urinary chromium excretion, and chromium picolinate, 600 mcg per day, can reverse steroid-induced diabetes in humans, with a decrease in mean blood glucose from 250 to 150 mg/dL. Chromium supplementation may be of benefit for patients receiving glucocorticoids who have impaired glucose tolerance.[116]

Iron

Anemia occurs in approximately 30% of patients with IBD.[117] The causes of anemia in these patients include iron deficiency from blood loss, cytokine-induced suppression of erythropoiesis, and side effects of medication. Some investigators have speculated that iron deficiency actually increases the IFN-gamma response in Th1-driven inflammation and may contribute to aggravation of CD.[118] Most clinicians, however, avoid oral iron supplements, however, because they believe that iron can increase oxidative stress in the gut, given that very-high-dose iron supplementation consistently aggravates experimental colitis in rodents.[118] The doses used in rodent studies are orders of magnitude greater than the doses given to patients, however. The relative risks and benefits of oral iron supplementation for patients with IBD are uncertain.

Fish Oils

Biochemical studies indicate that 25% of patients with IBD show evidence of essential fatty acid deficiency.[119] In experimental animals, fish oil feeding ameliorated the intestinal mucosal injury produced by methotrexate.[120] In tissue culture, omega-3 fatty acids stimulated wound healing of intestinal epithelial cells.[121] As mentioned earlier,[52] high dietary intake of omega-3 fatty acids is associated with a reduced incidence of UC. For patients with active UC, a fish oil preparation supplying 3200 mg of eicosapentaenoic acid (EPA) and 2400 mg of DHA per day decreased symptoms and lowered the levels of leukotriene B_4 (LTB_4) in rectal dialysates, with improvement demonstrated after 12 weeks of therapy.[122] A similar preparation improved histologic score and symptoms of patients with proctocolitis.[123] At a dose of 4200 mg of omega-3 fatty acids per day, fish oils were shown to reduce dose requirements for antiinflammatory drug therapy of UC.[124] At a dose of 5100 mg of omega-3 fatty acids per day, fish oils combined with 5-ASA derivatives prevented early relapse of UC better than 5-ASA derivatives plus placebo, but fish oils alone did not maintain remission.[125] In all studies of UC, the fish oil preparations consisted of triacylglycerols. In vitro, fish oil has a more pronounced antiinflammatory effect on tissue culture of colonic specimens from patients with UC than from patients with CD.[126] Controlled trials of omega-3 therapy for CD have been generally disappointing,[127] although an early study from Italy using a delayed-release preparation supplying free EPA (1800 mg per day) and free DHA (800 mg per day) was much more effective than placebo in preventing relapse of CD in patients not taking 5-ASA derivatives.[128] The main side effect of fish oils is diarrhea.

Glutamine

Glutamine appears to have a special role in restoring normal small bowel permeability and immune function. Patients with intestinal mucosal injury secondary to chemotherapy or radiation benefit from glutamine supplementation with less villous atrophy, increased mucosal healing, and decreased passage of endotoxin through the gut wall.[129] Although integrative practitioners often advocate glutamine therapy for treatment of IBD, controlled studies have shown no benefit from glutamine supplementation at doses as high as 20 g per day in patients with CD.[130,131] Glutamine excess aggravates experimental colitis in rodents[132] and increases oxidative stress,[133] so high-dose glutamine supplements may be contraindicated in patients with colitis.

N-*Acetylglucosamine*

N-Acetylglucosamine (NAG) is a substrate for synthesis of glycosaminoglycans, glycoproteins that protect the bowel mucosa from toxic damage. Synthesis of NAG by *N*-acetylation of glucosamine is impaired in patients with IBD.[134] In explants of bowel tissue from patients, incorporation of added NAG was depressed in patients with inactive UC and increased to control levels in those with active colitis, a finding probably indicating the response of gut tissue to inflammation.[135] In a pilot study, NAG (3 to 6 g per day for more than 2 years) given orally to children with refractory IBD produced symptomatic improvement in most patients and an improvement in histopathologic features.[136] In children with distal colitis or proctitis, the same dose of NAG was administered by enema with similar effects.[134]

N-*Acetylcysteine*

N-Acetylcysteine is needed for synthesis of glutathione, has antioxidant and antiinflammatory effects, and has been shown to ameliorate experimental colitis. In a small, short-term clinical trial, *N*-acetylcysteine (800 mg per day), when added to mesalamine therapy of patients with active UC, produced a significant improvement in clinical response compared with mesalamine plus placebo.[137]

Phosphatidylcholine

Phosphatidylcholine (PC) is a component of cell membranes that is secreted into the intestinal mucus barrier, where it down-regulates TNF-alpha signaling.[138] PC concentration of ileal and colonic mucus of patients with UC is approximately one sixth the concentration found in healthy controls or patients with CD, a finding suggesting that this deficit may play a specific pathogenetic role in UC.[139] A clinical trial of

delayed-release PC, 500 mg four times a day, allowed 80% of patients with steroid-dependent UC to withdraw from steroids without disease exacerbation; the response rate in the placebo arm of the trial was only 10%.[140] In other placebo-controlled studies by the same group, 6000 mg per day of delayed-release PC added to 5-ASA inhibitors effected significant reductions in clinical, endoscopic, and histologic disease activity and improved quality of life when compared with placebo.[141] Response to delayed-release PC takes a median of 5 weeks and occurs at doses as low as 1000 mg per day.[142]

Melatonin

Although some researchers have advocated melatonin as a therapy for IBD, melatonin is a potent inducer of Th1 lymphocytes, and aggravation of UC and CD with melatonin supplementation has been reported.[143-145]

Some supplements may be strongly contraindicated because of potential toxicity: the strongest evidence exists for melatonin in Crohn disease, glutamine in ulcerative colitis, and *Echinacea* in patients taking immunosuppressants.

Probiotics

Probiotic therapy of IBD is attracting considerable attention because of the recognition that alteration of intestinal microflora may modulate intestinal immune responses[146] and act as triggers for inflammation in patients with IBD.[147] Because of the large numbers of probiotic preparations available, this section discusses only those preparations that are commercially available in the United States and that have been studied in clinical trials of patients with IBD. More data exist for their benefits in UC than in CD.

VSL-3

VSL-3 is a proprietary mixture of *Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus plantarum, Bifidobacterium brevis, Bifidobacterium infantis, Bifidobacterium longum,* and *Streptococcus salivarius* ssp *thermophilus,* supplied in sachets containing 900 billion colony-forming units (CFUs) each. When added to therapy with the 5-ASA derivative balsalazide, VSL-3 (one sachet twice a day) induced faster remission of active UC than balsalazide or mesalamine alone.[148] Induction of remission with VSL-3 alone has been attained in 42%[149] to 54%[150] of adults with mild to moderate UC. VSL-3 also prevents relapse of pouchitis (postcolectomy inflammation of the ileal pouch).[151] Two sachets once a day produced remission rates far better than placebo over a 1-year period.[152] A clinical trial in children who were receiving steroid and mesalamine induction therapy for UC found that VSL-3, when compared with placebo, increased the rate of remission induction from 36.4% to 92.8% and reduced the rate of relapse within 12 months from 73.3% to 21.4%.[153] A possible problem with VSL-3 is poor compliance among patients not participating in clinical trials, perhaps because of the cost or inconvenience of administration.[154]

Lactobacillus *GG*

Lactobacillus rhamnosus var GG, at a dose of 10 to 20 billion CFUs per day, was found to prevent the onset of pouchitis in patients with ileal pouch–anal anastomosis during the first 3 years after surgery in a placebo-controlled trial.[155] *Lactobacillus* GG has been ineffective in inducing or maintaining remission of patients with CD[156] or in preventing relapse of CD after surgical resection.[157]

Saccharomyces boulardii

This plant-derived yeast demonstrated multiple antiinflammatory effects when it was administered to laboratory animals, including interference with the activity of NF-kappaB, a critical promoter of inflammatory cytokine transcription, and promotion of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) activity, which protects the gut mucosa from inflammation.[158] *S. boulardii* has shown benefit in both UC and CD. The addition of *S. boulardii* (250 mg three times a day) to maintenance mesalamine therapy of patients with chronic, active UC was associated with induction of remission within 4 weeks in 17 of 25 patients.[159] This trial was uncontrolled. In a placebo-controlled trial, the same dose was given to patients with stable, active CD and mild to moderate diarrhea. *S. boulardii* reduced the frequency of diarrhea and the CDAI when it was given over a 10-week period, with benefits apparent within 2 weeks.[160] When added to mesalamine therapy of patients with CD in remission, *S. boulardii* (1000 mg per day) reduced the frequency of relapse from 37% to 6.25% during 6 months, when compared with mesalamine alone,[161] and it also decreased the pathologic elevation of small intestinal permeability.[162]

Although *S. boulardii* is considered nonpathogenic, case reports of *S. boulardii* fungemia have been described in critically ill or immunocompromised patients exposed to this yeast. At least 18 reports of this complication have been published, including a report in which airborne spread of *S. boulardii* occurred in an intensive care unit.[163]

Prebiotics

Prebiotics are nondigestible food ingredients that stimulate the growth or modify the metabolic activity of intestinal bacterial species that have the potential to improve the health of their human host. Criteria for classification of a food ingredient as a prebiotic are that it remain undigested and unabsorbed as it passes through the upper part of the gastrointestinal tract and is a selective substrate for the growth of specific strains of beneficial bacteria (usually *Lactobacillus* or *Bifidobacterium*), rather than for all colonic bacteria. Prebiotic food ingredients include bran, psyllium husk, resistant (high-amylose) starch, inulin (a polymer of fructofuranose), lactulose, and various natural or synthetic oligosaccharides that consist of short-chain complexes of sucrose, galactose, fructose, glucose, maltose, or xylose. The best-known effect of prebiotics is to increase fecal water content, thus relieving constipation.

Bacterial fermentation of prebiotics yields short-chain fatty acids such as butyrate. Fructooligosaccharides (FOSs) have been shown to alter fecal biomarkers (pH and the concentration of bacterial enzymes such as nitroreductase and beta-glucuronidase) in a direction that may convey protection against the development of colon cancer.[164] FOSs have also been shown to reduce fecal concentration of hydrogen sulfide in healthy volunteers,[165] an effect that may decrease colonic inflammation in patients with UC. In fact, several studies suggested benefits of various prebiotics for the treatment of UC. Oat bran, 60 g per day (supplying 20 g of dietary fiber),

increased fecal butyrate by 36% in patients with UC and diminished abdominal pain.[166] A dietary supplement containing fish oil and two types of indigestible carbohydrate, FOS and xanthum gum, allowed reduction of glucocorticoid dosage when compared with a placebo in patients with steroid-dependent UC.[167] A Japanese germinated barley foodstuff (GBF) containing hemicellulose-rich fiber, at a dose of 20 to 30 g per day, increased stool butyrate concentration,[168] decreased the clinical activity index of patients with active UC,[169] and prolonged remission in patients with inactive UC.[170] Wheat grass juice, 100 mL twice daily for 1 month, tested in a small placebo-controlled trial of patients with distal UC,[171] produced a significant reduction in rectal bleeding, abdominal pain, and disease activity as measured by sigmoidoscopy.

Synbiotics

Synbiotics are combinations of probiotics and prebiotics. A mixture of *B. longum* and inulin-derived FOSs administered for 1 month as monotherapy to patients with UC produced improvement in sigmoidoscopic appearance, histologic features, and several biochemical indices of tissue inflammation when compared with a placebo control.[172] A Japanese study found that the administration of *B. longum,* 20 billion CFUs per day, with psyllium powder, 8 g per day for 4 weeks, to patients with UC reduced CRP by 76% and improved quality of life, whereas neither agent alone was effective.[173]

Bovine Colostrum

Colostrum is the first milk produced after birth and is particularly rich in immunoglobulins, antimicrobial peptides (e.g., lactoferrin and lactoperoxidase), and other bioactive molecules, including growth factors. Peptide growth factors in colostrum may provide novel treatment options for various gastrointestinal conditions.[174] Colostrum enemas, 100 mL of a 10% solution, administered twice a day by patients with distal UC, proved superior to a control enema in promoting healing; all patients were also taking a fixed dose of mesalamine.[175] Studies of oral colostrum in IBD have not been reported, but 125 mL three times a day fed to healthy human volunteers was shown to prevent the increase in intestinal permeability produced by indomethacin.[176] This finding suggests that peptide growth factors survive passage through the stomach and upper small bowel.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is the steroid hormone produced in greatest quantity by the human adrenal cortex and is circulating primarily in the sulfated form, DHEA-S. DHEA inhibits activation of NF-kappaB, which is activated in inflammatory lesions. Patients with IBD have lower levels of DHEA-S in serum and intestinal tissue than do controls.[177] This finding is partially associated with prior treatment with glucocorticoids.[178] In men with IBD, low DHEA-S is associated with increased risk of osteoporosis.[179] In a pilot study, 6 of 7 patients with refractory CD and 8 of 13 patients with refractory UC responded to DHEA (200 mg per day for 56 days), with decrease in the clinical activity index.[180] A case report demonstrated benefit of the same dose of DHEA in a woman with severe refractory pouchitis, with relapse occurring 8 weeks after discontinuation of DHEA.[181]

Botanicals

In traditional Chinese medicine and Ayurveda, herbal extracts are the mainstay of treatment for IBD and appear to be effective when used by practitioners trained in those systems. Botanicals commonly taken by patients with IBD include slippery elm, fenugreek, devil's claw, *Gingko biloba, Angelica sinensis* (Dong quai), and licorice. Although these botanicals all express antioxidant or antiinflammatory activity in vitro,[182–184] data from clinical trials are lacking. Four botanical therapies with high safety profiles and that are readily available in the United States have been studied in clinical trials and are discussed here.

Curcumin

A complex of flavonoids derived from the spice turmeric *(Curcuma longa),* curcumin has potent antiinflammatory effects in vitro.[185,186] Despite its poor solubility, stability, and systemic bioavailability, curcumin showed benefits in two small clinical trials of patients with CD and UC. In a placebo-controlled trial of patients with UC in remission, curcumin, 1000 mg twice a day, was administered with meals for 6 months along with maintenance sulfasalazine or mesalamine. The relapse rate in the curcumin group was 4.65%, compared with 20.51% in the placebo group. In an uncontrolled study, four of five patients with CD demonstrated reduction of the ESR and CDAI, and four of five patients with ulcerative proctitis were able to reduce concomitant medication dosage while they were taking a pure curcumin preparation.[187] A study of patients with colorectal cancer demonstrated that a dose of 3600 mg per day of curcumin orally yielded only trace levels in peripheral blood but reached a pharmacologically active concentration in neoplastic and normal colonic mucosa, thus inhibiting a key step in carcinogenesis.[188] Because IBD is a major risk factor for colon cancer, this finding makes curcumin an attractive therapeutic agent.

Boswellia serrata

The Ayurvedic herb *Boswellia serrata* (Indian frankincense) contains boswellic acids, which inhibit leukotriene biosynthesis in neutrophilic granulocytes by noncompetitive inhibition of 5-lipoxygenase.[189] During a small 6-week trial, 350 mg three times a day of *Boswellia* gum resin was as effective as sulfasalazine, 1000 mg three times a day, in reducing symptoms or laboratory abnormalities of patients with active UC.[190] The rate of remission was 82% with *Boswellia* and 75% with sulfasalazine.[191] A proprietary *Boswellia* extract, H15, was found as effective as mesalamine in improving symptoms of active CD in a randomized double-blind study from Germany.[192]

Aloe Vera

Aloe vera gel has a dose-dependent inhibitory effect on production of reactive oxygen metabolites, prostaglandin E_2, and (at high doses) IL-8, by human colonic epithelial cells grown in tissue culture.[193] Oral aloe vera gel, 100 mL twice a day for 4 weeks, produced a clinical response significantly more often than placebo (response ratio, 5.6) in patients with UC.[194] Remission occurred in 30% of patients taking aloe vera gel and in 7% of patients receiving placebo. Aloe also reduced histologic disease activity, whereas placebo did not. No significant side effects were described, although aloe vera gel is often used as a laxative. Acemannan, an extract of *Aloe vera*, concentrated

to a mucopolysaccharide concentration of 30% of solid weight, was demonstrated to reduce symptoms and indices of inflammation in controlled studies of patients with UC.[195]

Pistacia lentiscus *Resin (Mastic Gum)*

In the Mediterranean region, mastic gum has a long history of use as a food and herbal remedy for gastrointestinal complaints. A pilot study of 10 patients with mild to moderate active CD who were given 2220 mg per day of mastic gum over 4 weeks demonstrated reduction in the CDAI and circulating levels of CRP and IL-6.[196] These findings were associated with a reduction in TNF-alpha production by peripheral blood mononuclear cells.[197]

Mind-Body Therapy

Although investigators widely believe that stress aggravates IBD, a prospective study did not validate the notion that stressful life events can trigger relapse.[198] A significant relationship between stress and inflammation has been found only when UC and CD are studied independently, but studies of mixed samples of patients with CD or UC have mostly had negative results. The results of five studies of psychological interventions in IBD were negative or only modestly supportive of benefit.[199] Three prospective studies of different types of psychotherapy for patients with IBD failed to show any improvement in medical outcome compared with standard care.[200–202] Counseling by a trained IBD counselor focusing primarily on illness-related concerns, however, resulted in decreased rates of relapse and outpatient visits, but not of hospitalization, over a 2-year period.[203] Higher levels of social support are associated with improved outcomes among patients with CD, especially patients with low body mass index.[204]

Self-Management Training

Knowledge, skill, and confidence in self-health management are highly correlated with health-related quality of life in patients with IBD.[205] A patient-centered educational approach developed at the University of Manchester in the United Kingdom was shown to have a significant impact on health care use by patients with UC. When compared with a control group that received customary care, the intervention group required one third as many physician visits and one third as many hospitalizations. The difference in outcome was not related to specific treatments employed, but rather to the empowerment of patients to be actively involved in managing their own care.[206] The method used was as follows: During a 15- to 30-minute consultation, physicians specifically asked patients about the symptoms they had experienced during past relapses and reviewed past and current treatments used to control symptoms, with an emphasis on the specific effectiveness of each treatment and its acceptability to the patient. Physician and patient then design a personalized self-management strategy based on the patient's recognition of symptoms and a mutually acceptable treatment protocol for the patient to initiate at the onset of a relapse.

Acupuncture

Acupuncture and moxibustion are commonly employed by practitioners of Chinese medicine for treatment of UC. Uncontrolled studies from China claimed excellent results.[207,208] A review of studies from both the Chinese and Western literature supported the efficacy of acupuncture in the regulation of gastrointestinal motor activity and secretion through opioid and other neural pathways.[209] A review of clinical trials of acupuncture for gastrointestinal disorders found one clinical trial of UC and one of CD with robust research designs. In each trial, true acupuncture was superior to sham acupuncture with regard to effect on disease activity indices.[210] A meta-analysis from Korea of five clinical trials of moxibustion for UC found favorable results when compared with conventional drug therapy, but all studies were deemed of poor quality and subject to bias.[211]

Pharmaceuticals and Helminths

Antimicrobial Drugs

Antibiotics are sometimes helpful for exacerbations of IBD, especially for CD and for draining fistula.[212,213] Metronidazole is the most commonly used agent; it is the first-line drug for treatment of pseudomembranous colitis caused by *Clostridium difficile* toxin, a complication of IBD that, in patients with active colitis, may occur spontaneously without prior antibiotic exposure. *S. boulardii* (1000 mg per day) enhances the therapeutic efficacy of metronidazole in the treatment of recurrent *C. difficile* colitis.[214] Some other natural products may interfere with the efficacy of metronidazole: Silymarin, a group of flavonoids extracted from milk thistle, at a dose of 140 mg per day for 9 days, decreased the peak plasma concentration and bioavailability of metronidazole and its major metabolite by 30% in healthy volunteers.[215] Vitamin E (400 units per day) with vitamin C (500 mg per day) reduced the effectiveness of metronidazole against metronidazole-sensitive *Helicobacter pylori* infection by 40%.[216]

A discussion of antibiotic protocols for IBD is outside the scope of this chapter. Commonly employed agents include ciprofloxacin, clarithromycin, and rifaximin.[217,218]

Antifungal therapy is sometimes embraced by integrative practitioners. Its use was supported by a study from Poland.[219] Quantitative stool cultures revealed high levels of colonization with *Candida* species (primarily *Candida albicans*) in 37% of patients with active UC of at least 5 years' duration and 20% of those with shorter duration but in only 1% of controls with irritable bowel syndrome. Patients with high yeast levels who were treated with fluconazole for 4 weeks in addition to conventional therapy had a significant improvement in clinical and endoscopic disease activity compared with similar patients treated with placebo plus conventional therapy.

> Always ask patients about the effect of antibiotics, including those drugs used for unrelated illnesses, on their gastrointestinal symptoms. Improvement of symptoms during antibiotic therapy may be an indication to use that antibiotic empirically during an exacerbation of symptoms. Aggravation of symptoms during antibiotic therapy may be an indication to avoid the specific antibiotic and employ probiotics.

Naltrexone

The opioid antagonist naltrexone has been described as an immune modulator when it is used at low doses.[220] In an open study of 17 patients with active CD who were receiving 4.5 mg per day of naltrexone for 12 weeks, 89% exhibited

improvement in CDAI, and 67% achieved clinical remission. The benefits persisted for 4 weeks after therapy was discontinued. The most common side effect was sleep disturbance.[221]

Helminths

An application of the hygiene hypothesis to IBD reasons that loss of indigenous colonization with helminths is responsible for dysregulated immune responses.[222,223] Pork whipworm *(Trichuris suis)* and hookworm *(Necator americanus)* have been administered to patients with IBD in an effort to induce remission.[224] Clinical trials have demonstrated significant effects of oral administration of *T. suis* ova in both UC and CD. In patients with UC who received 2500 ova every 2 weeks for 12 weeks, the disease activity index was significantly reduced in 43.3% of patients receiving *T. suis* and 16.7% of those receiving placebo.[225] In an uncontrolled study of patients with active CD who received 2500 ova every 3 weeks for 24 weeks, the rate of clinical disease remission was 72.4%.[226]

5-Acetylsalicylic Acid Derivatives

Mesalamine, sulfasalazine, balsalazide, and olsalazine are used for inducing remission in mild cases of UC or CD and for maintenance of remission. The value of continuous therapy with 5-ASA derivatives at relatively high doses for maintenance of remission in UC is now well established. Side effects may include folate deficiency (discussed earlier), exacerbation of diarrhea, hair loss, and rash.

The efficacy of 5-aminosalicyclic acid (5-ASA) derivatives in inducing remission of inflammatory bowel disease can be enhanced by fish oils supplying 4000 mg of eicosapentaenoic acid plus docosahexaenoic acid per day and by probiotics (VSL-3, two packets a day, or *Saccharomyces boulardii,* 250 mg three times a day).

Glucocorticoids

Steroids are used to induce remission of IBD, but they have shown no benefit in maintaining remission. Not only do glucocorticoids suppress adrenal function, cause a decline in release of DHEA (discussed earlier), and impair immune function, but also their side effects include cataracts, growth failure, hypogonadism, and osteopenia. These agents decrease intestinal calcium absorption, increase renal calcium excretion, and induce parathyroid hormone secretion.

Immunosuppressants

6-Mercaptopurine and its derivative, azathioprine, are used for induction and maintenance of remission in IBD. Although usually well tolerated at low doses, these agents may cause leukopenia, anemia, and hepatic dysfunction and promote opportunistic infection. Immune-stimulating herbs, such as *Echinacea* and *Astragalus* species, may reverse the benefits of immune suppressants in the treatment of autoimmune disorders.[227,228] Concomitant use should be avoided.

Cyclosporine is occasionally used for inducing remission in refractory UC. Its absorption is drastically reduced by St. John's wort[229] and may be dangerously increased by peppermint oil.[230] Cyclosporine nephrotoxicity is diminished by administration of fish oil supplying 3000 to 4000 mg of omega-3 fatty acids per day[231,232] and by vitamin E (D-alpha tocopherol, 500 units per day).[233] Ipriflavone, a semisynthetic isoflavonoid used for prevention of bone loss, may produce lymphopenia.[234] Patients receiving immunosuppressants should avoid this agent.

Tumor Necrosis Factor-alpha Blockade

TNF-alpha blockade with infliximab (Remicade) is a major advance in drug therapy for inducing remission of IBD. Adverse events reported in patients treated with anti-TNF agents include acute infusion reactions, delayed hypersensitivity–type reactions, autoimmune diseases such as drug-induced lupus and demyelination, and infection.[235] Cigarette smoking interferes with response to infliximab in patients with CD.[236]

Surgery

Surgical resection of inflamed bowel is considered a last resort in the management of patients with IBD. Correction of malnutrition and the use of probiotics (discussed earlier) may enhance responses to surgery for IBD.

Prevention Prescription

- Observational studies suggest that diet influences the risk of developing IBD. The following dietary changes are associated with reduced risk:
  - High-fiber diet (at least 25 g per day)
  - Limited use of foods with added sugar or fat and avoidance of vegetable oils except olive oil
  - Limited consumption of beef or poultry (UC)
  - Omega-3 fatty acids from animal and vegetable sources should supply at least 1% of calories, and omega-6 fatty acids should supply no more than 7% of calories.
- For patients with IBD in remission, prevention of relapse may benefit from the following interventions:
  - Prolonged use of 5-aminosalicylic acid (5-ASA) derivatives plus folate, typically 1 mg/day
  - Along with a 5-ASA derivative, also prescribe *Saccharomyces boulardii,* 1000 mg per day. Constipation is a significant side effect.
- Additional evidence-based interventions for relapse prevention include the following:
  - Vitamin D_3: 1200 units per day for CD
  - Curcumin: 1000 to 1800 mg twice a day with meals for patients with UC. These interventions not only reduce the risk of relapse but also may reduce the risk of colon cancer.
  - For maintenance of remission in patients with UC, a high-fiber, low-meat diet with limited alcohol, supplemented with fish oils supplying approximately 5000 mg/day of omega-3 fatty acids (main side effect is diarrhea) and the probiotic VSL-3
  - A specific food exclusion diet, individually tailored, avoidance of tobacco exposure, and reduced consumption of sucrose for maintenance of remission in patients with CD
  - Folic acid, vitamin B_6, and vitamin B_{12} at doses that keep circulating homocysteine low, to prevent thrombotic complications
  - Vitamin D: 1200 units/day, to prevent bone loss and perhaps relapse

Therapeutic Review

All patients with inflammatory bowel disease (IBD) should be under the care of a gastroenterologist for regular endoscopic examination and prescription of appropriate drug therapy. The main role of the integrative practitioner is to help patients develop effective self-management strategies and enhance conventional treatment with an individualized nutritional prescription and the use of nutritional and botanical supplements.

Laboratory Tests

Certain laboratory tests are useful for fulfilling this role effectively. Commonly used tests include complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum albumin. Useful markers of nutritional status in IBD also include plasma zinc and homocysteine, serum and urine magnesium, serum iron, ferritin and transferrin, and 25-OH vitamin D. In steroid-treated patients with refractory disease, serum dehydroepiandrosterone sulfate (DHEA-S) may be useful. Patients with recent onset, relapse, or exacerbation of IBD—especially those with diarrhea—should undergo stool testing for parasites, pathogenic bacteria, *Clostridium difficile* toxins, and yeast.

Self-Management

- Spend an office visit ensuring that patients can recognize the symptoms of relapse and have a plan for controlling them.
- Use a mutually acceptable treatment protocol for the patient to initiate at the onset of a relapse.

Nutrition

- Avoid sucrose and symptom-provoking foods. A1
- As described earlier, the Specific Carbohydrate Diet, an exclusion diet, or a defined formula diet may help relieve symptoms and may help induce or maintain remission, especially in patients with Crohn's disease (CD). B1 A2 A2
- Balance dietary restrictions with the need for adequate macronutrient intake.
- Replace vegetable oils with olive, flaxseed oil, or coconut oil (1 to 2 tablespoons/day). B1
- Recommend oat bran, 60 g/day, for patients with mild-to-moderate ulcerative colitis (UC). B2

Supplements

- Folate: 1 mg/day or more especially for patients with high homocysteine or taking 5-ASA derivatives A1
- Vitamin B_{12}: 1 mg/month for patients with ileitis or previous ileal resection , receiving folic acid, or with high homocysteine A1 B1 B1
- Vitamin B_6: 10 to 20 mg/day, especially for patients with high homocysteine or taking high-dose folic acid or with urolithiasis B1 B1 B1
- Vitamin D_3: 1000 units/day or more to maintain levels of 25-OH vitamin D at 40 ng /mL B1
- Zinc: 25 to 200 mg/day to maintain plasma zinc at more than 800 mg/L B1
- Calcium: 1000 mg/day for patients taking steroids or with low dietary calcium A1
- Selenium: 200 mcg/day for patients with ileal resection or on liquid formula diets A1
- Magnesium citrate: 150 to 900 mg/day for patients with urolithiasis. Watch out for magnesium's laxative effect. B1
- Chromium: 600 mcg/day for patients with steroid-induced glycemia B1
- Fish oils supplying 4000 to 5000 mg/day of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) for patients with UC. Fish oils may cause diarrhea. Most fish oil capsules are only 50% omega-3 fatty acids. B2
- *N*-Acetylglucosamine (NAG): 3000 to 6000 mg/day B1
- Prebiotic oligosaccharides: approximately 10 g per day for UC. They can cause distention and flatulence. B2

Biologic Agents

- VSL-3: one sachet twice a day for patients with mild-to-moderate UC who are not sensitive to corn, the growth medium used. Any probiotic may aggravate bowel symptoms in patients with IBD. B2
- *Saccharomyces boulardii:* 250 mg three times daily or 500 mg twice daily for patients with chronic stable disease or to help maintenance of remission in patients not shown to be sensitive to yeast. *S. boulardii* may cause constipation. B2
- DHEA: 200 mg/day for patients with refractory disease and low DHEA-S B2

Botanicals

- *Boswellia serrata* gum resin: 350 mg three times daily for patients with UC who are intolerant of 5-ASA derivatives B1
- Curcumin: 1000 mg twice daily with meals B1
- Mastic gum: 1000 mg twice daily for patients with CD B1

Continued

- Aloe vera gel: 100 mL bid for patients with UC. Aloe may cause diarrhea. 

Pharmaceuticals

- 5-ASA derivatives for induction of remission in mild-to-moderate colitis and for maintenance of remission
- Antibiotics for acute exacerbations of CD or UC or perianal disease 
- Glucocorticoids for induction of remission in severe disease 
- 6-Mercaptopurine or azathioprine for steroid-dependent IBD or for maintenance of remission when 5-ASA derivatives fail 
- TNF-alpha blockers. For patients with severe CD, initiating pharmaceutical therapy with immunosuppressants and TNF-alpha blockers (step-down therapy) produces superior long-term results to initiating therapy with steroids and 5-ASA derivatives (step-up therapy) . None of these studies included dietary interventions, which are of proven value in CD. 

Surgical Resection

- For patients with colonic dysplasia or for those who fail to respond to medical management 
- Postsurgical recurrence rate is high for CD, and pouchitis is a frequent complication of ileal pouch–anal anastomosis for UC.

KEY WEB RESOURCES

PillAdvised.com: http://www.nutritionworkshop.com/medication-sandsupplementsinteractions/login.php	This free database details interactions involving drugs, nutrients, and supplements.
Crohn's and Colitis Foundation: www.ccfa.org	This Web site provides information about improving quality of life and ongoing research into inflammatory bowel disease (IBD).
Specific Carbohydrate Diet: www.breakingtheviciouscycle.info	This site contains a description of the Specific Carbohydrate Diet (SCD) and details about its implementation.
Digestive Wellness: http://www.digestivewellness.com	This online store is for patients using the SCD.
Imix Naturals: http://www.imixnaturals.com/index.aspm	This company supplies Absorb Plus, a palatable enteral feeding for patients with active Crohn's disease.
Ovamed: www.ovamed.org	This Web site is a source of information related to helminth therapy of IBD.

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Chapter 50

Postdates Pregnancy

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Pathophysiology

Postdates or postterm pregnancy is defined as a pregnancy that extends to or beyond 42 weeks of gestation (294 days or estimated date of delivery [EDD] plus 14 days). A normal pregnancy lasts approximately 40 weeks from the start of a woman's last menstrual period, but any pregnancy that lasts between 37 and 42 weeks is considered normal. Approximately 4% to 7% of all singleton pregnancies extend to 42 weeks, or 14 days beyond the EDD.[1]

Postterm pregnancy is associated with a higher perinatal mortality rate (stillbirth and newborn death within the first week) and a higher risk of complications during delivery, such as an emergency cesarean delivery, shoulder dystocia, postpartum hemorrhage, birth asphyxia, meconium aspiration syndrome, and neonatal birth injury.[2] Current research suggests that the lowest infant mortality rate is achieved when pregnant women have completed at least 41 weeks of gestation before labor is induced and when induction occurs before or at 42 weeks of gestation, although the absolute risk of problems from delivering beyond 42 weeks is low.[2] The overall risk of perinatal death is estimated at 0.4% in women who deliver beyond 42 weeks of gestation and 0.3% for women who deliver between 37 and 42 weeks of gestation.[3]

Because of this small increase in perinatal mortality, the induction of labor is widely practiced at or before 42 weeks of gestation, and postterm pregnancy has become the most common reason for induction.[4] Unfortunately, labor induction itself is not without risks. Obstetric problems associated with induction of labor in postterm pregnancy include cesarean section, prolonged labor, postpartum hemorrhage, and traumatic birth. These problems are more likely to result from induction when the uterus and cervix are not ready for labor.[2] Furthermore, induction of labor brings with it an increased risk of uterine rupture, uterine hyperstimulation, fetal distress, and instrumentation.[5]

Very few studies have taken into consideration women's experiences and opinions when it comes to the timing of induction of labor, and for women seeking a natural, unmedicated labor and birth, induction poses many philosophic challenges. Accurate dating is obviously important in reducing the need for induction, and studies have shown that early ultrasound is associated with a reduced incidence of pregnancies misclassified as postterm.[6] When women have accurate pregnancy dating and are approaching 41 weeks of gestation, many may seek nonpharmaceutical measures of cervical ripening and labor induction. One small study of 50 women showed that many were opposed to medical induction of labor, and yet they used self-help measures to stimulate labor at home.[7] More research is needed in the realm of nonpharmaceutical cervical ripening and labor induction options for women who have postdate pregnancies.

Integrative Therapy

Nutrition

Pineapple

Pineapple *(Ananas ananas),* which contains the compound bromelain, has historical medicinal use both as a whole food and in extract form. Bromelain has been proposed as the active ingredient, and it is present only in the fresh fruit because the canning process destroys it. Bromelain has been used to elicit uterine contractions as a means of shortening labor. Some animal model research suggests that instead of increasing cervical prostaglandins, bromelain may actually inhibit them.[8] No research is available on the possible effectiveness of bromelain for induction of human uterine contractions, although this use is widely suggested in lay pregnancy resources. Some investigators suggest that pineapple's effects on labor may result from gastrointestinal stimulation by fiber and sugar, thus affecting local neural pathways.[9] No known risks are associated with pineapple use in pregnancy.

Supplements

Castor Oil

Castor oil, derived from the bean of the castor plant, has a very rich history of use for labor stimulation that dates back to ancient Egypt. One survey completed in 1999 found

that 93% of U.S. midwives reported using castor oil to induce labor.[10] Despite this prevalence, research into the use of castor oil has been minimal. Only one study looking at safety was included in a Cochrane Review, and unfortunately, the study was small and of poor methodologic quality.[11] It included 100 women at term and compared ingestion of castor oil with no treatment. Outcomes evaluated included cesarean section rate, meconium staining of amniotic fluid, and Apgar scores. All women who ingested castor oil had nausea; otherwise, outcomes were no different from those in women who did not ingest castor oil. A retrospective observational study done in Thailand of 612 women looked at timing of delivery, fetal distress, meconium-stained amniotic fluid, tachysystole of the uterus, uterine rupture, abnormal maternal blood pressure during labor, Apgar scores, neonatal resuscitation, stillbirth, postpartum hemorrhage, severe diarrhea, and maternal death.[12] No differences were seen in outcomes between the women who ingested castor oil and the women who did not. This finding suggests that castor oil is safe to use but may not be helpful. Prospective randomized controlled trials are needed.

Evening Primrose Oil

Evening primrose oil *(Oenothera biennis),* a rich source of gamma-linoleic acid (GLA), is often used for several women's health conditions, including breast pain (mastalgia), menopausal and premenstrual symptoms, and labor induction or augmentation. This supplement is used widely during the last month of pregnancy by midwives in the United States for cervical ripening and to decrease the incidence of postdates pregnancy.[10] Evening primrose oil is typically administered as two capsules intravaginally at bedtime, starting after 38 completed weeks of pregnancy. When used as a cervical ripening agent, evening primrose oil has been shown to reduce the risk of postdates presentation.[10] Five studies, three of which were small randomized controlled trials, indicated the safety of vaginal evening primrose oil. One study investigated oral administration and showed that this route was not effective.[13] Furthermore, the oral use of evening primrose oil during pregnancy may also be associated with more prolonged labor and an increased risk of premature rupture of membranes, arrest of descent, oxytocin use, and vacuum extraction.[13] This finding is not surprising because oral administration during pregnancy was never a traditional use. Larger trials assessing efficacy are needed.

Homeopathy

Homeopathy is a safe choice for pregnant women and babies because the remedies used in this system of healing have no pharmacologic action.[14] In the United States, the use of homeopathic remedies has increased, and a survey among nurse-midwives in North Carolina reported that 30% recommend homeopathic substances for use during pregnancy.

The two most common homeopathic remedies used for labor induction are cimicifuga (homeopathic black cohosh) and caulophyllum (homeopathic blue cohosh), which are believed to act directly on the uterus and cervix. These remedies have been used around the world for labor stimulation, especially in Europe and India. Caulophyllum is used either to induce labor or to augment labor if uterine contractions are short and irregular or when uterine contractions stop. Caulophyllum and cimicifuga are both indicated for dysfunctional uterine contractions and are thought to help initiate a coordinated and effective contraction pattern. Cimicifuga is used specifically to ease the fear of labor and delivery in women who have a history of traumatic childbirth, miscarriage, or abortion.[15] Cimicifuga alone is administered as a single dose of 30 C or 200 C potency every 30 minutes for at least 2 hours, or together with caulophyllum 200 C, alternating doses of the two remedies for a total of six doses in 24 hours. Other remedies that are commonly used for labor induction include aconite, arsenicum, gelsemium, phosphorus, and pulsatilla. These are all given in 200 C potency, as a single dose (two pellets).[16]

A 2003 Cochrane Review examined the use of caulophyllum, cimicifuga, and some of these other homeopathic remedies.[14] The review looked at only two studies comparing homeopathy and placebo for cervical ripening or labor induction and found that small sample sizes and insufficient detail in the research made it impossible to draw any meaningful clinical conclusions. More research needs to be done to determine whether homeopathy is a potentially viable alternative to oxytocin and prostaglandins for labor induction. Furthermore, studies should be designed to incorporate individualized homeopathic treatments, prescribed by a trained homeopath, to account for the individualized nature of this modality.

For labor induction, caulophyllum and cimicifuga homeopathic remedies are as follows: 30 C or 200 C given every 30 minutes alternating, for a total of six doses in 24 hours. No remedy is given the next day. Repeat the same protocol on day 3 if needed. Other remedies to consider are gelsemium, for fear of birth, and pulsatilla, for when contractions come and go, but labor never becomes established.

Botanicals

Red Raspberry Leaf

Red raspberry leaf (*Rubus idaeus, Rubus occidentalis*) has been used as a uterine tonic and general pregnancy tea for at least 2 centuries. Although this botanical is often mistakenly recommended to induce labor, its actual role is to increase blood flow to the uterus and aid the uterine muscle fibers in more organized contraction. Studies indicate that some of the plant components, such as fragrine, an alkaloid, do act directly on smooth muscle.[17] Historical uses include prevention of miscarriage, prevention of postdates pregnancy, decrease of discomfort in prodromal labor, and decrease of morning sickness. Red raspberry leaf was probably also consumed for nutritional support because the plant contains many nutrients, including vitamins A, C, and E, as well as calcium, iron, and potassium. It is most commonly consumed as a tea, taken as 1 to 3 cups daily. Many studies have documented the safety of this botanical. One randomized controlled trial of 192 women showed no adverse effects to mother or baby, a shorter second stage of labor (a mean difference of 10 minutes), and a lower rate of forceps use.[16] One retrospective, observational study of more than 150 women also found that red raspberry leaf reduced the risk of postdates pregnancy, but more conclusive data are needed.[14]

Black Cohosh

This herb *(Cimicifuga racemosa)* also has a long history of use. Native Americans mixed it with chamomile, ginger, and raspberry tea to induce menses and labor. The active compounds in black cohosh include terpene glycoside fractions, such as actein and cimifugoside, which have been associated with an estrogenic effect and are thought to reduce levels of pituitary luteinizing hormone, thus decreasing ovarian production of progesterone.[15] This effect may contribute to the initiation of uterine contractions because the relaxing effect of the high levels of progesterone on the uterine muscle decreases before the initiation of labor. The plant also contains formononetin, which is thought to have a uterine-stimulating effect.[18] At least one case report has been published of toxicity in an infant whose mother was given an unknown dose of black cohosh at term.[19] At this time, the German Commission E, an expert committee established by the German Ministry of Health that evaluates herbal products, does not recommend the use of black cohosh in pregnancy.[20]

Blue Cohosh

The herb blue cohosh *(Caulophyllum thalictroides)* also has a long tradition of use as a uterine tonic. It was traditionally used by Native Americans during the 2 to 3 weeks before the onset of labor.[18] Between 1882 and 1905, blue cohosh was listed in the *United States Pharmacopoeia* for labor induction.[18] The plant contains the glycosides caulosaponin and caulophyllosaponin, which have documented oxytocic effects.[21]

Blue cohosh has some reported adverse neonatal effects, such as fetal hypoxia, myocardial infarction, and congestive cardiac failure.[22] Whether these effects resulted from the herb itself is not known, given that herbs are often used in combination with other plants, and adulteration and contamination problems can occur. Until further research on this plant is done, it is best avoided for labor induction.

At this time, the use of blue and black cohosh is best avoided in pregnant women, out of safety concerns.

Biomechanical Therapy

Breast Stimulation

Breast stimulation has historically been used to induce or augment labor since as early as the eighteenth century.[23] Stimulation of the breast is thought to increase the production of endogenous oxytocin in pregnant and nonpregnant women. The most commonly used protocol for breast stimulation involves using either a manual or electric breast pump or manual massage around the areola of the nipple for 1 hour a day, for 3 consecutive days.

The Cochrane Collaboration performed a systematic review of 6 trials, with a total of 719 participants, that compared breast stimulation with no intervention to induce labor in women at term.[24] The review found that breast stimulation significantly reduced the number of women who had not gone into labor at 72 hours compared with no intervention.[24] Breast stimulation also reduced the risk of postpartum hemorrhage by 84%.[24]

Breast stimulation for labor induction allows women participation in the induction process and has the advantage of being a low-cost and nonpharmaceutical means of labor induction. Observational studies have shown a link between bilateral breast stimulation and uterine hyperstimulation.[25] For this reason, unilateral stimulation is typically recommended. Until safety issues have been more thoroughly evaluated, this technique should not be used in high-risk populations.

Shiatsu

Shiatsu is an ancient form of massage based on Chinese acupuncture theory that often includes the use of breathing and stretching. Shiatsu can be done through the clothes or on bare skin and uses static pressure, which can vary from light holding to deep physical pressure applied with the palm of the hand or thumb. Shiatsu lends itself well to maternity settings because specific shiatsu techniques can be taught to birth partners or practitioners. It has historically been used in midwifery practices to induce or augment labor.[26]

One small pilot study evaluated shiatsu for induction and augmentation of postterm labor.[27] Sixty-six women with postterm pregnancies were studied in a hospital-based midwifery practice. Pregnant women were taught to massage three acupuncture points in conjunction with breathing techniques and exercises. The controls attended the same clinic, but they were not taught the techniques. The investigators found that the women with postterm pregnancies who used shiatsu were significantly more likely to have spontaneous labor than were the study participants who did not use shiatsu.

Bioenergetics

Acupuncture

As part of the ancient system of medicine known as traditional Chinese medicine, acupuncture has been used in pregnancy for thousands of years. Modern studies have evaluated the insertion of fine needles into specific points on the body, as well as the use of mild electrical currents through these needles, known as electroacupuncture. A 2004 Cochrane Systematic Review evaluated acupuncture for inducing labor.[28] The investigators identified 3 trials, including 212 women, for review. The first case series used electroacupuncture at 38 to 42 weeks of gestation to induce labor successfully in 21 of 31 women. The second series used acupuncture with and without electrical stimulation to induce labor in 10 of 12 women at 19 to 43 weeks of gestation. The third study induced labor with electroacupuncture in 78% of 41 women.[28] The overall conclusion was that fewer women using acupuncture required induction of labor by other methods.

Several studies have been published since the foregoing Cochrane Review. One randomized controlled trial of 45 women found that acupuncture at points LI4 and SP6 shortened cervical length at term and reduced the time between the EDD and delivery.[29] A larger double-blind randomized controlled trial of 181 women in Denmark did not show any benefit of induction of labor in women with postdates pregnancies who were treated with acupuncture.[30] No adverse effects were seen. Another smaller trial of 67 women in Brazil showed effects similar to those with misoprostol for cervical ripening, with a higher frequency of vaginal delivery and no obstetric complications.[31] The inherent difficulties in blinding for acupuncture treatment make the study of this

TABLE 50-1. Acupressure Points for Induction of Labor

1. Midway along the top of the trapezius muscles, if you were to draw a line from the acromion to C7
2. The motion sickness point at the angle between the first and second metacarpals
3. In the semicircle around the distal medial and lateral malleoli
4. The little toe, all over

Massage these points for at least 2 to 3 minutes each.

From Mallory J. Integrative care of the mother-infant dyad. *Prim Care.* 2010;37:149–163.

technique challenging. Certainly, the studies do agree that acupuncture is safe in pregnancy, and it may be worth trying in patients who wish to avoid pharmaceutical induction of labor. Table 50-1 provides acupuncture points that patients can massage at home to stimulate labor.

Lifestyle

Sexual Intercourse

Unprotected sexual intercourse is thought to encourage the onset of labor by two means. One is the release of endogenous oxytocin in the mother, and the other is cervical ripening caused by seminal prostaglandins. A Cochrane Review looked at an observational study of 28 women at term. Unprotected intercourse for 3 consecutive nights did not significantly change Bishop scores (1.0 with coitus versus 0.5 controls; $P > .05$), nor did it increase the number of women who went into labor at the end of 3 days (relative risk, 0.99; 95% confidence interval, 0.45 to 2.20).[32] Larger studies are needed to determine whether sexual intercourse has any significant effect on reducing the risk of postdates pregnancy.

Pharmaceuticals

Misoprostol

Misoprostol is a prostaglandin E_1 analogue widely used for off-label indications such as induction of labor in postdates pregnancy. This hormone is given by insertion through the vagina or rectum, or by mouth, to ripen the cervix and elicit uterine contractions. A Cochrane Review looked at 121 trials and found that small doses of misoprostol were as effective as other methods of labor induction.[33] Larger doses of misoprostol were found to be more effective than prostaglandins for induction, and larger doses also reduced the need for additional oxytocin. Another Cochrane Review showed that the oral route of administration is preferable to the vaginal route. The main risk of misoprostol use is hyperstimulation of the uterus. At this time, misoprostol is not approved by the Food and Drug Administration for induction of labor.

Dosage

The most common dose used in the United States is 25 mcg intravaginally every 4 hours (maximum, 50 mcg). Wait for more than 4 hours after last dose before adding oxytocin. Misoprostol comes in 100- and 200-mcg formulations.

Precautions

Uterine hyperstimulation, uterine rupture, diarrhea, nausea, vomiting, headache.

Although misoprostol is commonly used for labor induction in the United States, it has not been approved by the Food and Drug Administration for this use.

Oxytocin

Oxytocin is the most common induction agent used worldwide. It is used alone, in combination with amniotomy or following cervical ripening with other pharmacologic or nonpharmacologic methods. Oxytocin is a synthetic analogue of the natural labor hormone by the same name. It binds to oxytocin receptors in the uterine myometrium, increases intracellular calcium, and stimulates uterine contractions. A Cochrane Review of more than 61 studies concluded that it is safe and effective.[34] A black box warning placed on the drug by the FDA states that oxytocin is not to be used for elective labor induction.

Dosage

Start with 0.5 to 2 milliunits/minute, and increase by 1 to 2 milliunits/minute every 15 to 40 minutes until the uterine contraction pattern is established. The maximum for induction is 40 milliunits/minute. Oxytocin is available in intravenous and intramuscular preparations.

Precautions

Increased use of epidural anesthesia, uterine hyperstimulation, uterine rupture, abruptio placentae, fetal distress, nausea, vomiting.

Vaginal Prostaglandins (PGE_2 and PGF_{2alpha})

Prostaglandins have been used for the induction of labor since the 1960s. These drugs are synthetic analogues of the body's naturally occurring prostaglandins, which function to ripen the cervix and bring about contractions. A Cochrane Review looked at 63 randomized controlled studies of various forms of prostaglandins and found them to be a safe and effective means of labor induction.[35] Prostaglandin E_2 is the most commonly used type, and it increases the likelihood of vaginal birth in 24 hours without increasing the risk of cesarean section.[35]

Dosage

The dose is one 10-mg pessary intravaginally. The insert releases 0.3 mg/hour over 12 hours. Remove at 12 hours, at the onset of active labor, or if uterine hyperstimulation occurs. The agent is available as a 10-mg sustained-release insert. It is also available as an intravaginal tablet or gel.

Precautions

Uterine hyperstimulation, fetal distress, uterine rupture, bronchospasm, abdominal cramps, headache, nausea, diarrhea.

Mechanical Methods

Potential advantages of mechanical methods, compared with pharmacologic methods, for the induction of labor in postdates pregnancy include simplicity of use, lower cost, and reduction of side effects, such as uterine hyperstimulation and fetal distress. However, special attention should be paid to contraindications such as a low-lying placenta, risk of infection, and maternal discomfort.

Amniotomy

The deliberate rupture of membranes may be sufficient to bring about labor without the use of pharmaceuticals. This approach has the advantage of being cheap, but it may be uncomfortable for some women. If the time between amniotomy and delivery of the baby is long, infection may occur. The risk of umbilical cord prolapse is also increased, especially if the fetal head is ballotable at the time of membrane rupture. Anecdotal reports note that amniotomy may be less beneficial in nulliparous women. More evidence is needed regarding effectiveness compared with placebo or compared with other methods of induction of labor.[36]

Membrane Sweeping

Sweeping of the membranes, also known as membrane stripping, is a simple manual technique usually done in the outpatient setting. The technique involves inserting a finger into the cervical os during a sterile vaginal examination and sweeping the finger in a circular motion to detach the membranes from the lower uterine segment. This method sometimes works to initiate labor by increasing the local production of prostaglandins. A Cochrane Review of 72 studies found that sweeping of the membranes, performed routinely for women at term, was associated with a reduced frequency of pregnancy extending beyond 41 weeks.[37] This method is considered safe and reduces the need for pharmaceutical means of induction of labor in postdates pregnancy.[37] Adverse effects include maternal discomfort, vaginal bleeding, and irregular contractions.

Transcervical Foley Catheter Insertion

This approach involves placing a 30-mL Foley catheter bulb transcervically, inflating it with sterile saline solution, and applying maintenance traction. One randomized controlled trial found this technique equivalent to intravaginal misoprostol for cervical ripening, without the risk of uterine hyperstimulation.[38] Complications include acute febrile reaction, pain, vaginal bleeding, and altered fetal presentation.

Prevention Prescription

- Women can be encouraged in the preconception period to track their menstrual cycles and sexual activity closely to aid in accurate pregnancy dating. When women are unsure of their pregnancy dates, first trimester ultrasound reduces the number of women later incorrectly classified as having postdates pregnancies.
- Good self-care in pregnancy, including aromatherapy, good nutrition, massage, sexual intercourse, spiritual practices, chiropractic, and yoga during the latter weeks of pregnancy may serve to relax the mother and allow the natural rise of oxytocin and reduction of stress hormones, thus resulting in a greater likelihood of spontaneous onset of labor.[39–41]
- Membrane sweeping, done routinely at 38 weeks, may also reduce the risk of a pregnancy that continues beyond 41 weeks.

Therapeutic Review

These therapeutic options for prevention of postdates pregnancy and induction of labor in postdates pregnancy may be considered in the healthy, term patient, with no medical complications that would make delivery urgent.

Nutrition

- Pineapple consumption is commonly recommended for labor induction. Although pineapple has no proven benefit, the risks of this intervention are low. C 1

Supplements

- Castor oil has a long history of use for labor induction. It is considered safe, but it has not been proven effective. Side effects include nausea. Doses are not standardized. C 1
- Evening primrose oil is possibly effective as a cervical ripening agent when it is used to reduce the risk of postdates pregnancy. The dose is two capsules intravaginally at bedtime, starting at 38 weeks of pregnancy. This supplement should not be used orally in pregnancy. C 1
- The homeopathic remedies caulophyllum and cimicifuga can be dosed at 200 C potency, by alternating the two remedies every 30 minutes, for a total of six doses in 24 hours to help stimulate labor. The benefit is unknown, and risks are minimal. C 1

Botanicals

- Red raspberry leaf, taken as 1 to 3 cups of tea daily during the third trimester, may reduce the risk of postdates pregnancy. B 1
- Despite a strong history of use, black cohosh and blue cohosh should be avoided in pregnancy because of safety concerns until more data are available. C 2

Biomechanical Therapy

- Unilateral breast stimulation can be done for 1 hour per day for 3 consecutive days to induce labor at term. A 1
- Shiatsu may reduce the risk of postdates pregnancy. C 1

Acupuncture

- Evidence is mixed on the effectiveness of acupuncture to reduce the risk of postdates pregnancy, for cervical ripening, and for labor induction. Acupuncture is considered safe. B 1

Lifestyle

- Sexual intercourse may not be effective for reducing the risk of postdates pregnancy.

Pharmaceuticals

- Misoprostol is commonly used for cervical ripening and labor induction, despite a lack of approval by the Food and Drug Administration for this indication. See the doses and precautions discussed in the text.
- Oxytocin may be used to induce uterine contractions in postdates pregnancy, when cervical conditions are favorable. See the doses and precautions discussed in the text.
- Vaginal prostaglandins may be used for cervical ripening and labor induction, and they are a good choice in postdates pregnancy in patients with unfavorable cervical conditions. See the doses and precautions discussed in the text.

Mechanical Therapy

- Amniotomy may be used to induce or augment labor, and it may be more beneficial in multiparous women.
- Membrane sweeping can be considered routinely at 38 weeks to reduce the risk of postdates pregnancy.
- Transcervical Foley catheter insertion can be done for cervical ripening in postdates pregnancy, and it may have lower risks than pharmaceutical ripening agents.

KEY WEB RESOURCES

American College of Obstetricians and Gynecologists: http://www.acog.org/publications/patient_education/bp069.cfm	Patient handout on postdates pregnancy
American College of Nurse-Midwives: http://www.mymidwife.org/	Consumer information on pregnancy and midwifery

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References are available online at expertconsult.com.

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Chapter 51

Labor Pain Management

Michelle J. Mertz, MD, and Connie J. Earl, DO

We have the pleasure of discussing the only topic in this section of the book that is not a pathologic condition. Childbirth is uncomplicated in most women, and it typically results in a joyful outcome. To many, birth is considered a rite of passage, a sacred experience that should be honored. Birth experiences are widely variable in length of labor, severity of pain, and emotions surrounding the event. Women's preferences regarding birth are equally variable. For this reason, labor management is best when individualized and when options and preferences are discussed before the onset of labor. One systematic review noted that women's satisfaction with their childbirth experience was less affected by pain control than by personal expectations, the amount of support they received from caregivers, the quality of the caregiver-patient relationship, and their own involvement in decision making.[1]

After a period of heavily medicated birth in the United States during the midtwentieth century, a backlash against the medical model arose, and women began to demand the right to choose their own childbirth experience. Today, women are much more at liberty to influence these experiences. This chapter explores the birthing woman's many options for pain management.

Physiology

Labor is separated into three stages. The first stage involves dilation of the cervix and the beginning descent of the fetus into the pelvis. The second stage is full dilation and birthing of the fetus, and the third stage is passage of the placenta.

Pain in the first stage is primarily visceral, resulting from the mechanical dilation of the cervix and lower uterus. Nociceptive information is carried back on sympathetic fibers to the posterior nerve root ganglia at T10 through L1, as well as on parasympathetic fibers from the pelvic splanchnic nerves (S2 through S4).[2] The T10-L1 segmental levels also receive nociceptive information from the skin of the back.[2] This last mechanism may explain why many women feel contractions in their back. Pressure on the pelvic nerves may explain why labor pain can radiate to the thighs or buttocks as well. In some cases of fetal malposition, such as occiput posterior or occiput transverse, the woman may experience more severe back labor resulting from a relative increase in diameter of the head passing through the pelvis in these positions. Back labor is not isolated to the occiput posterior or occiput transverse position, however.

During the second stage of labor, pain primarily stems from mechanical stretching and distention of the perineum and pelvic floor musculature. This is somatic pain, carried to the central nervous system on the pudendal nerve fibers (S2 through S4).[2] It is often described as sharp. Many women report a sensation of rectal pressure during descent of the fetus. As the presenting part begins to stretch the perineum, many women describe a classic "ring of fire" sensation.

Pain Relief in Labor

Any acute pain, including labor pain, has two main physiologic components: the transmission of the physical pain stimulus to the brain and the interpretation of the information that is filtered through the hypothalamic and limbic systems. Thus, the experience of pain is influenced by emotions and memories.[3] Whereas pharmaceutical agents are typically geared toward relief of physical pain, many of the nonpharmacologic methods do not attempt to remove the sensation, but instead target the perception of the pain stimulus. One mechanism proposed for many of the therapies discussed in this chapter is the *gate control theory:* sensations such as pressure, vibration, pain, or temperature stimulate superficial tactile nerve endings, and this stimulation leads to inhibition of the pain signal transmission from the organs and deeper tissues at that segmental level.[4]

Integrative Therapy

Continuous Labor Support or Doula

Historically, women have long provided continuous labor support to other women in labor. In the twentieth century, a break in that tradition occurred as birth moved from an

out-of-hospital midwifery model of care to a more institutionalized model. Since the 1980s, a resurgence in labor support has attempted to integrate the two models. Research in this area typically focuses on the labor "doula," a person present solely to support the birthing woman and her family.[5] Doulas have no medical role in the labor or birth and are often hired in the second or third trimester of pregnancy to form a relationship with the birthing family before labor begins.

A large Cochrane Review demonstrated a significant decrease in pain medication required, length of labor, and incidence of cesarean delivery and operative delivery with continuous labor support by a doula.[6] This benefit was most pronounced when doula support was begun in early labor.[6] The most important factor appears to be the continuous presence of labor support.[7] An earlier study demonstrated that even the continuous presence of a silent female observer had a positive effect on the foregoing outcomes, although the greatest benefit was observed when a trained doula was present.[8] Continuous support is most efficacious when the provider is not a member of the hospital staff.[9,10] Given the benefits, all women in labor should be offered a doula.

Childbirth Preparation

Half of the women in the United States are estimated to attend some sort of childbirth education class during pregnancy.[11] Many approaches are used, but most classes aim to prepare women and their partners for childbirth and parenthood. Some of these classes introduce women and their partners to various pain relief techniques reviewed in this chapter. Data on pain in labor in relation to childbirth education are sparse. Although individual studies have demonstrated benefits of prenatal education besides pain relief, a review of the literature found the study methods too diverse to comment on benefits clearly.[12] A large randomized controlled trial (RCT) found no difference in epidural rate or pain level rated retrospectively with one form of childbirth education.[13] Given the popularity of antenatal education, more research is needed to determine its best use.

Lifestyle

Exercise

Research suggests that regular aerobic exercise during pregnancy is associated with decreased pain scores in labor.[14] Moderate-intensity exercise in labor has also been observed to lower pain scores, even after the exercise ends.[15] No known risks to the fetus are associated with moderate exercise, though some increased uterine activity occurs with exercise at term.[15,16] Women should be encouraged to exercise regularly during pregnancy.

Biomechanical Therapy

Positions During Labor and Ambulation

Western medicine long ago adopted the lithotomy position as the position of choice for childbirth, mostly for ease of the practitioner. In contrast, historically around the world, women have employed an upright position in the first and second stages of labor.[17]

Ambulation and an upright position during the first stage of labor is associated with a decreased length of the first stage, a decreased use of epidural anesthesia, and no difference in adverse maternal or neonatal outcomes.[18] Additionally, in women with a fetal malpresentation associated with back labor, the hand and knees position during labor appears to decrease back pain.[19]

The use of an upright or side-lying position in the second stage of labor is associated with a decreased length of the second stage. It was also associated with a decreased report of severe pain in a systematic review of 23 RCTs.[20] A small but significant increase in the incidence of blood loss greater than 500 mL was reported, but without adverse maternal or fetal outcomes. Unless medically contraindicated, all women should be allowed to ambulate and choose the positions they assume in labor and birth.

Water Immersion

Originally relegated to home birth and out-of-hospital birthing centers, water birth and water immersion in labor are now options in many hospital labor and delivery units. Laboring in water has many purported advantages, including ease of position change with the decreased effects of gravity, relaxation, decreased sensation of pain, and greater control for the laboring woman over her personal space.

A Cochrane Review of water immersion demonstrated a significant reduction in use of pain medication with water immersion in the first stage of labor and no difference in adverse maternal or neonatal outcomes.[21] Two of these RCTs also demonstrated increased maternal satisfaction with water immersion in the second stage of labor,[21] with no difference in mode of delivery or adverse maternal or neonatal outcomes.[21,22] A small RCT found increased normal vaginal delivery in water birth compared with land birth.[23] More research is needed to evaluate water birth. Water immersion in labor does not appear to increase the risk of chorioamnionitis or endometritis, even in women with ruptured membranes.[24]

The temperature of the water should be no more than 99°F to avoid raising maternal core temperature in labor.[21]

Chiropractic, Osteopathic, and Manual Therapy

Back pain is a common phenomenon in pregnancy because the body changes shape, joints relax from hormonal effects, and the spine and frame are required to support added weight. Some data suggest that back pain in pregnancy may be associated with increased back pain in labor.[25] One small retrospective study demonstrated that women who received prenatal chiropractic manual therapy reported less pain in labor than those who did not.[25] Manual therapy is an option for the management of musculoskeletal back pain in pregnancy, and it may lead to less pain in labor for women who receive regular treatments during pregnancy. Further study in this area is needed. No adverse events have been reported with the use of manual therapy in pregnancy.[26]

Massage

Although research is limited, intrapartum massage has been shown to reduce pain perception[27–31] and decrease anxiety[27–29] in early labor. No evidence indicates that it decreases the use of pain medication in labor. Regardless of the paucity of research on this topic, clinicians generally accept that massage can promote relaxation and enhance the quality of women's birth experiences.

Sterile Water Injections

Nearly 30% of women have severe continuous back pain in labor that persists between contractions. Sterile water injections in the low back can be used to relieve this pain. In contrast to isotonic saline, the salt-free water causes irritation as well as physical distention of the skin. The underlying mechanism of pain inhibition is not fully understood. Many investigators refer to the process of counterirritation,[32,33] in which one type of pain masks another, or to the gate control theory.

Several studies demonstrated that intracutaneous or subcutaneous sterile water injections provided good pain relief in the first stage of labor, particularly for low back pain.[34–40] The effect remained for up to 2 hours.[34–39] These injections are simple to administer, inexpensive, and carry no known risks. They were not shown to reduce the use of pain medication in these studies. Administration can be quite painful, but the pain is transient, and subcutaneous injection may be less painful than the intracutaneous route.[41] The precise location of the points does not appear critical to the success of the procedure.[42]

Technique

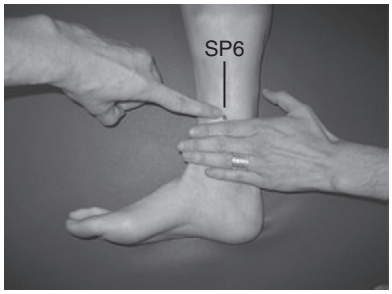
Palpate the posterior superior iliac spines, and mark them with a pen. From these sites, measure 3 cm inferiorly and 2 cm medially. Mark these two spots, and swab all four spots (two on the left and two on the right) with alcohol.[42] During a contraction, inject 0.1 to 0.5 mL of sterile water subcutaneously or intracutaneously with a fine needle, thus forming a small white bleb, as during a tuberculin skin test. Repeat at the remaining three sites as quickly as possible. It may help for two providers to inject simultaneously. Repeat as necessary.

Bioenergetics

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) emits low-voltage electrical impulses through electrodes, with operator-controlled variation in frequency and intensity. TENS units are portable, battery operated, and relatively inexpensive. TENS has typically been used to treat musculoskeletal and neuropathic pain, although its efficacy is controversial. The mechanism of action most often proposed is the gate control theory. Application of the electrodes is not standardized in labor. Although electrodes are typically applied paraspinally at T10 and S2, many studies also describe acupoints and cranial placement.[42]

FIGURE 51-1
Acupressure to SP6.



A Cochrane Review of studies with notably heterogeneous methods demonstrated little evidence of significant pain relief in labor from the use of TENS. Despite this finding, fewer women reported severe pain with the use of TENS, and women who had true TENS were more likely to want to use it in a future labor than those who received sham TENS.[43] The trials that applied TENS to known acupoints more consistently demonstrated pain relief.[44,45] Application can be intermittent or continuous, although continuous TENS may be more effective in active labor.[45]

The application of transcutaneous electrical nerve stimulation may interfere with electronic fetal monitoring.

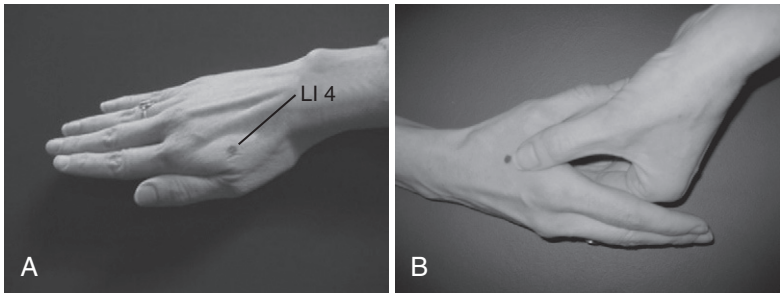
Acupuncture

In obstetrics, acupuncture has been used to promote version in a breech presentation, decrease nausea, induce or augment contractions, and provide pain relief.[46] It has also been used for pain management during perineal suture repair. Spleen 6 (SP6) and large intestine 4 (LI4) are the most commonly used acupoints in labor (Figs. 51-1 and 51-2).

Early data were quite hopeful,[47] but the most comprehensive meta-analysis to date found fewer optimistic results among more recent, well-designed trials.[48–51] The considerable heterogeneity among the study designs and outcomes evaluated makes it challenging to draw conclusions comfortably. When acupuncture was compared with minimal acupuncture (superficial needling), research remained equivocal regarding the efficacy of acupuncture for pain relief in labor.[49–51] Compared with no acupuncture, however, both manual acupuncture[51] and electoacupuncture[48,52] demonstrated decreased pain for 30 minutes after treatment. Additionally, women receiving acupuncture used fewer pharmacologic and invasive methods of analgesia,[53–55] were more satisfied with their pain relief,[48,50,52] and were more relaxed.[55] No adverse events have been demonstrated.[48-50,53–55]

SP6 and LI4 are purported to cause uterine contractions and should therefore not be used if labor is not desired.[56]

FIGURE 51-2
A and **B,** Acupressure to LI4.



Acupressure

Acupressure is a variation of acupuncture involving the application of constant pressure on specific acupoints. Like acupuncture, acupressure is frequently used to enhance labor, manage labor pain, and shorten the time to delivery.[57] Because the needles are replaced by pressure, this technique is noninvasive, requires no equipment, and can easily be taught to partners or support staff. Several RCTs have demonstrated reduction in labor pain with 30 minutes of acupressure at SP6.[57–59] One study found similar results with acupressure at LI4 and bladder 67 (BL67).[60] Pain relief has generally been found to last 1 to 2 hours after treatment. No study to date has found acupressure to replace the use of epidural or other pharmacologic analgesia.

Find SP6: Located one hand breadth (four finger widths based on the proximal interphalangeal joints) above the prominence of the medial malleus, in a depression just medial to the border of the tibia (see Fig. 51-1).[56]
Find LI4: Ask the patient to squeeze the thumb against the base of the index finger (see Fig. 51-2A). LI4 is on the dorsum of the hand, at the height of the muscle bulge, level with the end of the crease. It is between the first and second metacarpal bones (see Fig. 51-2B).[56]

Mind-Body Therapy

Hypnotherapy

Hypnosis is a state of focused concentration in which the patient is relatively unaware, but not completely blind to her surroundings.[46] *Hypnotherapy* refers to the clinical use of suggestions under hypnosis to achieve specific therapeutic goals.[64] During labor, these suggestions focus on the diminished awareness of pain, fear, and anxiety, thus leading to a decreased perception of each. Generally, this technique requires practice before the onset of labor.

A comprehensive review[61] included studies that demonstrated decreased use of pain medication,[62] higher pain thresholds,[62] shorter hospital stays,[63] less surgical intervention,[63] fewer complications,[63] and a more satisfying birth experience[64] in hypnotized women. Despite heterogeneity among trials, outcomes consistently favored hypnosis.[61] Hypnosis is relatively contraindicated in patients who are vulnerable to psychotic decompensation.

Yoga

Yoga uses the breath to focus on the interconnectedness between the mind and the body. It is thought to bring the individual toward a state of greater relaxation, increased self-awareness, and increased emotional well-being. Yoga also promotes muscle strength and flexibility.[65] Although yoga has been linked to improved birth weight[66,67] and decreases in labor duration,[66] preterm labor, intrauterine growth restriction, and emergency cesarean rate,[67] only two studies have focused on maternal comfort in labor. They demonstrated that regular yoga practice in pregnancy was associated with higher levels of maternal comfort during labor and 2 hours afterward and shorter duration of first stage and total time of labor.[65,68] Neither study demonstrated a decrease in use of pain medication, but investigators noted that the yoga group remained "in control" despite intensifying labor. The nonrandomized controlled trial demonstrated[68] that women who participated in a prenatal yoga program had significantly fewer pregnancy discomforts and increased childbirth self-efficacy. Participants also felt more in control and had lower pain levels that allowed them to be more active in their childbirth experience. Yoga is considered safe in pregnancy because all poses can be modified for the pregnant woman.

Music and Audioanalgesia

The use of music as adjunct therapy has been shown to reduce pain significantly in patients with chronic, postoperative, and cancer pain. Music has also been shown to decrease anxiety during colposcopy and in cardiac patients.[69–71] Many people have extrapolated the analgesic effects of music to labor as well. In the limited available studies, music therapy indeed appears to be mildly effective in reducing both labor pain and distress from that pain.[75,76] Music should be offered to women in labor if they desire.

Biofeedback

With biofeedback, physiologic information such as pulse or blood pressure is recorded through electrodes and shown in real time on a monitor while the patient adjusts her behavior or thoughts to control physiologic functions that were previously considered involuntary. Patients like biofeedback because it puts them in control and allows them to learn by trial and error.[46] Results are equivocal regarding the efficacy of biofeedback in labor.[74–76] The technique is risk free; however, it does require practice to master during pregnancy.

Biochemical Therapy: Aromatherapy

Aromatherapy is a natural healing art that uses essential oils extracted from aromatic botanical sources. These oils can also be used in the bath water, rubbed on clothing or towels for use as a compress, mixed with oil and applied, or kept available in small vials to open and smell. Examples of essential oils used in labor are lavender, chamomile, mandarin, clary sage, ginger, frankincense, eucalyptus, jasmine, lemon, and peppermint. In one large observational study, women consistently reported aromatherapy to be a helpful adjunct to their labor experience. Incidentally, a substantial overall reduction was noted in the use of systemic opioids in the hospital during the 8 years of the study. Frankincense was rated most highly for pain relief, followed by lavender. Rose and lavender were rated most highly for anxiety reduction. One percent of patients noted mild adverse reactions, such as nausea, itchy rash, and headache.[77] One small underpowered RCT demonstrated a positive trend for decreased pain perception with aromatherapy.[78]

Botanicals

Raspberry Leaf

Raspberry leaf is commonly used as a uterine tonic.[79] As many as 25% of women in the United States use raspberry leaf in pregnancy,[80,81] and up to one third of U.S. nurse midwives use raspberry leaf to stimulate labor.[81] A review of the existing studies demonstrated a positive trend toward decreases in length of first and second stage of labor and operative vaginal delivery.[82] No data are available on pain in labor with prenatal raspberry leaf. None of the studies have evaluated raspberry leaf tea, although this is typically how it is used.

Dose

The dose is 1.2 g orally twice daily,[83] starting in the third trimester.

Motherwort, Cramp Bark, and Black Cohosh

These botanicals are used by some herbalists to relieve back pain and spastic uterine contractions during labor.[79] No human studies have evaluated the efficacy of these botanicals. Black cohosh may be linked to hepatotoxicity and should be used with caution until more data are available.[79]

Skullcap

Skullcap is traditionally used for relief of anxiety during labor. No human trial has evaluated these claims, but rodent studies demonstrated an anxiolytic effect in vivo and a mild tocolytic effect in vitro.[84,85]

Pharmaceuticals

Maternal discomfort in labor is multifactorial. A few common combinations of pharmaceuticals are often given together in labor to address the pain, nausea, anxiety, and extreme fatigue that often accompany this process. Pharmaceuticals can be divided into two main categories: systemic and regional.

Systemic Agents

Essentially all analgesic agents cross the placenta.[86–89] Because of the complexity of fetal circulation, only a small percentage of the drug may reach the fetal brain.[90] Therefore, the mother may be affected by a certain concentration of drug without affecting the fetus. Providers should anticipate that beat-to-beat variability of the fetal heart rate may be reduced markedly with the use of these agents, but this may not necessarily affect the clinical status of the newborn. Systemic agents can be divided into three types: opioids, sedatives, and antiemetics (the last two are not fully discussed here).

Opioid Analgesia

Parenteral opioids are frequently used for pain relief in labor, although a large meta-analysis demonstrated that the efficacy is mild to moderate at best, and maternal satisfaction is moderate as well.[91] Whether one opioid is superior to the others remains unclear.[91] Institutional preference often dictates the choice. All opioids are associated with maternal and neonatal respiratory depression, delayed gastric emptying, and nausea and vomiting, which may increase the risk of aspiration if general anesthesia becomes necessary. Some centers use patient-controlled intravenous infusion pumps programmed to give a predetermined amount of drug at the patient's request. Please see Table 51-1 for a comprehensive list of parenteral opioids and their profiles.

Sedatives

Sedatives do not possess any analgesic qualities. They are often used in early labor to reduce anxiety, augment the analgesic effects of narcotics, and decrease the nausea often associated with narcotics. Barbiturates, phenothiazines, and benzodiazepines are examples. The last two classes are not commonly used because of their many maternal and neonatal risks.[92,93] Promethazine (Phenergan) is an antiemetic and is the most widely used sedative in labor. It rapidly crosses the placenta and has no known antagonist. In large doses or small doses combined with opioids, promethazine can depress the fetus for long periods of time. When used carefully with an opioid such as morphine in prodromal labor, however, promethazine may promote therapeutic rest for the patient. In some institutions, zolpidem, a sleep aid, is alternately given for therapeutic rest.

Local and Regional Anesthesia

Because local and regional analgesia methods do not depress the central nervous system, the birthing woman remains awake and able to participate actively, and the neonate is alert on delivery. Regional anesthesia provides the most effective form of pain relief in obstetrics, and the term refers to partial or complete loss of sensation below the T8 to T10 level.[94] Depending on the agent used, motor blockade may also be present. Examples of regional anesthesia include spinal anesthesia and epidural anesthesia. Several options for more localized anesthesia also are available, such as the pudendal block, paracervical block, and perineal block. Please refer to Tables 51-2 and 51-3 for detailed information regarding local and regional blocks, respectively.[95,96]

TABLE 51-1. Parenteral Analgesia

DRUG	DOSE	PROS	CONS	COMMENTS
Morphine Opioid	2–5 mg IV Onset less than 5 min Lasts 1.5–2 hr 10 mg IM Onset 10–20 min Lasts 2.5–4 hr	Long-acting when given IM	Nausea and vomiting[90] Urinary retention[90] Orthostatic hypotension[90]	Used primarily for therapeutic rest during early prodromal labor[90]
Meperidine (Demerol) Opioid agonist	25–50 mg IV every 1–2 hr Onset 5 min 50–100 mg IM every 2–4 hr Onset 30–45 min	Less respiratory depression than with morphine[90] Slightly less urinary retention than with morphine[90]	Active metabolites accumulate in fetal tissue after first hr[90] Active metabolites may cause dose-dependent neurobehavioral depression demonstrated up to 3 days[94] Neonatal risk if delivery occurs within 1–4 hr Nausea and vomiting[90] Delay in gastric emptying	Losing favor in pain management
Fentanyl Opioid	50–100 mcg IV every hr Onset 1 min Can load up to 200 mcg	Rapid pharmacokinetics No active metabolites Less neonatal neurobehavioral depression[90]	Requires frequent redosing May cause transient benign sinusoidal fetal heart tracing[94]	
Butorphanol (Stadol) Opioid agonist-antagonist	1–2 mg IV every 4 hr Onset 1–2 min 1–2 mg IM every 4 hr Onset 10–30 min	Ceiling effect for respiratory depression[90] Nausea and vomiting less common[90]	Somnolence[90] Dysphoria[90] Dizziness[90]	May cause increased blood pressure; avoided in hypertension or preeclampsia[94] Opioid antagonist effect may promote opioid withdrawal in opioid-dependent women[90]
Nalbuphine (Nubain) Opioid agonist-antagonist	10 mg IV Onset 2–3 min 10 mg IM every 3 hr Onset 15 min Maximum dose 160 mg over 24 hr	Ceiling effect for respiratory depression[94] Nausea and vomiting less common than with meperidine[94]	Maternal sedation[94] Dizziness[90] May cause benign transient sinusoidal fetal heart tracing[94]	Potency similar to morphine[90] Opioid antagonist effect may promote opioid withdrawal in opioid-dependent women[90]

75 mg meperidine = 10 mg morphine = 0.1 mg fentanyl = 10 mg nalbuphine.[95]
IM, intramuscularly; IV, intravenously.

TABLE 51-2. Other Analgesia

TYPE	DESCRIPTION	PRECAUTIONS	INDICATIONS	TECHNIQUE
Local Perineal Analgesia	Direct perineal infiltration with rapidly acting agent Local analgesia lasting 20–40 min[90]	Intravascular injection can rarely cause seizures, hypotension, and cardiac arrhythmias. Avoid injecting into the fetal scalp.	Used before episiotomies, outlet forceps, and laceration repair	Use 1%–2% lidocaine without epinephrine or 2-chloroprocaine. Aspirate for blood before injecting. Use as little as possible to avoid toxicity.
Paracervical Block	Simple, effective Duration of analgesia dependent on type of anesthesia used	Fetal bradycardia, which can be associated with fetal acidosis.[94] Do not use in mothers with fetuses with acute or chronic distress.[90]	Pain relief for cervical dilation Administration limited to first stage of labor	Inject 5–6 mL of local anesthetic without epinephrine into lateral fornices of cervix (4 and 8 o'clock or 3 and 9 o'clock).
Pudendal Nerve Block	Safe Variably effective	Risk of injecting directly into large vessels that lie in close proximity to injection site Hematoma[94] Infection[94]	Pain relief in second stage Spontaneous vaginal delivery, episiotomy, some outlet and low forceps, or to supplement epidural block	Inject 5–10 mL of local anesthetic slightly below the ischial spines bilaterally. Aspirate before injection to reduce the risk of local anesthetic toxicity.

TABLE 51-3. Regional Blocks

TYPE	DESCRIPTION	INDICATIONS/EFFECTS	PRECAUTIONS
Spinal Block	A single-shot long-acting local anesthetic is often used with or without an opioid agonist.	This is used for the second stage of labor and short procedures such as cesarean delivery.	Hypotension, which may lead to decreased uterine perfusion[94] Pruritus (when opioids are added)[94] Blunting of the pressure sensation during the second stage of labor Impaired ability to push if the motor block is too dense Increased risk for operative vaginal delivery[94] Prolongation of labor[94] Fever,[97] periodically leading to suspicion of infection and subsequent interventions Transient fetal heart rate deceleration[94] Increased need for oxytocin (Pitocin) augmentation[94] Headache[94] Transient painful sensation in legs or buttocks (with spinal)[94] Epidural or spinal hematoma (rare)[94] Abscess (rare)[94] High spinal anesthesia, resulting in paralysis of the respiratory muscles (rare)[94] Neurotoxicity (rare)[94]
Combined Spinal-Epidural Block	This combines the rapid onset of spinal analgesia with the ability for continuous infusion of analgesic though the epidural catheter.*	This widely used block provides immediate pain relief during the second stage of labor. It can convert to anesthesia adequate for cesarean section. It continues to provide postcesarean pain relief.	
Epidural Anesthesia	Local anesthetic and opioid are injected through a catheter into epidural space, to allow for continuous infusion. The dose can be titrated over the course of labor.	The same catheter can be used for labor, vaginal delivery, and cesarean section. The block is usually not initiated until active labor is established.	
"Walking" Epidural Anesthesia	This epidural block preserves motor strength for more effective pushing. Most women are not able to walk or support their weight.		

*Maternal satisfaction, obstetric outcomes, and neonatal outcomes do not appear to differ between the combined spinal-epidural block and the epidural block.[96]

Therapies to Consider

Hot or Cold Application

Although the use of hot or cold application for pain relief in labor is common practice among doulas and labor support staff, no RCTs have evaluated this therapy. Easy to initiate, the use of heat or ice should depend on the desires of the laboring woman. Typically, heat is applied to the back, neck, shoulders, or abdomen by using warm compresses, microwaveable rice-filled pillows, or electric heating pads. Caution should be taken to avoid burns; the heat should never be painful. Cold is typically applied to the forehead, back, or neck with a cool washcloth, ice-filled sac or glove, or ice pack. Cold soda cans, which can double as massage tools on the lower back, can also be used. One study demonstrated a decrease in pain scores with ice massage to the acupoint LI4 during contractions.[97]

Homeopathy

Although many birth attendants administer homeopathy for pain, anxiety, and labor management, the use of remedies is largely driven by traditional homeopathic literature. Currently, no data are available on homeopathy in labor and birth; however, research indicates that homeopathy is a very safe form of therapy with minimal side effects.[98] If a woman is interested in using homeopathy, consult a homeopath or homeopathic literature to find appropriate remedies.

Reflexology

Reflexology focuses on zones in the hands and feet that are believed to correspond to specific areas of the body.[99] The practitioner applies manual pressure in these zones to achieve therapeutic benefits in the target organ, gland, or body part. No studies to date have evaluated reflexology in labor, but reflexology can be assumed to help promote relaxation. The uterine point is located between the medial malleolus and the heel pad, and the cervical point is on the heel pad.[46] One proposed technique is to massage or hold the first three toes during a contraction.[100]

Prevention Prescription

- Cultivate the patient-provider relationship prenatally when possible.
- Discuss the woman's expectations about labor prenatally.
- Discuss preferences for labor pain management before labor begins.
- Involve the laboring woman in decision making.
- Recommend that women arrange for continuous labor support.
- Recommend regular moderate exercise or yoga practice during pregnancy.

Therapeutic Review

The laboring woman has many options for pain control. Individually, many of these therapies are quite effective in reducing pain, but nearly all may be used in combination. No research has evaluated the synergistic effect, but we recommend offering women multiple options.

- Plan for continuous labor support. Consider hiring a trained doula. A1
- Consider childbirth education classes to prepare for labor and birth. C1

Lifestyle

- Regular prenatal exercise B1
- Moderate exercise or movement during labor B1

Biomechanical Therapy

- Ambulation or upright position during first stage of labor A1
- Upright or side-lying position during second stage of labor A1
- Hands and knees position for back labor B1
- Water immersion
  - First stage A1
  - Second stage B1
- Massage during labor B1
- Regular chiropractic, osteopathic, or manual treatment in pregnancy B1
- Sterile water injections for back labor A1
- Hot or cold application B1

Bioenergetics

- Transcutaneous electrical nerve stimulation in labor, with possible focus on acupoints B1
- Acupuncture during labor B1
- Acupressure during labor A1
- Homeopathy C1

Mind-Body Therapy

- Regular yoga practice in pregnancy B1
- Hypnotherapy techniques prenatally to prepare for labor A1
- Music/audioanalgesia during labor B1
- Biofeedback techniques during pregnancy to prepare for labor B1

Biochemical: Aromatherapy

- Aromatherapy during labor (e.g., frankincense, lavender, rose) B1

Botanicals

- Raspberry leaf to shorten labor: 1.2 mg twice daily in the last trimester B1
- Motherwort or skullcap. This can have a calming effect for anxiety. C1
- Black cohosh C2

Pharmaceuticals

- Parenteral opioids for mild to moderate pain relief A2
  - Choice of medication and dose institutionally driven
  - See Table 51-1 for options and doses
- Promethazine: 12.5 to 25 mg orally or intravenously every 4 to 6 hours as needed for sedation and nausea C2
- Local anesthesia A2
  - See Table 51-2 for technique and details
- Regional anesthesia or epidural anesthesia A3
  - See Table 51-3 for options and details

KEY WEB RESOURCES

DONA International: www.dona.org	Find a doula, and learn about doulas.
Betts D. Natural Pain Relief Techniques for Childbirth Using Acupressure: http://acupuncture.rhizome.net.nz/downloads/Acupressure.pdf	Locate acupressure points, and find further information on acupressure in labor.
Hypnobabies: http://www.hypnobabies.com; and Hypnobirthing: http://hypnobirthing.com	Locate resources for using hypnosis during labor and childbirth.
Kaiser Permanente guided imagery: https://members.kaiserpermanente.org/redirects/listen	Listen to a free downloadable guided imagery session to help prepare for labor. This Web site also includes other guided imagery downloads for pregnancy and childbirth.

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Chapter 52

Nausea and Vomiting in Pregnancy

Andrea Gordon, MD, and Judy Platt, MD

Pathophysiology

Nausea and vomiting in pregnancy (NVP) represent a conundrum for the pregnant woman. On the positive side, NVP are correlated with better fetal outcomes than the absence of these symptoms,[1] but at the extreme NVP can interfere with nutrition and hydration for the mother and developing fetus. Symptoms may range from occasional mild nausea to multiple episodes of daily vomiting resulting in weight loss and electrolyte abnormalities. This severe manifestation is often referred to as hyperemesis gravidarum. Definitions of hyperemesis gravidarum vary, but commonly accepted criteria include weight loss (often more than 5% of prepregnancy weight), electrolyte disturbances, and ketonuria.

Usually appearing before the ninth week of pregnancy, NVP will affect up to 85% of normal pregnancies, with symptoms generally remitting by the fourteenth week. Initial presentation of symptoms after the ninth week should prompt a workup to determine an alternative cause. NVP may be mild, but up to 20% of women find their symptoms so significant that they cannot continue to work.[2] The reported incidence of hyperemesis gravidarum, the most severe end of the spectrum, varies from 0.5% to 2%. This severely debilitating condition is the most common reason for hospital admission in the first trimester and the second most common problem for which pregnant women are admitted to the hospital, after preterm labor.[3]

Even at the milder end of the symptom continuum, NVP can lead to decreased quality of life and missed time from work. The aptly named Motherisk Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index has been shown to demonstrate a significant correlation between the presence and severity of NVP and poorer quality of life.[4,5] This effect on quality of life and the economic impact of missed work emphasize the need to control these symptoms. Mild or moderate vomiting does not appear to have any significant effects on the fetus. Among women with severe hyperemesis, the reported incidence of low birth weight is higher, but increased reporting of birth defects has not been noted.[6] In fact, several investigators suggested that NVP represent an evolutionary adaptation that helps protect the developing fetus from exposure to foods that may contain potential toxins.[7,8]

The cause of NVP is unknown. Both biologic and psychological factors have been proposed. Human chorionic gonadotropin (HCG) and estrogen have been studied as triggers for these symptoms. Suggestive evidence includes the finding that pregnant women with higher levels of HCG, which occur in molar pregnancies and multiple gestations, have significantly more episodes of vomiting and higher rates of hyperemesis gravidarum. This theory is also supported by the observations that nonpregnant women who experience nausea and vomiting after exposure to estrogens are more likely to experience NVP, cigarette smoking is known to reduce both estrogen and HCG levels, and pregnant smokers are less likely to experience hyperemesis gravidarum.[9]

No controlled studies support the theory that NVP comprise a conversion disorder or an inability to respond to life stress.[10,11] The association of high levels of HCG and estradiol with increasingly severe episodes of vomiting in pregnancy indicates a physiologic origin, as do epidemiologic factors. Daughters and sisters of women who had hyperemesis are more likely to have NVP as well. Other risk factors include a previous pregnancy affected by hyperemesis, a female fetus, and a history of motion sickness or migraines.[12]

Integrative Therapy

When treatment is considered, risks and benefits must be clearly explained to the pregnant woman. Minimizing the risks of any treatment is desirable, but the presence of a developing fetus makes it more urgent to decrease any unnecessary

exposures. This is an ideal time to use integrative approaches because drugs generally represent more risk than do other modalities. In addition, some of the behavior modifications such as exercise are beneficial in and of themselves.

Lifestyle

Although lifestyle modifications have not been studied to determine their efficacy, these interventions are safe and have been anecdotally reported to be useful.[13]

Avoid Odors

Some women report that NVP are triggered by strong odors such as foods, cigarette smoke, or perfume. Avoiding these stimuli may be helpful. Women should be supported in doing so, for example, by passing off cooking duties to someone else, avoiding tasks with strong odors such as feeding the dog, or politely asking coworkers not to wear perfume for a few weeks.

Increase Rest

Sleep requirements increase in early pregnancy.[14] Women frequently report nausea in association with feelings of exhaustion. Caregivers should educate pregnant patients that fatigue is common and support them in trying to obtain the additional rest they need.

Exercise

Light to moderate aerobic exercise may help decrease NVP symptoms. Additional benefits may include improved sleep and lessened constipation and fatigue. If patients were active before the pregnancy, they can continue at their previous level (avoiding overheating), but even if they were not, becoming gently active can be beneficial.

Nutrition

Low blood glucose levels seem to trigger nausea and then vomiting in many women, so small, frequent, high-protein, high-fiber meals are often recommended.[15] A potentially helpful approach is to decrease simple carbohydrates that rapidly raise blood glucose and thus stimulate insulin secretion, which can cause rapidly falling blood glucose (see Chapter 85, The Glycemic Index/Load). However, this includes food such as pasta, white rice, potatoes, and white bread, whose blandness seems desirable when patients are nauseated, so education is key. Some patients find that eating something as soon as they wake up and then every 2 hours can suppresses nausea. Each pregnant woman may have specific foods she avoids because of a taste or smell that triggers nausea, but it may also be necessary to avoid spicy or fatty foods because they can exacerbate symptoms. Little published evidence exists on the efficacy of dietary changes, but benefit clearly outweighs harm. In one international survey, dietary interventions seemed to help 22% of women with hyperemesis gravidarum.[16]

Two studies found that taking a multivitamin before pregnancy or before 6 weeks of gestation was associated with a decreased incidence of NVP. Although this approach would not help a woman already suffering with symptoms, it could be helpful for women at risk for symptoms in their next pregnancy.[17,18]

Botanicals

Ginger Root (Zingiber officinale)

Historically, ginger has been effectively and safely used to treat nausea, including that of pregnancy. Randomized controlled trials have shown that ginger is effective for treating NVP,[19] and it is the most thoroughly studied herb for this indication. Some trials have shown ginger to be not only more effective than placebo,[20] but also comparable to or better than vitamin B_6[21,22] and comparable to dimenhydramate.[23] Patients should be advised that it may take longer for ginger to work: up to 3 days, rather than 1 day for the dimenhydrinate. The U.S. Food and Drug Administration (FDA) has listed ginger as a food supplement that is generally recognized as safe,[24] and studies have not shown any increased incidence of malformations in children of mothers using ginger.[25]

Ginger seems to work primarily in the gastrointestinal tract on serotonin receptors in the ileum, the same receptors affected by some antiemetics, such as ondansetron. Some evidence indicates that ginger constituents may also have some action in the central nervous system.[26] No toxicity has been demonstrated, although ginger can cause abdominal discomfort or heartburn when it is taken in large doses, especially on an empty stomach.

Dosage

Most of the studies have used 250 mg powdered ginger in capsules four times daily, or 500 mg twice daily has been used.[20,23,24,27] A higher dose of 650 mg three times daily has also been used.[28] However, ginger can be consumed in many forms, including as a food, candied, or an infusion (tea). To make a tea, use 1 teaspoon of grated fresh ginger root in 1 cup of hot water, and drink approximately 3 cups a day; dried leaves can also be used. One study showed that eating five cookies a day, each containing 0.5 g of ginger, was also effective.[29]

Precautions

In theory, doses greater than 2 g daily may have an anticoagulant effect.

> Using ginger throughout the day is helpful. Patients can incorporate ginger into their diet by sprinkling dried or candied ginger in oatmeal, having some ginger tea, and adding fresh ginger to soup or stir-fries.

Chamomile (Matricaria chamomilla)

Chamomile is a flowering plant that is often used for various types of gastrointestinal upset, including travel sickness, colic, and inflammatory diseases of the bowel. It is commonly used for NVP,[30–32] although no research on this application has been published. Chamomile appears to be safe and well tolerated, however, and the FDA labels it as safe.[33]

Dosage

Prepare it as a tea, and sip as needed.

Precautions

Chamomile should be used with caution in patients who are allergic to the Asteraceae/Compositae family, which includes ragweed, daisies, and many other flowers. Some erroneous

concern exists about teratogenicity, but that concern is based on a study with alpha-bisabolol at high doses that could not be achieved by someone drinking tea.[34]

Peppermint Leaf (Mentha piperita)

Peppermint is another herb often used in pregnancy.[35,36] The active parts are the stems, leaves, and flowers, as well as the peppermint oil that is distilled from these plant parts. Studies have shown peppermint oil to be effective for reducing bowel spasms in irritable bowel syndrome and for patients receiving barium enemas, but peppermint oil has not been studied in pregnancy.[37] Its mechanism of action is by reduction of spasm in smooth muscle, and it may help with NVP by reducing esophageal dysmotility. This effect can also reduce lower esophageal sphincter pressure, however, and result in reflux. Theoretical concerns exist with using the essential oil in pregnancy because it may cross the placental barrier, but the amount of peppermint ingested in teas or foods seems to be safe.[34] Peppermint has been rated as safe by the FDA.[33]

Dosage

The dose is 2 to 3 cups of tea daily. Many women find peppermint candies or gum to be effective in squelching nausea. A dose of 0.2 mL in 2 mL of isotonic saline solution has been used for postoperative nausea and can be tried if teas or foods containing peppermint are not tolerated.[38]

Precautions

Peppermint can aggravate reflux by decreasing lower esophageal sphincter tone.

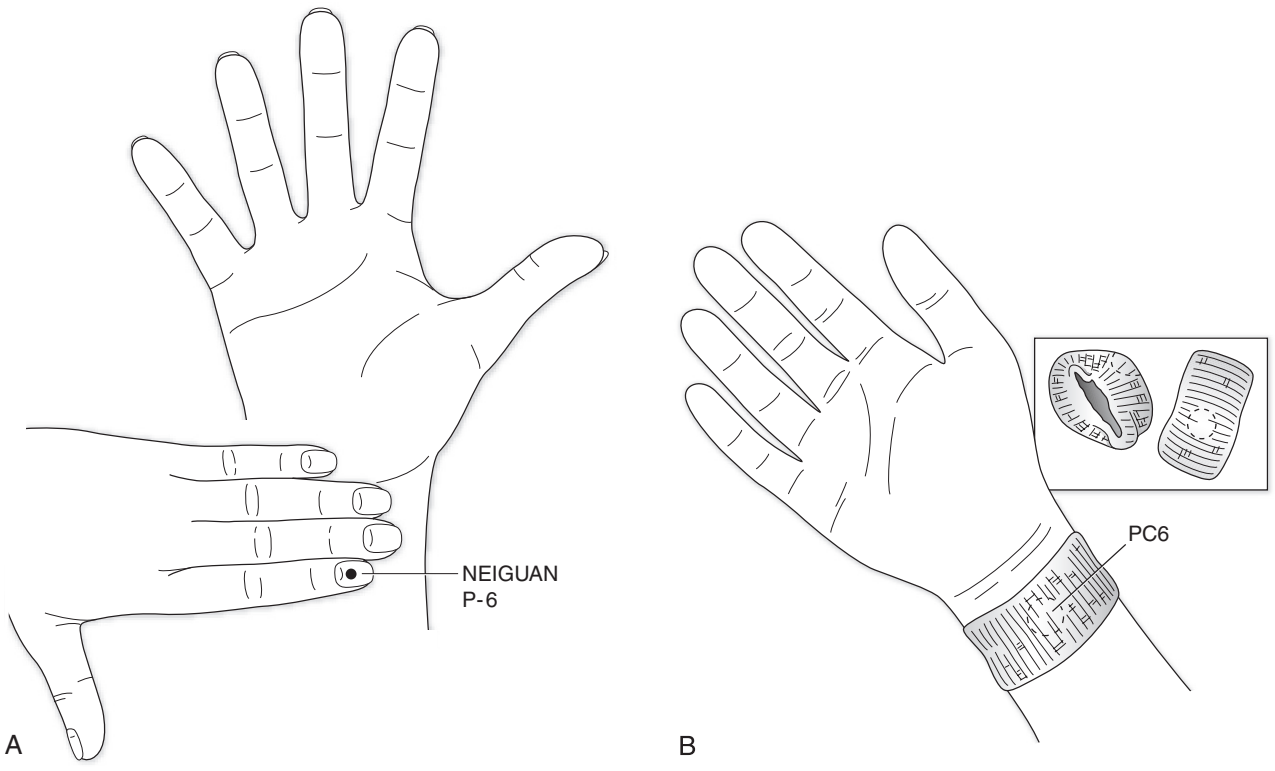
Bioenergetics

Acupressure: Stimulation of the P6 Neiguan Point

Acupressure of the pericardium 6 (P6) Neiguan (meridian) point, which is located on the inner wrist, may be beneficial. A Cochrane analysis noted equivocal results, based on limited evidence, for all forms of stimulation of the point, including acupuncture and acoustic stimulation.[39] A study conducted in Korea found significantly less NVP in a group of women with hyperemesis gravidarum.[40] Other studies using a crossover design, which were not included in the Cochrane analysis, also showed benefit to using acupressure at the P6 point,[40,41] and another trial found decreased nausea with P6 stimulation but no change in the frequency of vomiting.[42] Many patients are willing to try acupressure because it costs little and has no significant side effects.

Patients can be taught to find the P6 point and treat themselves with either manual pressure or the application of "Sea-Bands" (Fig. 52-1). These elastic bands with attached plastic disks were originally used for motion sickness. Patients can create their own version of such bands by placing a small, round object such as a bead over the point and securing it

FIGURE 52-1
A, The P6 Neiguan acupressure point is located on the volar aspect of the forearm by placing the examining hand three fingerbreadths below the wrist crease. The patient's finger widths should be used for measurement. The P6 point is essentially in the midline between the tendons of the palmaris longus and flexor radialis muscles. **B,** Location of this point. PC, pericardium.



with tape and then massaging the bead. This therapy has no known negative side effects.

To have a patient accurately locate the P6 point, have her lay one hand palm up, with the other hand placed palm down at right angles to the upturned arm. The first three fingers of the palm-down hand are held close together, and the edge of the ring finger is placed at the crease of the wrist closest to the palm in alignment with the middle finger of the upturned hand. The P6 point, between the palmaris longus and flexor radialis tendons, is now readily palpable under the tip of the index finger of the examining hand (see Fig. 52-1A). This point is often tender, a characteristic that aids in its location. Many patients use this acupressure in conjunction with other interventions because it has no known side effects or interactions.

Patients can stimulate the P6 point at any time, but they should be cautioned against using any other acupressure points without consulting a trained practitioner. Some commonly used points, such as the Ho-Ku point between first and second metacarpals (often used for headaches), can stimulate contractions.

Mind-Body Therapy

Hypnosis

Hypnosis has been studied as a treatment for hyperemesis gravidarum. A review of six studies showed encouraging effects, but methodologic problems did not allow a definitive recommendation.[43] This intervention is safe, however, and some women may want to try it for all levels of NVP. One approach has been to suggest to a woman that the "nausea center" in her brain is very sensitive to the hormones of pregnancy and to suggest that she is able to "turn down" that sensitivity as one would a thermostat.[44] This imagery may be helpful for some patients.

NVP may have an element of conditioned response, as noted with chemotherapy-associated vomiting. Some uncontrolled studies showed that hypnosis can reduce vomiting and anticipatory vomiting in patients undergoing chemotherapy,[10] so the potential exists for hypnosis to work for NVP. Because this treatment may require several sessions of training, the time and expense may be prohibitive for some patients.

Counseling and Psychotherapy

Although the general consensus is that NVP does not represent a conversion disorder and is not caused by emotional responses to the pregnancy,[10] evidence indicates that women with NVP may be under more stress. Two investigators stated that NVP "could subject any normal expectant mother to stress sufficient to trigger adjustment disorders, generalized anxiety or even depressive episodes."[10] In recognition of this extraordinary stress, counseling or psychotherapy may be helpful in coping with the symptoms and their effects on a woman's life.

Supplements

Vitamin B_6 (Pyridoxine)

Vitamin B_6 is a water-soluble vitamin that is an effective treatment for nausea in pregnancy. The benefit in reducing vomiting episodes is less clear.[45,46] The mechanism of action of pyridoxine remains unknown, but extensive analysis for teratogenicity shows no negative effect on pregnancy outcome.[47] A popular medication for nausea and vomiting, known as Bendectin in the United States and Diclectin in Canada, contained pyridoxine and doxylamine. Bendectin was withdrawn from the United States market in 1983 out of safety concerns about teratogenicity, but no studies validated this possibility. Diclectin remains available in Canada and is one of the most widely studied and used medications in pregnancy today. Following removal of Bendectin from the market, no reduction in birth defects was reported, but hospitalization rates for NVP doubled.[48]

Diclectin, a combination of doxylamine 10 mg and pyridoxine 10 mg, is available in Canada and can be purchased online (canadadrugs.com). It is expensive, at more than a dollar a pill. A less expensive alternative is to combine Unisom (contains 25 mg doxylamine), one half tablet at bedtime, with 50 mg of pyridoxine.

Patients can expect significant reduction of nausea with few side effects if they take vitamin B_6.

Dosage

The most effective dosage appears to be 30 to 75 mg daily in three divided doses. Studies performed with the higher end of the dosing range have shown effectiveness against vomiting as well as nausea.[45,46] When vitamin B_6 alone is not effective, many pregnant women combine it with doxylamine to obtain relief from NVP.

Precautions

Pyridoxine can cause sensory neuropathy, which is related to the daily dose and duration of intake. Doses exceeding 1000 mg daily or total doses of 1000 g or more pose the most risk, so the doses that have been used for NVP appear generally to be safe.[49]

Pharmaceuticals

Antihistamines

Several histamine (H_1) receptor antagonists have been studied for the treatment of NVP. The most frequently studied and used is doxylamine (Unisom, an over-the-counter sleep aid). An extensive review of safety data revealed no adverse pregnancy outcomes from doxylamine alone or in combination with pyridoxine.[50] Other drugs in this group, which all have shown some evidence of efficacy and safety for controlling NVP, are dimenhydrinate (Dramamine), cetirizine (Zyrtec), meclizine (Antivert), hydroxyzine (Vistaril), and diphenhydramine (Benadryl).[51]

Dosage

Most patients should use 12.5 mg of doxylamine, the amount in one half of a scored tablet. This is the amount of doxylamine that was contained in Bendectin. Indeed, many women try to "make" a form of Bendectin by combining doxylamine with vitamin B_6. This safe option can be suggested if

vitamin B_6 alone or with ginger or P6 point stimulation is not working adequately. Diphenhydramine, given in 25- to 50-mg doses up to every 6 hours, is also safe and easily obtained.

Precautions
All antihistamines can cause drowsiness.

Phenothiazines
The phenothiazines used to treat NVP include promethazine (Phenergan), prochlorperazine (Compazine), chlorpromazine (Thorazine), and perphenazine (Trilafon). Only promethazine has randomized, controlled study data supporting its efficacy and safety.[39,51] However, some evidence indicates that all medications in this group have some efficacy in the treatment of NVP.[47] These medications may be used in the outpatient setting, but therapy is often not started until hospital admission for treatment of dehydration or intractable vomiting. The variable dosing forms are advantageous for NVP: these drugs can be self-administered orally or rectally or given intramuscularly by medical personnel if needed.

Dosage
For promethazine, begin with 12.5 mg rectally or orally and progress to 25 mg every 4 hours as needed.

Precautions
Side effects of promethazine include sedation, hypotension, dystonia, and extrapyramidal symptoms. If needed, diphenhydramine, 25 mg, can be given orally every 6 hours to treat dystonia or extrapyramidal side effects.

Dopamine Antagonists
Two dopamine antagonists have been studied for treatment of NVP: trimethobenzamide (Tigan) and metoclopramide (Reglan). Trimethobenzamide has been shown to be safe,[52] but it has been largely studied for nausea in other settings such as chemotherapy.[53] Only one double-blind trial focused on the effectiveness of trimethobenzamide in treating NVP.[54] This study showed that trimethobenzamide alone or in combination with pyridoxine significantly improved symptoms of nausea and vomiting compared with placebo.[54]

Metoclopramide is not associated with malformation risk,[55,56] and it has been shown to be effective in hyperemesis gravidarum, with or without promethazine.[57,58] A combination of vitamin B_6 and metoclopramide was shown to be better than prochlorperazine or promethazine in improving the subjective symptoms of patients with NVP.[59]

Dosage
Metoclopramide can be given orally in 5- to 10-mg doses three times daily before meals.

Precautions
The side effects of metoclopramide are similar to those of the phenothiazines but occur less frequently.

5-Hydroxytryptamine$_3$ Receptor Agonists
Ondansetron (Zofran), a 5-hydroxytryptamine$_3$ receptor agonist, is a potent antiemetic originally used for treatment of chemotherapy-induced nausea and vomiting. Data on NVP are very limited, but a study of hospitalized patients who received intravenous ondansetron or promethazine showed that these medications were equally effective and had no negative effects on the fetus.[60]

Dosage
Ondansetron is given orally or intravenously, 2 to 8 mg up to every 8 to 12 hours.

Precautions
Adverse reactions to ondansetron include headache, fever, and bowel dysfunction, although this agent is reported to be better tolerated by patients than promethazine, with no dystonic or extrapyramidal side effects.

> Ondansetron is available in an orally disintegrating tablet. This can be useful if someone feels too nauseated to swallow any medication.

Corticosteroids
Several small studies evaluated corticosteroids, primarily methylprednisolone, for efficacy in reducing NVP and hyperemesis. Methylprednisolone reduced symptoms of NVP along with hospital readmission rates for hyperemesis.[61] Another trial found that promethazine worked more rapidly than prednisolone, but after a week both medications worked equally well, and the prednisolone group had fewer side effects.[62] Various oral and intravenous dosages have been studied, but the most common regimen is an oral 2-week course of 48 mg daily. Most patients respond within 3 days, so if no improvement has been seen by that time, longer treatment is generally not indicated. Methylprednisolone may be continued for up to 6 weeks, but longer use may result in adverse maternal effects related to prolonged steroid exposure.[61,63] Evidence also indicates that a shorter course of hydrocortisone is effective for treating intractable hyperemesis.[64] A meta-analysis found an increased risk of oral clefts associated with prednisone use.[65]

Dosage
The dose of methylprednisolone is 16 mg orally or intravenously every 8 hours for up to 2 weeks (tapered course to avoid adrenal suppression). The dose of hydrocortisone is 300 mg intravenously daily for 3 days.

Precautions
Avoid corticosteroid use before 10 weeks of gestation if possible. Avoid prolonged use for more than 6 weeks to reduce risk of maternal side effects.

Intravenous Fluids
Intravenous fluids have not been specifically studied for the treatment of hyperemesis, but they are often coadministered with other medications in the hospital setting for the treatment of dehydration. Intravenous fluid is generally recommended when patients fail to tolerate oral fluids for a prolonged period or show electrolyte abnormalities indicating dehydration. Dextrose and intravenous thiamine can be added to fluids when vomiting has been prolonged and persistent.[12]

Extreme Measures for Intractable Nausea and Vomiting in Pregnancy

Enteral or Parenteral Feedings

Evidence to support enteral or parenteral feedings comes from case reports and small series.[66,67] In general, the prudent approach is to start with enteral feedings and move on to peripheral parental nutrition and finally to total parental nutrition if all other methods fail. Serious and even life-threatening complications have been reported with parenteral nutrition, so it is used only as a last resort.[68]

Therapeutic Abortion

With current medical interventions such as intravenous hydration and medications, it is rare for NVP to be so severe as to be life-threatening. This was not the case in the early twentieth century, when severe NVP represented an important cause of maternal deaths.[69] However, maternal morbidity in the form of Wernicke encephalopathy caused by vitamin B_1 deficiency, esophageal rupture, acute tubular necrosis, and splenic avulsion have all been reported to be caused by intractable vomiting of pregnancy.[1] When the maternal condition is deteriorating as a consequence of hyperemesis gravidarum despite aggressive medical intervention, pregnancy termination may be indicated (Fig. 52-2). Fortunately, symptoms usually subside rapidly as HCG levels fall.

Therapies to Consider

Homeopathy

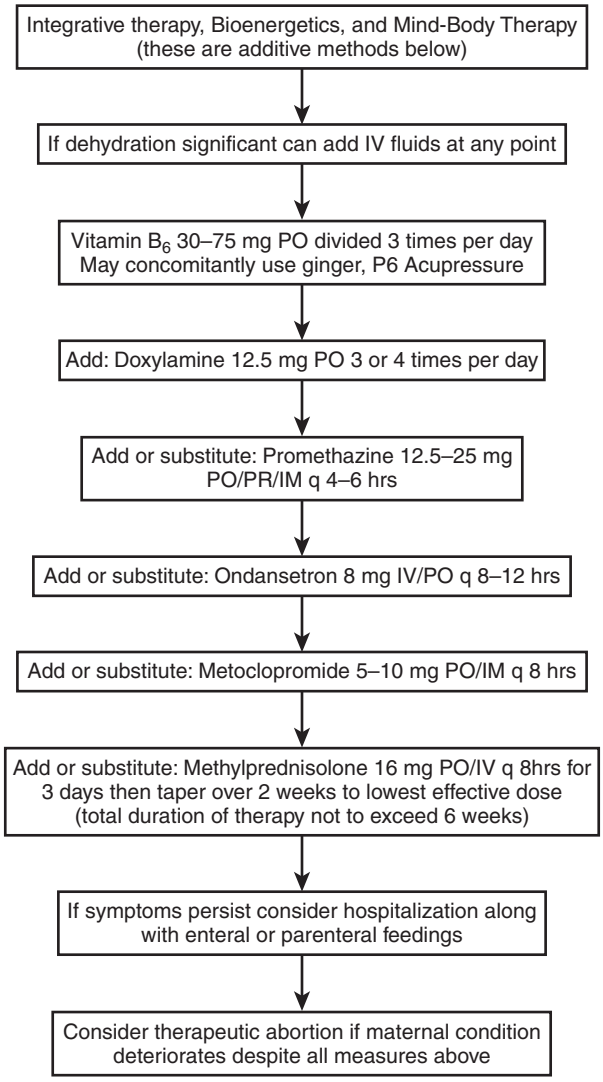
No studies have evaluated the efficacy of homeopathic remedies in the treatment of NVP. Practitioners cite anecdotal evidence of homeopathy use, but choosing the correct remedy can be complex because many subtle differences in symptoms are taken into account. Some of the remedies commonly used include nux vomica, sepia, and ipecac.[70] Because homeopathic preparations are extensively diluted, they should be safe for pregnant women and would likely have no adverse effects if they are not helpful. Some investigators recommend avoiding any remedies with potencies (dilutions) greater than 12 C, however.[71]

Traditional Chinese Medicine

Practitioners of traditional Chinese medicine (TCM) may recommend acupuncture, acupressure, and herbs, but they also use certain foods such as umeboshi plums (a very salty preserved fruit) to combat nausea. In addition, these clinicians may use practices such as moxibustion, cupping, or massage. Because the TCM views of health and the body's function are different from those in Western medicine, a certified TCM practitioner should advise on the use of these approaches.[72] Different patterns of symptoms lead to different treatments.[73] Information about training and accreditation of TCM practitioners can be found at the National Certification Center for Acupuncture and Oriental Medicine (www.nccaom.org).

Umeboshi plums can be found in most Asian grocery stores. If the plum itself is too salty, some women obtain relief of nausea by sucking on the pit only. Another option is to use one fourth to one half a plum at a time.

FIGURE 52-2
Integrative therapy, bioenergetics, and mind-body therapy algorithm. IM, intramuscularly; IV, intravenous; PO, orally; q, every; PR, per rectum.



Prevention Prescription

- Eat frequent, small meals that are high in protein to avoid low blood glucose levels.
- Avoid overconsumption of simple carbohydrates such as cakes, candy, and starchy foods because they may lead to low glucose levels, which could stimulate more nausea.
- Consider trying more salty foods and tart liquids because these are reported by some women to be better tolerated.
- Avoid triggers such as pungent odors or unpleasant visual stimuli that may worsen nausea.

Therapeutic Review

Lifestyle, botanical, bioenergetic, and mind-body therapies are additive to all the other methods listed here. If dehydration is significant, add intravenous fluids at any point. C-2

Bioenergetics

- Acupuncture (P6) B-1

Mind-Body Therapy

- Hypnotherapy B-1

Supplements

- Vitamin B_6: 30 to 75 mg PO divided three times per day A-1
- Ginger: 250 mg powdered in capsules four times daily, or 500 mg twice daily; can increase to 650 mg three times daily as needed B-1

Pharmaceuticals

- Doxylamine: 12.5 mg orally three or four times daily A-1
- Add or substitute promethazine: 12.5 to 25 mg orally, rectally, or intramuscularly every 4 to 6 hours B-2
- Add or substitute ondansetron: 8 mg intravenously or orally every 8 to 12 hours B-2
- Add or substitute metoclopramide: 5 to 10 mg orally or intramuscularly every 8 hours B-2
- Add methylprednisolone: 16 mg orally or intravenously every 8 hours for 3 days then taper over 2 weeks to the lowest effective dose (total duration of therapy not to exceed 6 weeks) B-2
- If symptoms persist, consider hospitalization along with enteral or parenteral feedings. C-3

Surgery

- Consider therapeutic abortion if the maternal condition deteriorates despite all the measures described here and in Figure 52-2. C-3

KEY WEB RESOURCES

Motherisk morning sickness information: http://www.motherisk.org/prof/morningSickness.jsp	This Web site contains a treatment algorithm for hyperemesis gravidarum.
Merck Manual: http://www.merckmanuals.com/professional/gynecology_and_obstetrics/symptoms_during_pregnancy/nausea_and_vomiting_during_early_pregnancy.html?qt=pregnancy&alt=sh	This Web site provides a brief overview of diagnosis and treatment of nausea and vomiting in pregnancy.
BMJ Clinical Evidence: http://clinicalevidence.bmj.com/ceweb/conditions/pac/1405/1405.jsp	This article describes the effects of treatment for nausea and vomiting in pregnancy and the effects of treatments for hyperemesis gravidarum. Registration is required to access this Web site.
Motherisk Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index: http://www.medscape.com/viewarticle/712662_3	This index can be used as a way for patients to quantify and track symptoms and may be helpful when comparing treatments. This index can also be found at Koren G, Boskovic R, Hard M, et al. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. *Am J Obstet Gynecol*. 2002 May;186(5 Suppl Understanding):S228-S231.

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Chapter 53

Premenstrual Syndrome

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Pathophysiology

Premenstrual syndrome (PMS) is defined as a recurrent, cyclic set of physical and behavioral symptoms that occurs 7 to 14 days before the menstrual cycle and is troublesome enough to interfere with some aspects of a woman's life. PMS is estimated to affect up to 40% of menstruating women, and the most severe cases occur in 2% to 5% of women who are between 26 and 35 years of age.[1] Although PMS has been recognized as a medical disorder for many years, the cause remains a mystery (Table 53-1). The complex relationships that exist among hormones may offer insight into why some women suffer more than others. For instance, mild elevations of prolactin, a hormone that is primarily involved in regulating the development of the breast during pregnancy, have been associated with PMS, menstrual irregularities, and breast tenderness, whereas low levels of thyroid hormone can contribute to depression, fatigue, and heavy menses.

Hormonal Influences

A deficiency of progesterone or an abnormally high estrogen-to-progesterone ratio during the luteal phase has been a popular theory of the origin of PMS for many years, although studies comparing hormone levels in women with PMS with those in women without the disorder have failed to support this hypothesis.[2] In the 1950s, Dr. Katherina Dalton was one of the first to postulate this theory. Dr. Dalton administered natural progesterone in the form of injection, suppositories, or subcutaneous pellets; 83% of women in the study reported complete relief of PMS symptoms.[3] Because of the strict inclusion criteria of the study, however, only 18% of women with PMS appeared to be suitable candidates for this therapy. A 1985 study using oral micronized progesterone (100 mg in the morning and 200 mg before bedtime), starting 3 days after ovulation and continuing for 10 days, found progesterone to be clearly superior to placebo for the symptoms of anxiety, stress, and poor concentration.[4]

Prolactin

Prolactin levels peak at ovulation and generally remain elevated during the luteal phase of the menstrual cycle. Prolactin excess is associated with menstrual irregularities, diminished libido, depression, and hostility.[5] Some authorities suggested that up to 62% of women with menstrual disorders have some elevation of prolactin.[6] Prolactin plays a role in breast stimulation and may be related to premenstrual breast tenderness. However, no consistent abnormalities have been found in women with PMS.[2]

Aldosterone

Aldosterone levels normally rise at ovulation and remain elevated during the luteal phase of the menstrual cycle. This elevation of aldosterone may be responsible for the congestive symptoms of PMS, such as edema, breast swelling, abdominal bloating, weight gain, and headaches. However, differences in absolute levels of aldosterone between symptomatic and asymptomatic women are not noted in the literature.[7]

Endogenous Opiates

Some researchers, who observed an increase in beta-endorphin levels after ovulation, hypothesized that women with PMS may have a lower level of these circulating endogenous opiates or a more sudden withdrawal that causes them to experience greater sensitivity to pain and depression in the luteal phase of the menstrual cycle.[8]

Vitamin B_6 and Magnesium

Vitamin B_6 (pyridoxine) is required for the metabolism of amino acids, carbohydrates, and lipids. The active forms of this vitamin are necessary coenzymes for the decarboxylation of 5-hydroxytryptophan to 5-hydroxytryptamine (5-HT) and of dopa to dopamine. Pyridoxine deficiency is associated with elevations of prolactin and low levels of serotonin and dopamine.[9] Pyridoxine deficiency can lead to depression, peripheral neuropathy, and mood changes.

TABLE 53-1. Proposed Causes of Premenstrual Syndrome

Hormonal Factors	Estrogen deficiency Estrogen excess High estrogen-to-progesterone ratio Progesterone deficiency Prolactin excess Beta-endorphin deficiency
Fluid and Electrolytes	Aldosterone excess Vasopressin excess High sodium-to-potassium ratio Renin-angiotensin abnormalities
Neurotransmitters	Serotonin deficiency Cortisol excess Hypoglycemia Reduced glucose tolerance Thyroid abnormalities Adrenal insufficiency
Prostaglandins	Prostaglandin excess Prostaglandin deficiency Essential fatty acid deficiencies
Vitamins and Minerals	Pyridoxine deficiency Vitamin A deficiency Vitamin E deficiency Magnesium deficiency Calcium excess Calcium deficiency Potassium deficiency Trace mineral deficiency Zinc deficiency Dopamine deficiency Norepinephrine deficiency Low platelet monoamine oxidase activity
Hereditary	Genetic risk
Psychological Factors	Beliefs about menstrual cycle Coexisting psychiatric disorders Poor coping skills Poor self-esteem
Social Factors	Current marital and sexual relationships Former marital and sexual relationships Social stress Psychosexual experiences Cultural attitudes about PMS Societal attitudes about PMS Poor social network

PMS, premenstrual syndrome.

Although serum levels of magnesium are often normal in women with PMS, researchers have noted lowered red blood cell magnesium levels in women with the disorder.[10] Calcium and dairy products may interfere with absorption, whereas refined sugar increases urinary excretion of magnesium. Magnesium deficiency can reduce dopamine and thyroid activity (with resultant increase in prolactin) and lead to depression, mood changes, and muscle cramping.

TABLE 53-2. Symptoms of Premenstrual Syndrome

Abdominal bloating	Insomnia
Acne	Irritability
Anxiety	Joint pain
Back pain	Lethargy
Change in appetite	Low libido
Clumsiness	Low self-esteem
Constipation	Mood swings
Depression	Nervousness
Diarrhea	Social isolation
Dizziness	Sugar cravings
Fatigue	Tender breasts
Headache	Water retention

Hypoglycemia

The body appears to be more sensitive to insulin in the luteal phase of the menstrual cycle, a finding that led some researchers to hypothesize that transient hypoglycemia may account for some PMS symptoms.

Prostaglandins

Prostaglandins are associated with breast pain, fluid retention, abdominal cramping, headaches, irritability, and depression.[11] Patients with physical premenstrual complaints and dysmenorrhea have been shown to respond to prostaglandin inhibitors.

Psychosocial Theory

Emotional and physical stressors have been found to influence the menstrual cycle. Travel, illness, stress, weather changes, and other environmental factors may affect ovulation, length of menstrual cycle, and severity of PMS.[12] Cultural, societal, and personal attitudes toward menstruation also appear to play a role in the presence and severity of PMS. The dynamic interplay of environment, spirit, and physiology demands an integrated biopsychosocial approach to treatment.

Symptoms

More than 150 symptoms have been associated with PMS. The most common are listed in Table 53-2.

The American Psychiatric Association (APA) defined the diagnostic criteria for premenstrual dysphoric disorder (PMDD), a more severe form of PMS. To be diagnosed with PMDD, a woman must have at least five of the following symptoms, and they must occur cyclically and be serious enough to interfere with her normal activities:

1. Feeling of sadness or hopelessness; possible suicidal thoughts
2. Feelings of tension or anxiety
3. Mood swings marked by periods of teariness
4. Persistent irritability or anger

5. Disinterest in daily activities and relationships
6. Trouble concentrating
7. Fatigue or low energy
8. Food cravings or binging
9. Sleep disturbances
10. Feeling out of control
11. Physical symptoms such as bloating, breast tenderness, headaches, and joint or muscle pain

Although this addition to the fourth edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders,* published in 1994 (DSM-IV), is useful for recognizing PMDD as a valid disorder, that behavioral aspects comprise the primary focus is disturbing. With the vast numbers of physiologic and hormonal interactions taking place in a woman's body, a multitude of explanations would seem to exist for the variety of symptoms. Thus, assuming that numerous therapies may help and that not all remedies are universally effective is reasonable.

Classifications

Dr. Guy Abraham developed a system for categorizing PMS into four distinct subgroups.[13] They can be summarized as follows:

PMS-A (anxiety) is believed to be related to high levels of estrogen and deficiency of progesterone. Women experience irritability, anxiety, and emotional lability.

PMS-C (carbohydrate craving) is of unclear origin but may be caused by enhanced intracellular binding of insulin. Women with this subtype experience increased appetite, sugar and carbohydrate craving, headache, and heart palpitations.

PMS-D (depression) is most likely caused by low levels of estrogen that lead to excessive breakdown of neurotransmitters. Low estrogen levels may be caused by enhanced adrenal androgen or progesterone secretion.

PMS-H (hyperhydration) is the result of increased water retention secondary to elevations of aldosterone. Elevations of aldosterone in the premenstrual period may be the result of excess estrogen, excessive salt intake, stress, or magnesium deficiency. Women with this subtype report weight gain, breast tenderness and fullness, swelling of the hands and feet, and abdominal bloating.

Although used by many practitioners, these categories should be considered only guidelines, because the basis for their separation has not been adequately confirmed by current research, and most women do not neatly fit into just one of the groups.

Clinical Evaluation

A complete physical examination, including pelvic evaluation and laboratory tests, should be performed to rule out anemia and hypothyroidism. A prolactin test may be included. An extremely useful approach is for a woman to record her symptoms on a daily basis for at least two complete menstrual cycles to allow the clinician to see just what her symptoms are and how they are related to her menses.

The clinician must address any other underlying medical conditions that may masquerade as PMS. One report found that 75% of women receiving care for PMS at specialized clinics had another diagnosis that accounted for many of their symptoms, primarily major depression and other mood disorders.[14]

Integrative Therapy

Once the diagnosis has been established, an integrative approach should be considered. Therapies to be explored include exercise, dietary manipulation, dietary supplements, mind-body approaches, acupuncture, traditional Chinese medicine, counseling, and conventional medications.

Exercise

Exercise remains understudied in the scientific world because it does not fit well into the double-blind placebo-controlled study design. The few studies that have been conducted on the role of exercise in PMS have clearly shown that women who engage in regular physical exercise have fewer symptoms of PMS than women who do not. Women who exercise regularly note improvement in all symptoms of PMS.[15] The frequency, rather than the intensity, of exercise appears to diminish the negative mood and physical symptoms that occur during the premenstrual period.[16] Exercise may reduce symptoms by reducing estrogen levels, decreasing circulating catecholamines, improving glucose tolerance, and raising endorphin levels.[17] Aerobic activity appears to be most beneficial; however, yoga and tai chi are probably equally effective if they are performed at least three times per week.

Diet and Nutrition

Many people in the United States fail to eat a healthy diet, but some researchers have found this observation to be even more accurate for women with PMS. A 1983 report noted that women with PMS consumed 275% more refined sugar, 79% more dairy products, 78% more sodium, 62% more refined carbohydrates, 77% less manganese, and 53% less iron than women without PMS.[18] These dietary excesses and deficiencies may explain some of the symptoms women experience in the premenstrual period. Dairy products are high in sodium and interfere with magnesium absorption. Refined sugars increase the urinary excretion of magnesium.[19] Heavy intake of sugar also increases sodium and water retention owing to the rapid release of insulin. Dietary salt may exacerbate swelling. Consumption of caffeine-containing beverages was associated with increases in both the prevalence and severity of PMS in college students.[19] A study of Chinese women found that increasing tea consumption was linked to a rising prevalence of PMS.[20] Women experiencing irritability or difficulty sleeping during the premenstrual period should be encouraged to reduce or limit their intake of caffeine (Table 53-3).

Fiber-rich, low-fat diets suppress the ability of fecal bacteria to deconjugate estrogen and thereby enhance fecal estrogen excretion.

Dietary Fat

Fiber-rich, low-fat diets may be beneficial for women with PMS because these diets reduce blood levels of estrogen. Estrogen is conjugated in the liver and sent to the small intestine for elimination in the feces. Intestinal bacteria can deconjugate estrogen and allow it to be reabsorbed into the body.

TABLE 53-3. Caffeine Amounts in Common Foods and Beverages

SERVING SIZE (oz)	CAFFEINE (mg)
Coffee, instant (6–8)	65–100
Coffee, percolated (6–8)	85–135
Coffee, filtered (6–8)	115–175
Coffee, decaffeinated (6–8)	1–5
Tea, instant (6–8)	35–70
Tea, brewed (6–8)	28–150
Tea, iced (6–8)	40–45
Chocolate, dark semisweet (1)	5–35
Chocolate, milk (1)	1–15
Cola beverage (8)	25–30

From Thys-Jacobs S, Starkey P, Bernstein D, et al. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. *Am J Obstet Gynecol.* 1998;179:444–452.

Several studies showed that reducing fat (less than 20% of total calories) and increasing fiber for only 3 months can lower a woman's serum estrogen level.[20] If one accepts the theory that elevations of estrogen can worsen PMS symptoms, then consuming a diet high in fruits, vegetables, and whole grains and low in saturated fat may be wise. Four to six small meals should be consumed throughout the day to ease both food cravings and mood swings. Alcohol consumption should be limited because it can worsen PMS symptoms.

No food-based strategy has been adequately tested to determine its effects on PMS. However, recommendations such as eating a high-fiber diet, limiting caffeine, and cutting back on high-sugar foods have few drawbacks and numerous health benefits.

Supplements

Calcium

Ovarian hormones influence calcium, magnesium, and vitamin D metabolism. Estrogen is involved in calcium metabolism, calcium absorption, and parathyroid gene expression and secretion. Clinical trials in women with PMS found that calcium supplementation improves several mood and somatic symptoms.

A prospective randomized double-blind placebo-controlled parallel-group multicenter clinical trial was conducted to evaluate the effectiveness of calcium carbonate for PMS. Healthy premenopausal women were recruited nationally at 12 outpatient centers and screened for moderate to severe, cyclically recurring premenstrual symptoms. Symptoms were prospectively documented over 2 menstrual cycles with a daily rating scale that included 17 core symptoms and 4 symptom factors (negative affect, water retention, food cravings, and pain). Of the 720 women screened for the trial, 497 were enrolled, and results for 466 were valid for the efficacy analysis. Women were randomly allocated to receive 1200 mg calcium carbonate or placebo daily for 3 menstrual cycles. Routine blood chemistry analysis, complete blood cell count, and urinalysis data were obtained for all participants. Each participant kept a daily diary to document symptoms, adverse effects, and compliance with therapy. The primary outcome measure was a 17-parameter symptom complex score. No differences in age, weight, height, use of oral contraceptives, or menstrual cycle length were reported between the treatment and control groups. No differences existed between the groups in the mean screening symptom complex score of the luteal phase ($P = .659$), menstrual phase ($P = .818$), or intermenstrual phase ($P = .726$) of the menstrual cycle. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was noted in the calcium-treated group by the third month ($P < .001$). The researchers concluded that "calcium supplementation is a simple and effective treatment in premenstrual syndrome, resulting in a major reduction in overall luteal phase symptoms."[21]

A review of studies focusing on calcium for the management of premenstrual symptoms was published in the *Annals of Pharmacotherapy*.[22] On the basis of the medical literature, the reviewer concluded that "calcium supplementation of 1200 to 1600 mg/day, unless contraindicated, should be considered a sound treatment option in women who experience premenstrual syndrome."

Dosage

The dose is 500 to 600 mg twice per day elemental calcium as carbonate or citrate.

Precautions

Calcium products made from oyster shell, dolomite, or bone meal occasionally contain lead.[23] Labels containing the letters "USP" indicate that the product meets the purity and dissolution standards established by the U.S. Pharmacopeia; however, this is a voluntary standard, and many products do not bear USP on their labels. Calcium supplements should not be taken at the same time as tetracycline, iron supplements, thyroid hormones, or corticosteroids because calcium binds to these substances and interferes with their effectiveness and its own absorption. Iron absorption can be reduced by as much as 50% by many forms of calcium supplementation.

Magnesium

Women with PMS have been shown to have low levels of magnesium in their red blood cells. Magnesium deficiency produces fatigue, irritability, mental confusion, PMS, menstrual cramps, insomnia, muscle cramps, and symptoms of heart disturbances. A 2002 Cochrane Review found that magnesium was superior to placebo for relieving dysmenorrhea, likely through inhibition of prostaglandin $F_{2\alpha}$.[24] Whether magnesium would be helpful for women with PMS who do not experience menstrual pain is unclear, although some integrative practitioners empirically use magnesium as part of a treatment strategy for PMS, particularly in women with menstrual migraine or a tendency to constipation. Dietary sources of magnesium include green leafy vegetables, tofu, legumes, nuts, seeds, and whole grains.

Dosage

The dose is 200 to 600 mg/day of magnesium as chelate, citrate, or glycinate.

Precautions

Adverse effects of magnesium excess include abdominal cramping and diarrhea. Signs of magnesium toxicity are hypotension, irregular heartbeat, muscle weakness, nausea, diarrhea, and change in mental status. The kidneys excrete magnesium, so women with renal insufficiency must be cautious with magnesium supplementation.

Vitamin B_6

Pyridoxine is a water-soluble B vitamin that serves as a cofactor in more than 100 enzyme reactions, many of which are related to the production and metabolism of neurotransmitters. The use of pyridoxine (vitamin B_6) to alleviate PMS symptoms has been evaluated in more than 28 trials since 1975. This research was inspired by the work of Adams et al,[25] who first reported that vitamin B_6 successfully alleviated the depression associated with use of oral contraceptives. Wyatt and associates[26] performed a systematic review of these studies. Ten randomized placebo-controlled double-blind parallel or crossover studies were examined. Studies of cyclic mastalgia and multivitamin preparations with at least 50 mg of vitamin B_6 were also included. Only 3 of these trials scored higher than 3 on the Jadad scale for methodologic quality. Most trials were small (fewer than 60 women). One of the largest studies included women who were also taking oral contraceptives, analgesics, diuretics, and psychotropic medications, thus making the effects of vitamin B_6 difficult to ascertain. None of the trials included power calculations. Using a random effects model, Wyatt et al[26] found the overall odds ratio in favor of pyridoxine to be 1.57 (95% confidence interval [CI], 1.40 to 1.77). When the researchers looked at the effects on depressive symptoms in 5 trials, they found the overall odds ratio in favor of pyridoxine to be 2.12 (95% CI, 1.80 to 2.48).

Current thinking postulates that pyridoxine may ease symptoms of PMS through its ability to increase the synthesis of serotonin, dopamine, norepinephrine, histamine, and taurine.[27] Serotonin is important for the regulation of sleep and appetite and the prevention of depression. Low levels of serotonin and dopamine may play a role in premenstrual symptoms.[28] Trials used doses ranging from 50 to 500 mg/day. For most women, the prudent approach is probably to limit single doses of vitamin B_6 to 50 mg and not to exceed 100 mg/day. Research suggests that the liver cannot process more than a 50-mg dose of pyridoxine at one time.[29] Conversion of pyridoxine to its active form depends on other nutrients, such as magnesium and riboflavin. Taking vitamin B_6 as part of a multiple-vitamin supplement or using the active form, pyridoxal-5-phosphate, may be advisable.

Dosage

The dose is 50 to 100 mg/day of pyridoxine or pyridoxal-5-phosphate.

Precautions

Although pyridoxine is a water-soluble vitamin, it can be associated with toxicity when it is taken in moderate to large doses over time. A few reports have noted nerve damage occurring with prolonged ingestion of 150 mg/day.[30] Toxicity may occur if large doses of pyridoxine overwhelm the liver's ability to add a phosphate group to form pyridoxal-5-phosphate, the active form of vitamin B_6.

Combining chaste tree with vitamin B_6 may be a beneficial first step in the treatment of premenstrual syndrome.

Botanicals

Chaste Tree (Vitex agnus-castus)

Dioscorides, the Greek physician, described the dried ripe fruits of the chaste tree *(Vitex agnus-castus)* some 2000 years ago. The Latin name *agnus castus* means "chaste lamb," in reference to the belief that the seeds reduce sexual desire. From this belief stemmed the other common name of the herb, monk's pepper. Many herbalists consider *V. agnus-castus* one of the primary herbs for alleviating PMS, a use that is supported by randomized human trials. The most rigorous study to date of chaste tree for PMS was a 3-month double-blind placebo-controlled trial by Schellenberg[31] that randomized 170 women diagnosed with PMS to receive 20 mg of fruit extract (Ze 440: 60% ethanol mass/mass [m/m], extract ratio, 6 to 12:1; standardized for casticin) or placebo. Five of six self-assessment items indicated significant superiority for chaste tree (irritability, mood alteration, anger, headache, and breast fullness). Other symptoms, including bloating, were unaffected by treatment. Overall, the reduction in symptoms was 52% for the active versus 24% for placebo ($P < .001$). The trial investigators concluded: "*Agnus castus* is a well tolerated and effective treatment for premenstrual syndrome, the effects being confirmed by physicians and patients alike."

Two studies conducted in Chinese women also reported favorable results. A randomized double-blind placebo controlled multicenter 16-week study of 217 women with moderate to severe PMS found that 40 mg of chaste tree extract was superior to placebo, as measured by the PMS diary 17-item daily rating scale ($P < .0001$).[32] No serious adverse events were reported. A smaller randomized placebo-controlled 3-month study of 64 Chinese women with moderate to severe PMS also found that 40 mg per day chaste tree extract significantly reduced symptoms in the PMS diary 17-item daily rating scale ($P < .05$).[33]

One study evaluated the use of chaste tree in PMDD. A single-blind rater-blinded study of 41 women (ages 25 to 45 years) who were diagnosed with PMDD and who had regular menstrual cycles failed to note any significant difference between fluoxetine and chaste tree with respect to the Hamilton Depression Rating Scale (HAM-D), the Clinical Global Impression Scale-Severity of Illness (CGI-SI), or the Clinical Global Impression-Improvement (CGI-I).[34] Unfortunately, the investigators did not provide any details regarding the chaste tree product (e.g., extraction method, extract strength).

One comparative trial found chaste tree to be as effective as pyridoxine for relieving PMS symptoms,[35] whereas a pilot study using the combination of St. John's wort *(Hypericum perforatum)* and chaste tree found the combination highly effective for relieving PMS symptoms in perimenopausal women.[36]

A chaste tree preparation is known to act, in part, by reducing prolactin, increasing progesterone, and binding opiate receptors.[37] Binding of opioid receptors may be the primary mechanism involved in PMS, given that symptoms

such as anxiety, food cravings, and physical discomfort are directly and inversely proportional to the decline of beta-endorphin levels. *Vitex* has an inhibitory action on prolactin because of its dopamine agonist properties. Women with hyperprolactinemia often experience menstrual dysfunction. Some researchers postulate that the correction of hyperprolactinemia causes the reversal of luteinizing hormone suppression and results in full development of the corpus luteum during the luteal phase of the cycle.[38] Studies in both animals and humans have demonstrated prolactin inhibition with *Vitex*. The German health authorities approved the use of chaste tree fruit for irregularities of the menstrual cycle, premenstrual complaints, and mastodynia.[39]

Dosage

The dose varies according to the preparation used in trials. Generally, practitioners recommend 250 to 500 mg/day of dried fruit or 20 to 40 mg daily of chaste berry extract.

Precautions

Chaste tree has been rarely associated with gastrointestinal reactions, alopecia, headaches, tiredness, dry mouth, and increased menstrual flow.

Binding of opioid receptors may be the primary mechanism of action of chaste tree. As beta-endorphin levels decline, so do common premenstrual syndrome symptoms such as anxiety, food cravings, and physical discomfort.

Black Cohosh (Actaea racemosa, Cimicifuga racemosa)

The Eclectics (early physicians who used botanical medicines extensively) used black cohosh for restlessness, nervous excitement, breast pain, and menstrual headaches.[40] Although most research has focused on black cohosh for the alleviation of menopausal complaints, a study of 135 women found a standardized extract of black cohosh to be effective in reducing the symptoms of anxiety, tension, and depression in women with PMS.[41] Researchers found that compounds in black cohosh bind 5-HT7 receptors, a characteristic that could partially explain the positive effects of this botanical on mood.[42] The German health authorities endorsed the use of black cohosh for premenstrual discomfort and dysmenorrhea.[43]

Dosage

The dose is 20 to 40 mg of the standardized extract twice daily (generally standardized to triterpene glycosides as a marker compound).

Precautions

The most common complaint is gastrointestinal disturbance. Other potential adverse effects are headache, heaviness of the legs, and weight gain. Two safety reviews concluded that black cohosh is relatively safe when it is used appropriately; since these reviews, however, case reports suggesting a possible link between black cohosh use and liver damage were published in the medical literature. After an extensive review of the literature, the U.S. Pharmacopeia Dietary Supplements Expert Information Committee recommended that women who have, or who are at risk for, liver disease check with their health care provider before they use black cohosh.[44]

Ginkgo (Ginkgo biloba)

If women experience primarily congestive symptoms in the premenstrual period (fluid retention, breast tenderness, weight gain), a trial of ginkgo may offer some relief. A double-blind placebo-controlled trial of ginkgo was conducted with 165 women complaining of premenstrual symptoms. Participants received placebo or a standardized extract of ginkgo (EGb761 24% ginkgo flavones and 6% terpenes; Dr. Willmar Schwabe GmbH & Co, Karlsruhe, Germany), 80 mg twice daily, from day 16 of one menstrual cycle through day 5 of the next cycle. Evaluation by patient and physician found ginkgo to be effective for alleviation of breast pain and tenderness and fluid retention.[45] Ginkgo is known to augment venous tone and reduce capillary fragility.

Dosage

The dose is 80 mg of a standardized extract twice daily from day 16 of one menstrual cycle through day 5 of the next cycle.

Precautions

Ginkgo may cause gastrointestinal symptoms, headache, dizziness, palpitations, and allergic skin reactions.

Caution

Patients should be carefully supervised if ginkgo is used with anticoagulant medications; however, bleeding risk is probably quite low in otherwise healthy individuals taking ginkgo. A randomized double-blind placebo-controlled crossover study found no change in coagulation factors, platelet aggregation, or bleeding times in 50 healthy male volunteers who took 240 mg ginkgo extract (EGb761).[46]

Evening Primrose Oil (Oenothera biennis)

Evening primrose oil is extracted from the seeds of the evening primrose plant, a wildflower native to North America and introduced to Europe in the early 1600s. The seed oil has been studied for medicinal effects for decades because it is a rich source of linoleic acid and gamma-linolenic acid. Some researchers reported that women with PMS have impaired conversion of linoleic acid to gamma-linolenic acid, thus leading to the investigation of gamma-linolenic supplementation for symptom alleviation. However, a systematic review identified seven placebo-controlled trials of evening primrose oil and reported that all suffered from methodologic flaws.[47] The two highest-quality studies failed to show any beneficial effects of evening primrose oil in PMS, although the sample sizes were small in both trials.

Dosage

Evening primrose oil products are generally standardized to specific amounts of gamma-linoleic acid. Capsules typically contain 320 to 360 mg linoleic acid and 40 mg gamma-linolenic, although levels vary among manufacturers. Vitamin E is often added to prevent

rancidity. The range of doses used in clinical studies is 1 to 6 g/day.

Precautions

Evening primrose oil is extremely well tolerated. Minor gastrointestinal symptoms are sometimes reported in the literature.

St. John's Wort (Hypericum perforatum)

Clinical trials using selective serotonin reuptake inhibitor (SSRI) medications have shown that approximately 60% of women with severe PMS obtain significant relief with use of these drugs. This finding is interesting, given that some herbalists recommend the popular herbal antidepressant St. John's wort *(Hypericum perforatum)* for women reporting depression and irritability in the premenstrual period.

The only trial located addressing the question of St. John's wort and PMS was a prospective, open uncontrolled observational study. Nineteen physically and mentally healthy women with PMS completed a daily symptom ratings diary for one cycle and attended a medical screening interview before they were given the diagnosis of PMS. Participants were then given 300 mg/day St. John's wort extract standardized to 900 mcg hypericin. Symptoms were rated daily with the use of validated measures. The Hospital Anxiety and Depression Scale and the Social Adjustment Scale were administered at baseline and after one and two menstrual cycles. The researchers report a reduction of PMS symptom scores between baseline and the end of the trial of 51%. More than two thirds of participants noted a 50% decrease in symptom severity. The researchers concluded: "The results of this pilot study suggest that there is scope for conducting a randomized, placebo-controlled, double-blind trial to investigate the value of *Hypericum* as a treatment for premenstrual syndrome."[48]

Dosage

The dose generally used for depression is 300 to 600 mg of St. John's wort standardized to contain 3% to 5% hyperforin or 0.3% hypericin three times per day.

Precautions

Women taking medications that increase photosensitivity, protease inhibitors (for human immunodeficiency virus), cyclosporine, or other medications that are metabolized by the cytochrome P-450 CYP3A4 system or P-glycoprotein should avoid St. John's wort.

Kava (Piper methysticum)

Physicians sometimes prescribe alprazolam, a benzodiazepine, for the treatment of PMS. Because of the risk of habituation and side effects, practitioners have looked for other anxiolytics that could be of benefit. Numerous practitioners have recommended the South Pacific herb kava for this purpose. A meta-analysis concluded that kava is an effective treatment for anxiety when compared with placebo, although no studies of kava in PMS are available for review.

Concerns have been raised about the safety of kava, however. Approximately 30 cases of hepatotoxicity potentially related to the use of kava products have been reported in the literature. Numerous countries have banned the sale of kava, including Germany, Switzerland, Ireland, Canada, Australia, and the United Kingdom. The U.S. Food and Drug Administration (FDA) issued a cautionary statement, but the herb is still sold in the United States. Until the safety issue is further elucidated, looking for other approaches to help alleviate troublesome symptoms of PMS seems wise. A better option for women reporting irritability and difficulty sleeping during the premenstrual period may be valerian (discussed next).

Valerian (Valeriana officinalis)

Valerian is a common ingredient in over-the-counter relaxants and sleep aid products in both Europe and the United States. It is often included in herbal formulations for PMS with a dominant profile of anxiety or irritability. The herb is sold as a single ingredient but is often found in combination with other relaxant herbs such as hops *(Humulus lupulus),* passionflower *(Passiflora incarnata),* or lemon balm *(Melissa officinalis).* The German Commission E endorses valerian for restlessness and sleeping disorders caused by nervous conditions,[49] and the World Health Organization recognizes it as a "mild sedative, sleep-promoting agent, milder alternative to or possible substitute for stronger sedatives (e.g., benzodiazepines), and for treatment of nervous excitation and sleep disturbances induced by anxiety."[50] No clinical trials have evaluated the use of valerian for PMS, but this botanical is often included in formulations on the basis of its mild anxiolytic effects and ability to promote sleep.

Dosage

The crude herb is usually taken at a dose of 2 to 3 g (equivalent to 10 to 15 mL of tincture [1:5 strength]) approximately 1 hour before bedtime. Smaller doses are often used during the day for relieving mild irritability and anxiety. Standardized extracts are also widely available and should be taken as directed on the label.

Precautions

Valerian is generally safe when taken appropriately and is not considered habit-forming. The World Health Organization noted that the use of valerian is contraindicated during pregnancy and lactation because of the lack of studies in this area.

Mind-Body Therapy

Mind-body therapies are approaches grounded in the emerging scientific understanding that thoughts and feelings affect physiology and physical health. Mind-body therapies for PMS include psychotherapy (cognitive-behavioral therapy and group therapy), relaxation techniques and training, body work (massage and reflexology), hypnotherapy, biofeedback, guided imagery, yoga, and qi gong. Most studies are preliminary, but practitioners should not be dissuaded from recommending them if they are deemed beneficial for a particular patient.

Acupuncture

Acupuncture is only one tool used in traditional Chinese medicine (TCM) for the treatment of disease and promotion of health. traditional Chinese medicine uses a different system for diagnosis and has a long history of treating what

would be called PMS in conventional medicine. Although many women report benefit, a systematic review of clinical trials using acupuncture for the relief of PMS found the data inconclusive.[51] Given the overall safety of acupuncture, clinicians should not dissuade women who choose to explore traditional Chinese medicine or acupuncture for relief of their symptoms.

Pharmaceuticals

Selective Serotonin Reuptake Inhibitors

In addition to numerous lifestyle recommendations already mentioned, growing numbers of physicians are prescribing SSRIs for the treatment of PMS and PMDD. A Cochrane Review of 15 trials that evaluated the efficacy of SSRIs in the management of PMS reported that these medications are very effective for improving both behavioral and physical symptoms. However, withdrawals related to side effects were 2.5 times more likely to occur in treatment groups, particularly at higher doses.[52] SSRIs should be considered for women with severe forms of PMS (PMDD) that do not respond to lifestyle, mind-body, or supplement approaches.

Prevention Prescription

Recommending preventive strategies is difficult because clinicians are still uncertain about what causes some women to experience PMS. Given this conundrum, the following suggestions seem to make sense, given our current understanding:

- Limit alcohol consumption and avoid drugs of abuse.
- Exercise at least three times per week for a minimum of 30 minutes.
- Limit consumption of salt, sugar, and caffeine, especially 10 days before the onset of menses.
- Eat a well-balanced diet that is rich in fiber and low in saturated fat.
- Take a multivitamin every day and ensure that diet provides 1000 to 1200 mg of calcium and 320 to 400 mg magnesium every day; supplement to make up any shortcomings.

Therapeutic Review

Lifestyle

- Learn strategies for effective stress management, obtain adequate sleep, and maintain a regular exercise routine. Consider mind-body approaches such as breathing techniques and yoga. B1

Nutrition

- Eat a well-balanced diet rich in fiber and low in fat. B1
- Limit intake of alcohol, salt, caffeine, and refined sugar products. B1

Supplements

- Calcium: 500 to 600 mg twice daily A2
- Vitamin B_6: 50 to 100 mg/day B2
- Magnesium: 200 to 600 mg/day C2

Botanicals

- Chaste tree *(Vitex):* 250 to 1000 mg crude herb or 20 to 40 mg daily of a standardized extract A2

Treatment for Specific Symptoms

- Breast tenderness
  - Caffeine restriction B1
  - Chaste tree (Vitex): 250 to 500 mg crude herb or 20 to 40 mg daily of a standardized extract A2
  - Evening primrose oil: 1.5 g twice daily (continuous) C2
  - *Ginkgo biloba:* 80 mg standardized extract twice daily (ovulation through menses) C2
- Anxiety and mood swings
  - Black cohosh: 20 to 40 mg standardized extract twice daily (continuous therapy) C2
  - Calcium: 500 to 600 mg twice daily A2
  - Chaste tree *(Vitex):* 250 to 500 mg crude herb or standardized extract daily A2
  - Valerian root: 2 to 3 g crude herb or standardized extract 45 minutes before bed C2
  - Kava root: up to 210 mg kavalactones in standardized extract per day B3
- Depression
  - St. John's wort: 300 to 600 mg standardized extract three times daily (continuous therapy) A2
  - Vitamin B_6: 50 mg once or twice daily B2
- Cramps
  - Magnesium: 200 to 600 mg/day A2
  - Black haw: 1 to 6 g/day C2
- Insomnia
  - Valerian root: 2 to 3 g crude herb or standardized extract before bed B2
- Severe PMS or PMDD
  - Chaste tree *(Vitex):* 250 to 1000 mg crude herb or 20 to 40 mg daily of a standardized extract B2
  - Serotonin reuptake inhibitors A2

KEY WEB RESOURCES

U.S. Department of Health and Human Services Office on Women's Health: www.womenshealth.gov	This Web site has numerous resources on women's health, including premenstrual disorder.
PMS Symptom Tracker: http://www.womenshealth.gov/faq/pms-ymptracker45.pdf	This form allows patients to record their symptoms throughout the month.
American College of Obstetrics and Gynecology handout on premenstrual syndrome: http://www.acog.org/publications/patient_education/bp057.cfm#premenstrual	This handout also contains a symptom record.
National Women's Health Network: www.nwhn.org	This Web site is an online resource on women's health issues.

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Chapter 54

Dysmenorrhea

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Dysmenorrhea refers to painful uterine cramping associated with menses. In addition to lower pelvic discomfort, women may also experience low back pain, radiation of pain to the anterior thighs, nausea, vomiting, diarrhea, headache, and various other symptoms starting 1 to 3 days before the onset of menses and typically lasting through the first few days of bleeding. *Primary dysmenorrhea* refers to pain that is not associated with other, obvious pelvic disease and typically begins with the onset of ovulatory cycles just after menarche. *Secondary dysmenorrhea* is associated with another diagnosis (e.g., cervical stenosis, endometriosis) and typically has a later onset, usually after age 20 years. This discussion focuses on primary dysmenorrhea because treatment for secondary dysmenorrhea is determined by the underlying cause.

Estimates of the percentage of women affected by dysmenorrhea range from 16% to 90%. Some investigators claim the most reliable estimate to be approximately 75%, based on a large Swedish study of 19-year-old women. Most of these women's symptoms were mild, but 23% and 15% reported suffering from moderate and severe pain, respectively.[1] In addition to the discomfort endured by affected women, dysmenorrhea also results in significant missed school and work and in decreased quality of life.[2]

Dysmenorrhea seems to be more significant in women with earlier age at menarche and in those with longer episodes of bleeding. Being overweight appears to affect the likelihood of painful cramping, as well as the duration, significantly. Smoking has been associated with prolonged pain, and although alcohol consumption does not increase the probability of painful cramping, it seems to increase the duration and severity of cramping in women with dysmenorrhea.[3] Other predisposing factors include age less than 30 years, low body mass index, longer menstrual cycles, heavy menstrual bleeding, nulliparity, clinically suspected pelvic inflammatory disease, history of sexual abuse, psychological symptoms, chronic exposure to stress, and exposure to secondhand smoke.[4-7]

Pathophysiology

The pathogenesis of primary dysmenorrhea seems to involve elevated levels of prostaglandins in response to the rise and fall of progesterone that occur after ovulation. As progesterone production decreases by the corpus luteum, lysosomes in the endometrial cells break down and release phospholipase A_2, which converts cell membrane fatty acids into arachidonic acid, the precursor to prostaglandins. In women with dysmenorrhea, excessive elevation of prostaglandins, specifically prostaglandin $F_{2\alpha}$ and prostaglandin $E_{2\alpha}$, leads to uterine hypercontractility, painful cramping, and other prostaglandin-related symptoms such as nausea, vomiting, and diarrhea. These contractions decrease blood flow to the uterus and cause ischemia, which sensitizes nerve fibers to the inflammatory prostaglandins and endoperoxides.[8,9] Elevated levels of vasopressin have also been found in women with dysmenorrhea. This hormone increases uterine contractility, thereby contributing to cramping and ischemia.[10]

Integrative Therapy

Lifestyle

Exercise

Evidence for exercise as a treatment modality for dysmenorrhea has been mixed and limited in quality.[11] Early studies indicated that the type of exercise was less important than the desire to alleviate symptoms with exercise.[12] However, chronic stress seems to increase perimenstrual symptoms,[5] and exercise is certainly a valid tool for managing stress. Given that exercise is important for overall health and weight management (and being overweight is a risk factor for dysmenorrhea, as mentioned earlier), discussing regular exercise with patients suffering from dysmenorrhea certainly has a place.

Substance Use

Tobacco and alcohol use have been associated with worse symptoms of dysmenorrhea. Patients should be counseled on this and supported in addressing unhealthy use of these substances.

Nutrition

Omega-3 Fatty Acids

The release of arachidonic acid from the membranes of cells of the endometrium leads to an increase in proinflammatory prostaglandins. Omega-6 fatty acids are precursors to arachidonic acid, and our consumption of omega-6 compared with omega-3 fatty acids has greatly increased over the past century. The antiinflammatory diet (see Chapter 86, The Antiinflammatory Diet) can change the ratio of omega-6 to omega-3 polyunsaturated fatty acids in our bodies and may thereby modulate the levels of prostaglandins, inflammation, and painful uterine contractions produced. Studies have shown that higher consumption of omega-3 polyunsaturated fatty acids (either through supplementation or diet) leads to a decrease in painful menses.[13–15]

Table 54-1 lists dietary sources of omega-3 polyunsaturated fatty acids, as well as other nutrients described in the next section that have been found to be helpful in the treatment of primary dysmenorrhea.[16,17]

Dosage

If supplementing with omega-3 fish oil capsules, the dose is 1500 to 2000 mg daily of docosahexaenoic acid and eicosapentaenoic acid or two to three servings of cold-water fish per week.

Supplements

Magnesium

Magnesium has been found to be beneficial in the treatment of arrhythmias, severe asthma, migraine, dyspepsia, and constipation. Its role in dysmenorrhea may be related to its effect on intracellular calcium concentration,[18] a reduction in prostaglandin synthesis,[19] or its muscle relaxant properties. A Cochrane Review found three studies showing that magnesium was more effective than placebo in decreasing menstrual pain and the use of analgesic medications. The studies were small, but the results encouraging.[20a]

The form of magnesium is important because some forms are more likely to cause diarrhea (see the section on dosage). Foods rich in magnesium include fish, nuts, leafy greens, whole grain cereals, and baked potatoes with the skin.[17] Magnesium is a largely intracellular cation, so red blood cell magnesium may be a more accurate measure of nutrient status than the typically used serum magnesium.

Dosage

Unless constipation is present, consider doses of 200 to 600 mg daily of forms of magnesium less likely to cause loose stools: magnesium glycinate (chelated magnesium), magnesium gluconate, or magnesium chloride. See Table 54-1 for dietary sources of magnesium.

Precautions

Use magnesium with caution in individuals with impaired renal function. If diarrhea develops, decrease the dose until this condition is relieved because diarrhea is one of the first signs of magnesium toxicity.

Vitamin B_6 (Pyridoxine)

A series of small studies ($N = 21$ to 24) in 1988 compared various permutations of vitamin B_6 versus magnesium versus vitamin B_6 and magnesium versus placebo and found that vitamin B_6 was better than placebo and better than a combination of vitamin B_6 and magnesium at decreasing visual analogue pain scores and tablets of ibuprofen used.[20a] A mechanism offered to explain the possible beneficial effect of vitamin B_6 is its role in increasing the influx of magnesium into the cell, thereby supporting the effects of magnesium described earlier.

Dosage

The dose is 100 mg daily. If a higher dose is used, close monitoring is needed. See Table 54-1 for dietary sources of vitamin B_6.

Precautions

Vitamin B_6 toxicity typically manifests as neuropathy that reverses with decreased intake.[17] Doses described were 100 mg twice daily; however, the Institute of Medicine established the upper tolerable intake level for vitamin B_6 as 100 mg daily for adults.

Vitamin B_6 and magnesium may work synergistically because vitamin B_6 increases the influx of magnesium into the muscle cell.[20b]

TABLE. 54-1. Dietary Sources of Nutrients Found to Decrease Pain of Dysmenorrhea

OMEGA-3 FATTY ACIDS	MAGNESIUM	VITAMIN B_1	VITAMIN B_6	VITAMIN E
Cold-water fish (e.g., salmon, herring, sardines)	Halibut	Fortified grains (breads, cereals, pasta, wheat germ)	Fortified cereals	Vegetable oils (wheat germ, sunflower, safflower)
Leafy green vegetables	Almonds, dry roasted	Lean pork	Potatoes with skin	Almonds
Flaxseeds (ground)	Cashews, dry roasted	Fish	Bananas	Sunflower seeds
Walnuts	Soybeans	Dried beans	Garbanzo beans (chickpeas)	Spinach
	Spinach	Peas	Chicken breast	Broccoli
		Soybeans	Pork loin, lean only	Fortified cereals, juices, and spreads

Data from MedlinePlus. *Thiamin*. http://www.nlm.nih.gov/medlineplus/ency/article/002401.htm Accessed 24.02.11; and Office of Dietary Supplements, National Institutes of Health. *Dietary Supplement Fact Sheets*. http://ods.od.nih.gov/factsheets/ Accessed 20.02.11.

Vitamin B_1 (Thiamine)

One of the largest double-blind placebo-controlled studies investigating the effect of a nutritional supplement on dysmenorrhea was a trial of vitamin B_1. This crossover trial involved 556 Indian adolescents who were randomized to receive 100 mg of vitamin B_1 daily for 90 days, followed by placebo for 60 days or placebo for 60 days, followed by 100 mg daily of vitamin B_1. In both groups, complete resolution or significant improvement in pain did not occur until the participants had received thiamine for at least 30 days. "Cure" rates by the end of the trial were approximately 90% in both groups.[21] This overwhelming success at "curing" dysmenorrhea certainly raises the question of whether the results could be confirmed with another study in a different population. The mechanism by which this treatment works may simply be reversal of a deficiency that can manifest with decreased pain tolerance, muscle cramping, and fatigue, which are symptoms similar to those of premenstrual syndrome.[19]

Dosage

The dose is 100 mg daily for 90 days. Consider continuing treatment if symptoms recur after initial improvement. See Table 54-1 for dietary sources of thiamine.

Precautions

Orally, thiamine is usually well tolerated. It rarely can cause dermatitis or a hypersensitivity reaction.[22]

Vitamin E

Vitamin E has been proposed to provide relief from dysmenorrhea through antiinflammatory action and through induction of a marked rise in beta-endorphin level.[23,24] Several randomized placebo-controlled studies including a total of 383 women 15 to 21 years old, showed a significant decrease in the severity and duration of pain with vitamin E compared with placebo. Doses used varied from 150 to 500 units daily for either 2 days before and 3 days after or for 10 days before and 4 days after the onset of menses.[25–27] The tolerable upper intake level in healthy people is 1000 mg/day, equivalent to 1100 units of synthetic vitamin E (D-L-alpha-tocopherol or alpha-tocopherol or SRR-tocopherol) or 1500 units of natural vitamin E (D-alpha tocopherol or RRR-tocopherol).[28,29]

Dosage

The dose is 400 units daily for a few days before and a few days after the onset of menses. See Table 54-1 for dietary sources of vitamin E.

Precautions

Doses higher than 400 units of vitamin E have higher potential for adverse effects in unhealthy individuals.

Botanicals

French Maritime Pine Bark Extract (Pinus pinaster)

Pycnogenol is the trade name for this extract of French maritime pine bark. It has numerous active constituents such as flavonoids, procyanidins, and phenolic acids, and the list of indications ranges from asthma, chronic venous insufficiency, and hypertension to coronary artery disease and diabetes. In dysmenorrhea, it may have antispasmodic effects and inhibit uterine contractions through its components ferulic acid and caffeic acid. A study of 116 women with low menstrual pain (did not require analgesic medication) or dysmenorrhea were monitored for two cycles and then treated with either 30 mg twice daily of Pycnogenol or placebo through another two menstrual cycles. Although no difference was noted in the treatment group compared with placebo in the women with low menstrual pain, a significant decrease in pain scores and in analgesic use was reported in women with dysmenorrhea, and the effect seemed to persist for at least 1 month after cessation of the extract.[30]

Dosage

The dose is 30 mg twice daily for 2 months. The effect may last for at least 1 month after cessation.

Precautions

Pycnogenol is generally well tolerated. Side effects may be limited to gastrointestinal problems, dizziness, and vertigo but have possibly included headache and mouth ulceration.[31]

Fennel (Foeniculum vulgare)

Fennel essential oil has been found to be comparable to the nonsteroidal antiinflammatory (NSAID) medication mefenamic acid.[32,33] The mechanism seems to involve the inhibition of uterine contraction induced by prostaglandin E_2 and oxytocin.[34]

Dosage

The dose is 30 drops of fennel extract at the onset of menses and then continuously every 6 hours for the first 3 days of menses.

Precautions

Fennel has a Generally Recognized as Safe (GRAS) status in the United States, but case reports exist of neurotoxicity in two breastfeeding infants whose mothers drank an herbal combination tea containing fennel.[35] Fennel supplements should be avoided during pregnancy because in vitro studies have shown some toxic effects on fetal cells.[36]

SCA by Gol Daro Herbal Medicine (Saffron [Crocus sativus], *Celery Seed* [Apium graveolens], *Anise or Fennel* [Foeniculum vulgare]*)*

An Iranian blend of highly purified extracts of saffron, celery seed, and anise (SCA by Gol Daro Herbal Medicine) was compared with mefenamic acid and placebo for effectiveness in alleviating symptoms of dysmenorrhea in 163 women 18 to 30 years old. SCA, at 500 mg three times daily, was found to be more effective than placebo and the NSAID, at 250 mg three times daily, in decreasing menstrual pain intensity and duration. All agents were taken for 3 days at the start of the menstrual cycle. No side effects were noted.[37]

Dosage

The dose is 500 mg of SCA three times daily for three days starting with onset of pain or bleeding.

Precautions

Saffron is generally well tolerated and has a GRAS rating unless it is taken at high doses. Taking 5 g or more of saffron can cause severe side effects, and doses of 12 to 20 g can be lethal.[38] Celery seed also has a GRAS rating but may cause allergic reaction (especially in individuals sensitive to mugwort, birch, dandelion, or wild carrot); large amounts should be avoided in pregnancy because of potential abortifacient effects.[39]

Willow Bark Extract (Salix cortex)

The major active ingredient of willow bark, salicin, was the original source of aspirin. It appears to inhibit the cyclooxygenase-2 pathway. Other components of willow bark may have other antiinflammatory properties. Willow bark does seem to inhibit platelet aggregation, but not as much as aspirin.

Dosage

The dosage is 240 mg daily of salicin, in divided doses. This is roughly equivalent to 87 mg of aspirin. Willow bark extract may work better if it is started the day before expected symptoms.[40]

Precautions

Willow bark extract is generally safe, but avoid it in children with viral infections, given theoretical risk of Reye syndrome. It can cause gastrointestinal side effects but less than those seen with NSAIDs. Avoid in kidney disease and in patients allergic to aspirin.

Cramp Bark (Viburnum opulus) *and Black Haw* (Viburnum prunifolium)

Traditionally, these herbs have been used as uterine relaxants. Very few data are available regarding their efficacy. The root bark and stem bark of black haw contain certain active ingredients, including scopoletin and oxalic acid. Scopoletin may be a uterine relaxant. Because of the presence of oxalic acid, black haw should be avoided in patients with a history of renal stones. Black haw also contains salicylates that could trigger an allergic reaction in patients sensitive to aspirin.[41]

Dosage

The dose is 2 to 3 mL of a tincture made in 1:3 proportion every 2 hours or as needed; or 4 to 8 mL of fluid extract (1:1) three or four times daily; or simmer 1 tablespoon of bark in 12 oz of water for 15 minutes, and drink one third cup every 2 to 3 hours as needed.[42]

Precautions

Avoid black haw in persons with a history of renal stones or aspirin allergy.

Pharmaceuticals

Nonsteroidal Antiinflammatory Drugs

As inhibitors of prostaglandin formation, NSAIDs such as naproxen, ibuprofen, and mefenamic acid have been shown to be quite effective for the treatment of dysmenorrhea when compared with placebo or acetaminophen. These medications are used and tolerated by a great many women and bring relief from painful menstrual cramping. NSAIDs are not effective in approximately 20% of cases, however, and they can be associated with significant side effects. Gastrointestinal symptoms such as nausea and indigestion seem to be especially common with naproxen. Overall, NSAIDs are associated with a higher risk than placebo of such mild neurologic adverse effects as headache, drowsiness, dizziness, and dryness of the mouth. Naproxen and indomethacin seem to be especially more likely to produce these types of symptoms.[43]

Hormonal Treatments

Combined oral contraceptive pills have been shown to reduce menstrual pain significantly. A meta-analysis of nearly 500 women showed decreased pain with both low-dose and medium-dose estrogen formulations. The type of progesterone does not seem to matter. Side effects noted were nausea, headache, and weight gain.[44] More serious side effects of oral contraceptive pills include thromboembolic and cardiovascular events, and the risks of these adverse effects rise greatly with age and cigarette smoking.

Levonorgestrel-containing intrauterine devices have been reported to decrease menstrual cramping,[45] perhaps by inhibiting buildup of the endometrium and thus reducing total prostaglandin load. Such devices also frequently reduce menstrual flow, which may be desirable in some cases. Uterine perforation, one of the more serious risks of placement of an intrauterine device, occurs at a rate of approximately 2 in 1000. The expulsion rate is approximately 5% in the first year. These devices have the advantage of providing contraception for up to 5 years before they must be replaced.

Mind-Body Therapy

A comprehensive health plan for any individual with chronic pain often involves recognition of the component of the experience of the pain that is influenced by perception of that experience. Chronic pain is frequently accompanied by mood disturbances such as depression and anxiety. At times, distinguishing whether mood affects pain or the other way around may be difficult; the relationship is likely bidirectional. Given the risk factors listed earlier of a history of sexual abuse and psychological symptoms, it is easy to see that a significant mind-body relationship may play a role in some cases of dysmenorrhea.

A 2007 Cochrane Review (reprinted in 2010) included five studies that looked at behavioral interventions such as biofeedback, relaxation techniques, and pain management training. An overall benefit was apparent, but the studies were small, and some had relatively poor methodology.[46] In areas such as this, the relationship between the provider and the individual is so important. Listening to and understanding the individual on a deeper level allow the provider to determine more appropriately whether, for example, referral to a counselor or health psychologist may be beneficial. Providers skilled in relaxation techniques or guided imagery may be able to strengthen their therapeutic relationship with patients by employing those skills for symptoms of dysmenorrhea.

Bioenergetic Therapy

Heat Therapy

Patients may report that they have tried using heating pads or microwavable bean bags, with some relief of symptoms. Studies have shown that heat does indeed decrease pain and, when combined with NSAIDs, reduces the time until

noticeable pain relief is achieved.[47,48] Recommend heat of approximately 39 °C (102 °F) for up to 8 to 12 hours on the lower abdomen or back.

Precautions

Ensure that the heat is not so high that it causes burns or is applied to areas of decreased sensation because injury may not be recognized.

Magnet Therapy

A study of 35 women in London found a significant decrease in pain over one menstrual cycle by using a 2700-gauss magnet that attached to the underwear over the suprapubic area. The noncompletion rate in this study was significant, but the investigators reported that this was a pilot study for a much larger study using the same device. The manufacturer of the device was involved in funding of the study.[49] The device is sold in England and on the Internet for approximately $40 U.S. A Korean study using 800- to 1299-gauss magnets over the suprapubic area, lower back, and medial lower leg had similar results.[50]

Transcutaneous Electrical Nerve Stimulation

By delivering electrical currents and various frequencies through the skin, transcutaneous electrical nerve stimulation (TENS) machines appear to affect the body's ability to receive and understand pain signals. TENS devices are used quite commonly for musculoskeletal pain, including low back pain, and are portable, thus making them available for home and clinic use. A 2010 Cochrane Review found 7 small studies covering a total of 164 women suffering with dysmenorrhea that compared high- or low-frequency TENS therapy or TENS therapy with placebo TENS, placebo pill, or medical treatment (NSAIDs). The results of the meta-analysis showed that high-frequency TENS (using 50 to 100 Hz) was significantly more effective than placebo for relief of dysmenorrhea. The effect of low-frequency TENS (1 to 4 Hz) was not significant but trended toward benefit over placebo. Neither was as effective as medical therapy.[51] Consideration of the long-term effects of electromagnetic radiation to the pelvis, especially in young women, may be wise.

Acupuncture

Acupuncture is becoming more and more widely accepted in the Western world as a treatment modality for various indications, pain among the most common. Investigating efficacy can be difficult, however, in that control arms for acupuncture studies are challenging to design because even sham acupuncture may indeed have some therapeutic benefit. A 2009 systematic review of 27 trials showed that only 9 trial groups adequately described their randomization methods, and none described their allocation concealment methods. However, the results of the studies included did support significant benefit of acupuncture over pharmaceutical or herbal interventions. Two of the studies did not show benefit of acupuncture over sham acupuncture.[52] A 2011 Cochrane Review found 34 trials studying acupuncture and acupressure for dysmenorrhea.[53] Ten trials were included in the review: 6 involving acupuncture and 4 involving acupressure. Of the 24 trials not used, nearly all were excluded because of either details around randomization or the use of multiple interventions (e.g., Chinese herbs, moxibustion). Meta-analysis of the 6 included acupuncture trials ($N = 673$) did indeed show significant benefit of acupuncture for dysmenorrhea compared with control, NSAIDs, and Chinese herbs. Acupuncture also was shown to have a positive impact on other menstrual symptoms (e.g., headache, nausea) and quality of life.[53]

Several reviews[54,55] pointed to a methodologically sound trial of 48 women randomized to acupuncture, sham acupuncture, no treatment control, or visitation control (office visits only without treatment). This study found a significant decrease in the number of patients who had "improved" symptoms (greater than 50% reduction in pain scores) with true acupuncture compared with controls.[56] A larger study of similar design would certainly be beneficial in securing acupuncture's role in the treatment of dysmenorrhea.

The World Health Organization lists primary dysmenorrhea as one of the indications "for which acupuncture has been proved—through controlled trials—to be an effective treatment."[57] Dysmenorrhea was also on the National Institute of Health's 1997 list of indications for which acupuncture was deemed potentially useful.[58]

Acupressure

Acupressure has an advantage over acupuncture in that it can be performed on oneself or with simple devices and is therefore practically and financially more accessible to greater numbers of women with primary dysmenorrhea.

A 2010 review of randomized controlled trials of acupressure alone as treatment for primary dysmenorrhea, trials that used outcome measures of pain relief and adverse effects, found four that met inclusion criteria (total $N = 458$; range, 61 to 216). Although considerable deficits were noted in descriptions of randomization and allocation concealment methods, acupressure treatments did seem to bring about an overall significant reduction in menstrual pain.[59] Points used varied in each study. One study that showed benefit used a "cotton Lycra panty brief with a fixed number of lower abdominal and lower back latex foam 'acupads' that provide pressure" on specific acupressure points and that was worn for as long as comfortable.[60] The 2011 Cochrane Review of acupuncture and acupressure for primary dysmenorrhea also included four acupressure studies ($N = 271$).[53] Meta-analysis of these studies did show a significant decrease in pain with acupressure compared with placebo. Two of the four studies in this review used auricular acupressure,[61,62] which may decrease the accessibility of treatment.

Simple regimens described have used the acupressure points spleen 6 (SP6) and large intestine 4 (LI4).[63,64] Figures 54-1 and 54-2 illustrate the locations of these points. Consider alternating between 6 seconds of pressure and 2 seconds off for a total of approximately 5 minutes. Pressure should initially be relatively light (just shy of "really hurting") but increase as the treatment continues. Work on each point on both sides of the body for a total treatment of approximately 20 minutes. To decrease time if performing on oneself, consider acupressure on the right SP6 with the left hand while pressing on the left LI4 with the right hand for 5 minutes and then reversing for another 5 minutes.

FIGURE 54-1
Spleen 6 (Sanyinjiao): Four finger widths superior to the prominence of the medial malleolus posterior to the medial margin of the tibia. When a patient is experiencing dysmenorrhea, the point may be very tender.

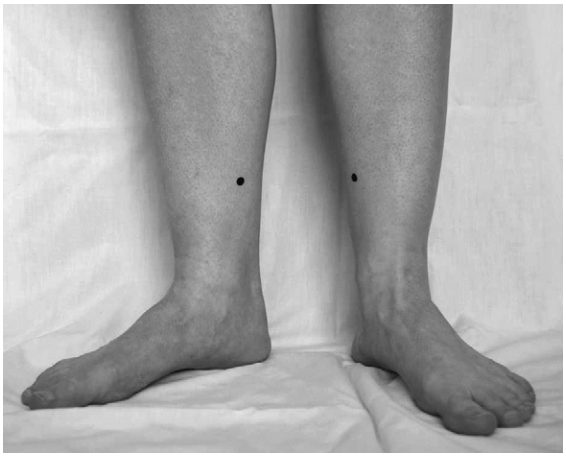
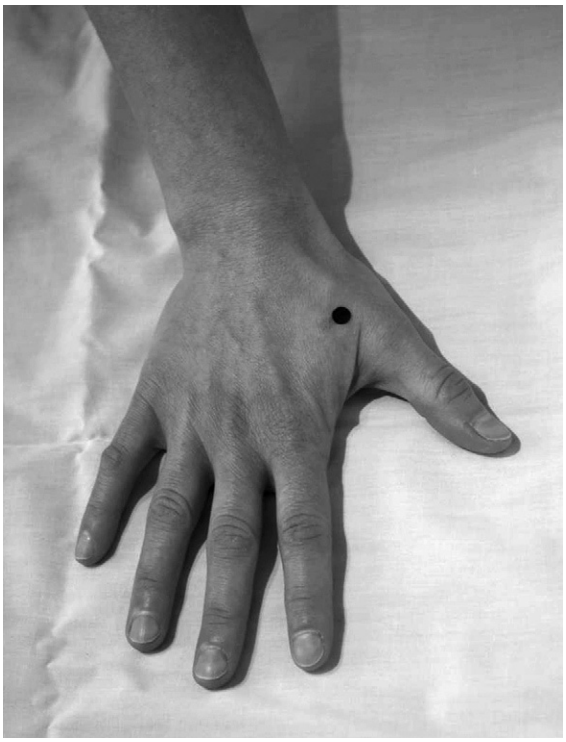


FIGURE 54-2
Large intestine 4 (Hegu): On the dorsum of the hand midway between the first and second metacarpals at the level of the midpoint of the shaft of the second metacarpal. When a patient is experiencing dysmenorrhea, the point may be very tender.



Biomechanical Therapy

Spinal Manipulation Therapy

Therapies such as osteopathic or chiropractic manipulation of the spine may increase spinal mobility and blood flow to the pelvis and lead to improvement in symptoms of dysmenorrhea. A 2006 Cochrane Review concluded that spinal manipulation therapy showed no benefit over sham manipulation in improvement of symptoms of dysmenorrhea, although both interventions decreased pain.[59] The investigators acknowledged, however, that significant challenges exist with the control arm in such studies in that, similar to acupuncture, sham manipulation may actually have some clinical benefit.[65] One of the studies included in the review also measured pretreatment and posttreatment serum levels of a prostaglandin $F_{2\alpha}$ metabolite. Pain and the metabolite were decreased in both spinal manipulation therapy and sham manipulation groups.[66] This finding may indicate that spinal manipulative therapies do indeed have a role in the treatment of dysmenorrhea, but the evidence is challenged by the inability to find a true placebo.

Surgery

Laparoscopic presacral neurectomy and laparoscopic uterine nerve ablation (LUNA) are surgical approaches to relieving dysmenorrhea. A 2010 update of a 2005 Cochrane Review found 2 studies with a total of 68 women that showed decreased menstrual pain after LUNA compared with diagnostic laparoscopy at 12 months but not at 6 months postoperatively. A third trial in the review found that laparoscopic presacral neurectomy resulted in significantly better relief scores compared with LUNA at 12 months but not at 3 months after surgery.[67]

Therapies to Consider

Aromatherapy With Massage

A study of 57 Korean college women with dysmenorrhea compared abdominal massage with aromatherapy (a mix of 2 drops of lavender, 1 drop of clary sage, and 1 drop of rose in 5 mL of almond oil), abdominal massage with almond oil only, and no intervention. The aromatherapy group showed a significant decrease in menstrual discomfort based on scoring using a visual analogue scale compared with massage alone or no treatment. Massages in the study took place for approximately 15 minutes daily for 1 week before the start of menses. No side effects were reported.[68]

Aromatherapy Massage for Dysmenorrhea
Use slow, smooth, and continuous strokes with mild to moderate pressure and a mixture of lavender, clary sage, and rose oils in almond oil (see earlier). The strokes should start with the masseur's left hand on top of the right in the right lower quadrant of the abdomen, go up to the ribs, and then across the abdomen to the left lower quadrant. The masseur can then provide gentle kneading of the left and right lower abdomen, followed by stroking across the abdomen. This sequence can be repeated for a total of 15 minutes and done daily for one week before the expected onset of menses.

Prevention Prescription

- Maintain a healthy weight.
- Follow an anti-inflammatory diet.
- Participate in regular, moderate-intensity aerobic exercise.
- Avoid use of tobacco.
- Avoid alcohol in excess.
- Employ effective stress management techniques.

Therapeutic Review

Exercise

- The benefits of exercise on stress reduction and maintenance of a healthy weight may reduce risk factors for dysmenorrhea. C 1

Nutrition

- Diets rich in omega-3 fatty acids can reduce menstrual pain. Supplement with 1500 to 2000 mg daily of docosahexaenoic acid and eicosapentaenoic acid. Through diet, omega-3 fatty acids can be obtained with two to three servings of cold-water fish weekly and other, plant-based sources. B 1

Supplements

- Magnesium (glycinate, gluconate, or chloride): 600 mg daily, decreased if diarrhea develops. Use with caution in patients with kidney disease. B 2
- Vitamin B_6 (pyridoxine): 100 mg daily (may work better with magnesium) B 2
- Vitamin B_1 (thiamine): 100 mg daily for 90 days, or longer if symptoms recur after cessation B 1
- Vitamin E: 400 units daily B 1

Botanicals

- French maritime pine bark extract/Pycnogenol: 30 mg twice daily. The effect may last for at least 1 month after cessation. B 1
- Fennel: 30 drops of extract at the onset of menses, then every 6 hours for the first 3 days of menses. Avoid during pregnancy or lactation. B 1
- SCA (saffron, celery, and anise, by Gol Daro Herbal Medicine): 500 mg three times daily for three days starting with onset of pain or bleeding. B 2
- Willow bark extract: 240 mg daily of salicin in divided doses, started the day before expected symptoms. C 2
- Cramp bark and black haw: 2 to 3 mL of a tincture made in 1:3 proportion every 2 hours or as needed; or 4 to 8 mL of fluid extract (1:1) three or four times daily; or simmer 1 tablespoon of bark in 12 oz of water for 15 minutes, one third cup consumed every 2 to 3 hours as needed C 2

Pharmaceuticals

- Nonsteroidal antiinflammatory drugs such as ibuprofen, 400 to 600 mg with food every 6 hours, starting the day before symptoms expected to occur until symptoms cease A 2
- Combined contraceptive pills B 2
- Levonorgestrel-containing intrauterine device C 3

Mind-Body Therapy

- Consider counseling or health psychology referral for relaxation techniques, biofeedback, or pain management training, for example, if determined relevant given the individual's history. C 1

Bioenergetic Therapy

- Use a heating pad or microwavable bean bag on the low back or abdomen for up to 8 to 12 hours. B 1
- Consider purchasing a magnet therapy device (e.g., mn8; see Key Web Resources). B 1
- Consider using a transcutaneous electrical nerve stimulation unit. B 2
- Consider acupuncture. B 2
- Consider acupressure. B 1

Biomechanical Therapy

- Consider spinal manipulation therapy (chiropractic or osteopathic treatment). B 2
- As a last resort, laparoscopic presacral neurectomy may be more effective than laparoscopic uterine nerve ablation. B 3

Other Therapies to Consider

- Aromatherapy with abdominal massage using 2 drops of lavender, 1 drop of clary sage, and 1 drop of rose in 5 mL of almond oil B 1

KEY WEB RESOURCES	
mn8: http://www.mn8.uk.com/about.php	Web site for purchase of magnet devices for dysmenorrhea that insert into underwear
Environmental Defense Fund Seafood Selector: http://www.edf.org/page.cfm?tagID=1521	Guide for safe fish consumption
Office of Dietary Supplements, National Institutes of Health: http://ods.od.nih.gov/	Health information for nutritional supplements
AcuMedico: http://www.acumedico.com/acupoints.htm	Acupuncture points database describing how to locate acupuncture points
Young Living Essential Oils: http://www.youngliving.com/essential-and-massage-oils	Organic essential oils for combining with olive oil for uterine massage for dysmenorrhea

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References are available online at expertconsult.com.

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Chapter 55

Uterine Fibroids (Leiomyomata)

Allan Warshowsky, MD

Pathophysiology

Prevalence and Etiology of Uterine Fibroids

Prevalence estimates for uterine fibroids indicate that they affect 5.4% to 77% of women, depending on the method of diagnosis.[1] A fibroid tumor can be very small and difficult to feel, especially in obese women. These tumors have also been known to grow as large as a watermelon. Most gynecologists do not consider fibroid tumors a problem until they reach the size of a 12-week pregnancy. At that size, it becomes difficult to feel small ovarian tumors. Newer imaging techniques make this issue less of a concern because even large fibroid tumors allow for evaluation of ovaries through sonography and other imaging techniques. Other reasons for considering surgery would be symptoms such as bleeding and painful menstruation or dysmenorrhea. Historically, hysterectomy has been the procedure of choice for patients with large fibroid tumors. Approximately 300,000 hysterectomies are performed per year for these benign tumors. Hysterectomy is an invasive procedure; in 1975, 1700 deaths occurred among the 787,000 hysterectomies performed.[2] More recent studies have confirmed the morbidity of these invasive procedures.[3,4] Conventional medicine has little else to offer other than a "watch and wait" attitude to women who suffer from small fibroids. If these small fibroids are approached from an integrative holistic perspective when they are initially observed, much of the disability and many invasive surgical procedures can be avoided.

The second edition of the American College of Obstetrics and Gynecology's *Guideline for Women's Health Care* suggests the following: "As benign neoplasms, uterine leiomyomata (fibroids) usually require treatment only when they cause symptoms."[5] If we can use an integrative, holistic approach that eliminates symptoms and stops growth of these benign fibroid tumors, women can avoid invasive surgery and disability.

Hormonal Changes in the Normal Ovulatory Menstrual Cycle

The healthy menstrual cycle is a marvel of nature. In the first part of the cycle, the follicular cells of the ovary produce estradiol. This follicular phase lasts from 7 to 21 days. During this part of the cycle, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are produced and secreted by the anterior pituitary gland in the brain.

The necessary midfollicular phase peak of estradiol affects an LH surge during this part of the cycle. Ovulation occurs after the LH surge. Only after ovulation is progesterone produced and secreted by the corpus luteum of the ovary.

LH and FSH are in a feedback loop inhibition relationship with the main ovarian hormone, estradiol. The anterior pituitary gland is also under the control of the hypothalamus through the secretion of gonadotropin-releasing hormone (GnRH). The limbic system, which contains the amygdala and hippocampus, encircles the hypothalamus and the pituitary gland and is known to be the repository of emotions in the body. The limbic system and thus our emotions and perceptions affect the production and secretion of GnRH. The physiology of this is not clear, but clinicians all know of women who become menopausal after a significant stressor in their lives.

We must also consider the association of ovarian hormones with the thyroid and adrenal glands. Alterations of thyroid function are invariably associated with menstrual irregularities of all kinds. Low progesterone-to-estradiol (P/E_2) ratios are associated with reduced conversion of less

active thyroxin (T_4) to more active triiodothyronine (T_3). Therefore, hypothyroidism with normal levels of T_4 and low levels of T_3 can be an indicator of sex hormone imbalance and estrogen dominance. Adrenal gland function also affects sex hormone production and metabolism and must be evaluated along with the thyroid and ovarian hormones.

The origin of fibroids is not well understood. Some evidence indicates that chromosomal abnormalities may play a role. Chromosomal translocations, deletions, inversions, and breakpoints have been shown to be associated with familial patterns of fibroid growth.[6] Some of the fibroids in affected families tend to be quite large.

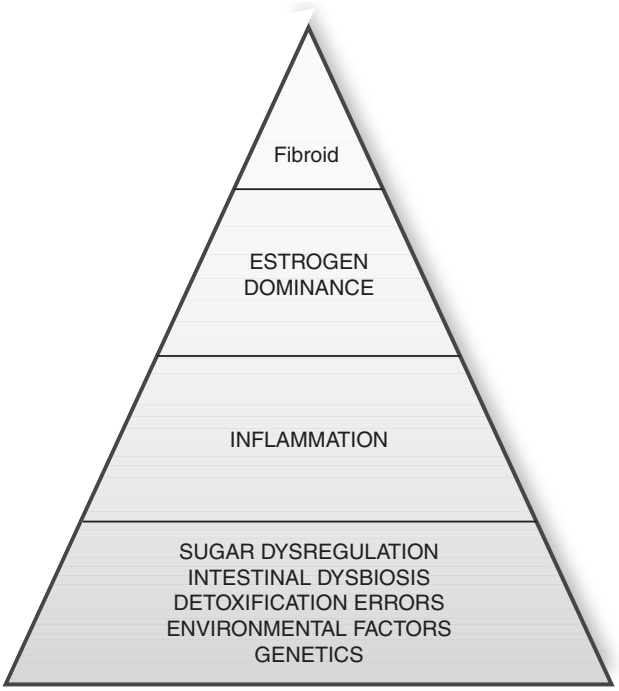
The incidence of uterine fibroids is higher in African American, obese, nonsmoking, and perimenopausal women than in other women. Fibroid tumors are associated with high estrogen levels, or estrogen dominance. Obesity and the perimenopausal state are often associated with higher estrogen levels. Studies have shown that estrogen levels are actually higher in perimenopausal women, and adipocytes are endocrine organs capable of producing estrone, a strong estrogen. The inflammatory mediators interleukin-2 (IL-2), IL-6, tumor necrosis factor-alpha (TNF-alpha), and leukotriene B_4 (LTB_4) are also produced in the adipocyte and contribute to fibroid formation.[7]

Vitamin D research has begun to shed some light on the higher incidence of fibroids in African American and other dark-skinned women.[8] Low vitamin D (measured as 25-hydroxyvitamin D_3) levels are associated with increased inflammatory cytokines and have been shown to be associated with higher incidence of epithelial cancers such as those of breast, colon, and prostate. Vitamin D is necessary for healthy cell apoptosis, or regulated cell death, and also has profound effects on glucose metabolism. Later discussion explains how unhealthy glucose metabolism can contribute to fibroid growth through the development of insulin resistance.[9] Measuring 25-hydroxyvitamin D_3 is important because this form of the vitamin circulates to all cells of the body and is a good measure of total body reserve of vitamin D_3. The optimal range of 25-hydroxyvitamin D_3 is between 40 and 100 ng/mL.[10] Replenishment is with vitamin D_3 at the range of 50,000 units/week for 12 weeks, at which time the measurement should be repeated.[11]

Studies by Dr. Elizabeth Stewart et al[12] in Boston supported the connection between systemic inflammation and fibroid growth. She proved that various growth factors, such as fibroblast growth factor, vascular endothelial growth factor, and transforming growth factor, which are concentrated in fibroid cells, are responsive to inflammatory mediators. These stimulated growth factors increase blood vessel growth or angiogenesis in the fibroid and thereby stimulate and support growth. All successful tumors increase their own blood supply and enable growth. Controlling vascularity with antiangiogenesis factors, as shown by the work of Dr. Judah Folkmann,[13] can then reduce the growth of the tumor or fibroid by decreasing its blood supply.

The theorized gut connection to fibroid growth concerns bacterial imbalance or dysbiosis. A dysbiotic intestinal environment creates gut-associated inflammatory mediators. These inflammatory mediators include IL-2, IL-6, TNF-alpha, and other leukotrienes and cytokines. These substances bathe the pelvis, where nature's fertilizer, estradiol, stimulates the growth of atypical cells that develop into autonomously growing leiomyomata, or fibroids. Intestinal dysbiosis with associated bacterial and yeast overgrowth also contributes to estrogen dominance through the estrogenic effects of bacterial toxins and yeast mycotoxins.

FIGURE 55-1
The fibroid that can be felt and measured is the physical manifestation of estrogen dominance and inflammation. Estrogen dominance and inflammation in the body are created and supported by the underlying sugar dysregulation, intestinal dysbiosis, detoxification errors, environmental factors, and genetics.



Estrogen Dominance

Estrogen dominance is a term coined by the late Dr. John Lee (Fig. 55-1).[14] It applies to conditions associated with stronger estrogen effects than can be balanced with existing progesterone. Estrogen dominance can also manifest through imbalanced estrogen metabolism, as discussed later. Fibroids are just one condition associated with estrogen dominance (Table 55-1). Others are as follows:

- Autoimmune diseases: Hashimoto thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, ulcerative colitis, scleroderma, Sjögren syndrome, and others
- Fibrocystic breast problems
- Gallbladder disease
- Cervical dysplasias and other hormone-dependent cancers (breast, uterine, and ovarian)
- Endometriosis
- Infertility
- Menstrual irregularities of all kinds
- Polycystic ovary syndrome
- Premenstrual syndrome

TABLE 55-1. Factors That Promote Estrogen Dominance and Subsequent Fibroid Growth

Poor Dietary Choices*	Low-isoflavone, low-fiber foods (constipation) High–glycemic index foods Hormone-rich meats, poultry, and dairy Excessive inflammation-causing saturated fats Excessive-gluten grains
Intestinal Dysbiosis	High beta-glucuronidase levels† Estrogen-like mycotoxins Intestinal parasites
Sugar Dysregulation	Insulin resistance Low sex hormone–binding globulin Anovulation with low progesterone-to-estradiol ratios
Environmental Issues‡	Xenobiotics Polychlorinated biphenyls, dioxins, heavy metals Birth control pills and hormone replacement therapy§ Violence and sex effects on limbic system
Stress	High cortisol levels contributing to low progesterone
Reduced Estrogen Detoxification	Leading to estrogen dominance

*Data from Goldin BR, Adlercreutz H, Gorbach SL, et al. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med.* 1982;307:1542–1547.
†Data from Minton JP, Walaszek Z, Hanausek-Walaszek M, Webb TE. β-Glucuronidase levels in patients with fibrocystic breast disease. *Breast Cancer Res Treat.* 1986;8:217–222.
‡Data from Wolff MS, Toniolo PG, Lee EW, et al. Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst.* 1993;85:648–652.
§Data from Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. *N Engl J Med.* 2002;346:340–352.

Effects of Diet, Digestion, Absorption, and the Intestinal Environment on Hormone Balance

Hormone imbalance and estrogen dominance are often associated with intestinal dysbiosis. Intestinal dysbiosis designates an unhealthy gut environment often associated with greater intestinal permeability or "leaky gut." Signs and symptoms of dysbiosis include digestive issues, such as bad breath, body odor, bloating, gas, nausea, and constipation. The concept of leaky gut describes a condition in which, instead of protein disassembly into amino acids that are transported through the intestinal cells, large peptides and proteins are absorbed intact into the body and stimulate inflammatory reactions, as well as immune and hormonal imbalance.

Intestinal dysbiosis can be caused by antacid abuse and resultant hypochlorhydria, antibiotics, chronic stress, eating practices that do not enhance digestion and absorption (eating on the run), intestinal infection, and birth control pills.

Intestinal dysbiosis can contribute to estrogen dominance through several mechanisms. beta-Glucuronidase is an enzyme produced by pathogenic gut bacteria.[15] It cleaves the glucuronic acid molecule conjugated to estradiol that would enable its excretion and thus allows the estradiol to reenter the body. The result is an elevation of total body estrogen that puts more stress on the liver and its detoxification capacities. Pathogenic intestinal bacteria and pathogenic yeasts can also produce bacterial and mycotoxins that have strong estrogenic effects. Concomitant inflammation can increase estrogen production and the growth factors that reside in the fibroid tissue and support angiogenesis.

Intestinal dysbiosis can be diagnosed with the proprietary Comprehensive Digestive Stool Analysis (Genova Diagnostics; see Key Web Resources). Elevations of the organic acid indican can indicate poor protein digestion and suggest intestinal dysbiosis (Organix test, Metametrix Clinical Laboratory; see Key Web Resources). Greater intestinal permeability is evaluated using the lactulose-mannitol test. In this test, the variable absorption of the two sugars lactulose and mannitol determines whether permeability in the intestines is increased. The larger sugar lactulose should not find its way into the urine, unlike the smaller sugar mannitol. Finding abnormal ratios of these two sugars in the urine after oral ingestion indicates increased intestinal permeability or dysbiosis.

Intestinal dysbiosis is treated with an intestinal restoration program such as the 4-R program described by Jeffrey Bland.[16] The four Rs are as follows:

- Remove irritants affecting the gut. This includes microorganisms, food allergens, and other toxins.
- Replace betaine hydrochloride, enzymes, bile salts, and fiber.
- Reinoculate with prebiotics (inulin) and probiotics.
- Repair, which is done with gut restorative nutrients, including zinc, glutamine, *N*-acetylcysteine, *N*-acetylglucosamine, *Boswellia*, cat's claw, licorice root, and curcumin.

For further information, see Chapter 84, Food Intolerance and Elimination Diet.

For a woman to have symptomatic fibroids and not to have functional intestinal dysfunction and associated dysbiosis is uncommon.

Effects of Insulin Resistance on Hormone Balance and Estrogen Dominance

Elevations of insulin and insulin-like growth factor-I can also contribute to estrogen dominance and fibroid growth. Metabolic syndrome (prediabetes) is a disorder of elevated insulin related to increasing insulin resistance.[17] The syndrome is defined by a constellation of signs and symptoms including abdominal obesity with a waist-to-hip ratio greater than 0.8:1 (waist circumference larger than 35 inches in women), a high level of triglycerides with a low level of high-density lipoprotein cholesterol and a high level of low-density lipoprotein cholesterol, hypertension, impaired glucose tolerance, increasing hypoglycemia, and a higher incidence of adult-onset diabetes. Metabolic syndrome is associated with these laboratory markers:

- Elevation of fasting insulin and blood glucose
- Elevation of fasting fructosamine
- High hemoglobin A1c measurement (greater than 6%)
- Increased inflammatory mediators: IL-2, IL-6, TNF-alpha, LTB_4

- Increased levels of prostaglandin 2 series, thus increasing inflammation
- Greater estrogen production in adipocytes in the form of estrone (E_1)
- Estrogen dominance, most apparent in polycystic ovary syndrome, which is highly associated with insulin resistance
- Decreased sex hormone–binding globulin (SHBG) that increases the amount of free estradiol available at the cellular level[18]
- Increased aromatase enzyme levels, which increase conversion of testosterone and androstenedione (testosterone precursor) to estradiol and estrone and also increase estrogen dominance

Insulin sensitivity can be improved by various methods, all thoroughly discussed in Chapter 31, Insulin Resistance and the Metabolic Syndrome.

Liver Detoxification and Estrogen Dominance

Systemic detoxification consists of two phases that need to be in balance. In phase 1, lipid-soluble substances—toxins, hormones, or drugs—are transformed into intermediate substances by the cytochrome P-450 set of enzymes.[19] This enzyme system can be up-regulated or down-regulated by various drugs, stressors (e.g., alcohol, cigarette smoke, smoke from charred meat), and herbs. An example in the world of estrogen dominance and uterine fibroids is the effect of gluten grains on estrogen metabolism. Gluten, the active protein in the wheat, rye, and barley reduces the cytochrome P-450 isoenzyme 3A4 and leads to reduced estrogen metabolism and subsequent estrogen dominance.

The intermediate substances that are formed in phase 1 must then be made water soluble. In phase 2 of the detoxification process, the intermediates are conjugated with amino acids and peptides such as glucuronic acid, glutathione, and glycine, or they undergo conjugation processes such as methylation, sulfation, acetylation, and sulfoxidation.[20] These now water-soluble substances can be excreted in stool, urine, or sweat or as water vapor through the lungs.

The ready for excretion estradiol–glucuronic acid molecule previously discussed is cleaved in the dysbiotic gut by elevated amounts of the enzyme beta-glucuronidase, which is produced by imbalanced gut bacteria.

Phase 1 and phase 2 detoxification errors cannot be determined by conventional aspartate aminotransferase and alanine aminotransferase enzyme levels, which are indicators only of hepatocyte breakdown. More integrative and functional assessments of detoxification can be made through organic acid testing or functional detoxification tests that evaluate the phase 1 cytochrome P-450 enzyme system and phase 2 conjugation factors. Estrogen metabolites and their intermediaries consist of the catechol (hydroxy) estrogens and the methylestrogens. The anticarcinogenic estrogen modulator 2-hydroxyestrone ($2OH\text{-}E_1$) comes from naturally produced ovarian estrogens; high levels of this substance as 2-methoxyestrone reduce the risk of breast cancer. Higher amounts of 4-hydroxyestrone ($4OH\text{-}E_1$) occur with metabolism of conjugated estrogens (Premarin) to form DNA-damaging quinones. Epigallocatechin gallates (a catechin in green tea) and other antioxidants such as vitamins A and C and E, selenium, *N*-acetylcysteine, and lipoic acid convert quinones to mercapturates. This process occurs through the production of glutathione. 16alpha-Hydroxyestrone ($16OH\text{-}E_1$) forms a very strong bond with the estrogen receptor, is a strong estrogen, and has carcinogenic potential. These estrogen metabolites are not all good or bad. Like everything else in nature, they need to be in balance.

Appropriate levels of 16alpha-hydroxyestrone support good bone density. The ratio of the three hydroxyestrogens and their methylated end products, which can be measured in urine (Metametrix Clinical Laboratory) or blood (Genova Diagnostics), can help evaluate risk in estrogen dominance conditions. In menstruating women, the ratio of $2OH\text{-}E_1$ to $16OH\text{-}E_1$ should be evaluated during the luteal (late) phase of the cycle. The following factors increase either this ratio or the level of $2OH\text{-}E_1$:

- A diet rich in the cruciferous vegetables (broccoli, Brussels sprouts, kale, cabbage, cauliflower)
- Indole-3-carbinol (I-3-C), which comes from cruciferous vegetables (broccoli, Brussels sprouts, cabbage, kale): 200 to 800 mg/day
  - Diindolylmethane (I-3-C activated by stomach acid), used alone or in conjunction with I-3-C
- Epigallocatechin gallates (green tea extract)
- Isoflavones, including soy, flaxseed, and kudzu[21]
- Omega-3 fatty acids
- Vigorous exercise, a minimum of 30 minutes three times/week

The ratio of $2OH\text{-}E_1$ to $16OH\text{-}E_1$ can be reduced, with an increased proportion of $16OH\text{-}E_1$, by the following conditions:

- Obesity
- Hypothyroidism
- Xenoestrogens: any estrogenic substances, including dioxins and polychlorinated biphenyls
- Cimetidine (Tagamet) and other drugs that interfere with the cytochrome P-450 system[22]
- Estriol: Although in most people estriol is a metabolic end product, concern exists that as a stereoisomer it can revert to the $16alphaOH\text{-}E_1$ from which it was formed; this is more of a concern when estriol is prescribed as part of a bio-identical hormone replacement therapy program.

Most of the studies of hormone imbalance and fibroid tumors of the uterus have concerned themselves with estrogen dominance, although mifepristone studies create some controversy and doubt.[23] Mifepristone is better known as RU-486, the "abortion pill." It functions as a progesterone receptor antagonist. Long-term use of mifepristone has been associated with fibroid regression.[23] As a progesterone receptor antagonist, mifepristone's action would suggest that progesterone also stimulates fibroid growth. The answer may not be that simple because progesterone also increases blood

vessel support of the endometrium in anticipation of a fertilized egg. My opinion is that some fibroids may take advantage of the increased progesterone-supported blood supply and increase in size because of it. The negative effects associated with long-term mifepristone use are bone loss and endometrial hyperplasia, conditions indicating that more complicated mechanisms may be at work. Mifepristone may also affect estrogen receptors. More studies are needed.

Determining Whether a Fibroid Has Malignant Potential

The malignant potential (sarcomatous change) of fibroids or leiomyomata is less than 1%. Whether a fibroid changes from benign to malignant or is malignant to begin with is not well established. One sign that can indicate a malignant fibroid or leiomyosarcoma is rapid growth. Unfortunately, the only conventional way to evaluate malignancy is to remove the fibroid and examine a sample for the number of mitotic events per high-power field; more than 20 mitoses per high-power field would indicate sarcomatous change. Table 55-2 lists tests that should be considered in evaluating a patient with fibroid tumors of the uterus.

Complementary and Alternative Medicine Studies on Fibroid Tumors of the Uterus

To date, few complementary and alternative medicine studies on holistic approaches to fibroids have been conducted.[24] Most studies are concerned with comparisons of the various invasive treatments.

Zhongli and Shurong conducted a study in 223 women with fibroids who were treated with acupuncture and Chinese botanicals. Effectiveness in reducing symptoms was rated at more than 90%.

The U.S. herbal literature describes treatments for fibroids with the herbs gossypium, *Hydrastis, Phytolacca, Rubus,* the viburnums, *Achillea,* and trillium. One study combined visualization, imagery, body therapy, and Chinese botanicals to treat symptoms and reduce growth of fibroids in 37 women.[25] The age-matched controls used progestins, birth control pills, and nonsteroidal antiinflammatory drugs (NSAIDs). Outcome measures were reduced growth, fewer symptoms, and patient satisfaction. At the end of the 6-month study period, a statistically significant benefit of the complementary and alternative medicine approach over the conventional medical treatment was found in each of the outcome measures.

Integrative Therapy

Nutrition

The patient should begin a hormone-balancing diet involving foods with low inflammation effects, low acidity, and a low glycemic load.

Foods That Increase Estrogen Dominance

Acidic and inflammatory foods, such as red meats, poultry, and dairy products, are sources of arachidonic acid, which increase inflammatory prostaglandins and other inflammatory mediators that help to support fibroid growth through the process of angiogenesis. Avoiding commercial meat products also reduces exposure to the added hormones in these products.[26] Small amounts of range-fed meats can be added back as inflammation subsides (see Chapter 86, The Antiinflammatory Diet).

Sweets and other foods with a high glycemic index are potentially stressful and can raise insulin levels, increase estrogen dominance, and also support fibroid growth. Eating a breakfast containing good-quality protein, fats, and carbohydrates in combination is imperative to avoid hypoglycemic stress–induced cortisol and epinephrine elevations, which deplete lean muscle and increase the tendency for insulin resistance through gluconeogenesis (see Chapter 85, The Glycemic Index/Load).

TABLE 55-2. Tests to Consider for Evaluation of a Patient With Fibroid Tumors of the Uterus

25-Hydroxyvitamin D measurement*	Low levels increasing fibroid growth by several mechanisms (see text)
Vitamin A measurement†	Low levels shown to increase menorrhagia
Iron or total iron-binding capacity measurement, ferritin measurement	Low iron stores reducing myometrial contractility and increasing menstrual blood loss
Progesterone/estradiol ratio (100–300:1) Luteal phase progesterone measurement	Low luteal phase progesterone level support estrogen dominance and fibroid growth
Thyroid function testing	Hypothyroidism associated with menstrual dysfunction
MTHFR polymorphism	35% weakness in methylation, increased estrogen dominance
Comprehensive digestive stool analysis	Intestinal dysbiosis a cause of estrogen dominance through several mechanisms (see text)
Phase 1 and phase 2 detoxification evaluation	Unhealthy estrogen metabolism contributing to estrogen dominance
Transvaginal and abdominal ultrasonography	To determine the size and location of fibroids and rule out ovarian tumors
Testing for celiac disease (antigliadin antibodies)	Gluten grain sensitivity common in fibroid tumor sufferers and can lead to further estrogen dominance

*Data from Chiu KC, Chu A, Vay LWG, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr.* 2004;79:820–825.
†Data from Lithgow DM, Politzer WM. Vitamin A in the treatment of menorrhagia. *S Afr Med J.* 1977;51:191–199.

Gluten grains, especially wheat, rye, and barley, contain genetically engineered gluten that is much stronger than what was found in the more ancient gluten grains such as spelt. These newer grains can increase estrogens by inhibition of the cytochrome P-450 3A4 enzyme system and can also affect thyroid hormone. All people with chronic estrogen dominance must be tested for gluten sensitivity by antigliadin antibody testing.

Alcohol is not a problem if it is consumed in moderation. Studies show that women consuming more than five alcoholic drinks per week have a higher risk of breast cancer. This increase probably results from the effect of alcohol on the detoxification of estrogens. Organic coffee in moderation (1 to 2 cups per day) is also safe. Artificial ingredients, colorings, flavorings, and preservatives should be eliminated. Margarines and other sources of trans fatty acids and hydrogenated oils are also unhealthy and must be avoided.

Foods That Reduce Estrogen Dominance

Deep sea, cold-water fish, such as wild Pacific salmon, sardines, mackerel, and cod, have large quantities of the omega-3 oils (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]).[27] Because heavy metals such as mercury contribute to estrogen dominance, I recommend eating fish with lower levels of mercury. These are fish at the lower end of the food chain. The larger game fish such as swordfish, tuna, and bass concentrate the contaminants from eating the smaller fish. The small crustaceans, krill, are a good source of noncontaminated EPA and DHA. Algae sources of DHA are also available.

Seeds and nuts, especially flaxseed, hemp seed, and chia seed, contain isoflavones much like soy.[28] They tend to be hormone balancing. I recommend 2 to 4 tablespoons per day added to a soy- or kudzu-containing protein powder shake first thing in the morning. Seeds and nuts such as pumpkin seeds, sunflower seeds, and walnuts are also good sources of omega-3 oils.[29]

Cruciferous vegetables such as broccoli, Brussels sprouts, cabbage, and cauliflower support healthy estrogen metabolism (Fig. 55-2). Legumes such as adzuki beans, peas, lentils, and edamame all have hormone-modulating flavonoids and can safely be eaten.[30]

A head of cabbage contains approximately 1200 mg of indole-3-carbinol. Eating one fourth of a cabbage daily would provide 300 mg of indole-3-carbinol daily.

I have been consistently impressed by the reduction of symptoms related to estrogen dominance by the elimination of milk casein, high-glycemic carbohydrates, and gluten grains. The symptoms that seem to be most affected are gastrointestinal symptoms, headache, dermatologic rashes, fatigue, insomnia, and mood issues.

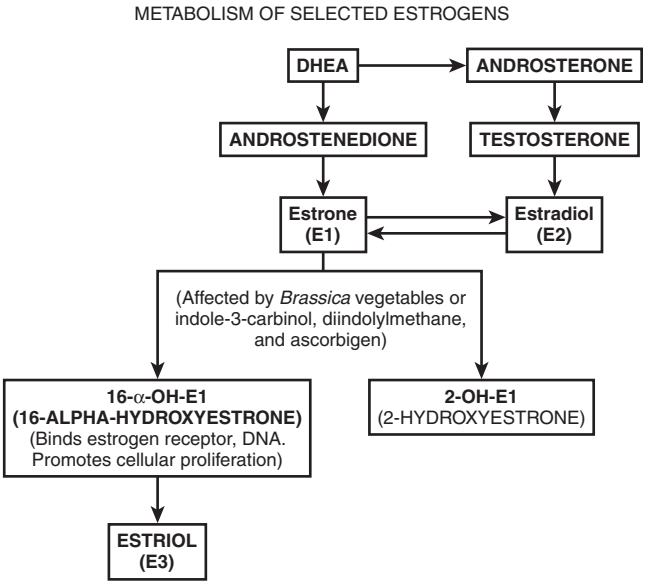
Lifestyle

Exercise

Aerobic exercise consumes oxygen and helps to "burn" carbohydrates. Oxygen-consuming exercises are exemplified by running, fast walking, and swimming. Because carbohydrates are consumed during aerobic exercise, this form of exercise is associated with improvement in insulin resistance and sugar use.

Anaerobic exercise classically uses fats as an energy source. That is why weight trainers consume medium-chain triglycerides during their workouts. Weight training also helps stabilize hormones such as growth hormone and testosterone. Because fat cells (adipocytes) are known to produce inflammatory mediators and estrogens, limiting adipose tissue also reduces estrogen dominance. A regimen of 30 minutes of regular exercise three times per week has also been shown to lower the incidence of breast cancer and colon cancer.

FIGURE 55-2
Metabolism of selected estrogens. DHEA, dehydroepiandrosterone.



Botanicals: Overview

Botanical therapies can be very useful in reducing fibroid growth and in decreasing fibroid symptoms.[31] Not much is available in the way of scientific study, but many of these herbs have been used by naturopaths and herbalists for many years.

Botanicals for Liver and Detoxification Support

Healthy estrogen metabolism must be reestablished to reverse estrogen dominance. By obtaining functional liver detoxification studies performed by laboratories such as Genova Diagnostics, Metametrix, and Doctor's Data, the clinician can determine which specific aspects of the detoxification pathway the patient is lacking and give the appropriate nutritional support. Many botanicals and nutraceuticals can be helpful in restoring and maintaining healthy detoxification.

Epigallocatechin Gallates From Green Tea

Epigallocatechin gallates reduce the DNA-damaging effects of 4OH-E_1. They may also be antiangiogenesis factors.

Dosage
The dose is 3 cups/day (240 to 320 mg of polyphenols).

Precautions
These agents can cause insomnia if they are consumed in large amounts.

Indole-3-Carbinol or the Stomach-Activated Diindolylmethane
I-3-C increases the production of estrogen-modulating 2OH-E_1.[32]

Dosage
The dose is 200 to 400 mg/day.

Precautions
I-3-C is generally free of side effects.

Milk Thistle (Silybum marianum)
Milk thistle is a general liver antioxidant that supports healthy detoxification and estrogen metabolism.

Dosage
The dose is 280 to 420 mg of milk thistle per day standardized to 70% to 80% silymarin content.

Precautions
This agent is virtually devoid of negative effects.

Botanicals to Modulate Pelvic Lymphatic Drainage

These botanical formulas are used in combination to modulate pelvic lymphatic drainage. Scudder's alterative (a combination herbal product containing corydalis, alder root, mayapple root, figwort, and yellow dock) modulates cellular metabolism. Echinacea/Red Root compound modulates toxin elimination, immune system, and inflammatory mediators.

Dosage
The dose is 30 drops of Scudder's alterative combined with Echinacea/Red Root compound as a tea twice/day for 3 months. This is followed by 2-weeks without this treatment.

Precautions
This combination of formulas has no known negative effects.

Botanicals and Herbal Combinations Shown to Reduce the Growth of Fibroids

Fraxinus
Fraxinus is also known as white ash or *Ceanothus* compound.

Dosage
The dose is 30 to 40 drops of tincture in hot water twice/day for 3 months, followed by a 2-week break; repeat.

Precautions
Fraxinus has no known toxicity.

Turska's Formula
Turska's formula (aconite, phytolacca, gelsemium, bryonia) is used by naturopaths and U.S. herbalists to reduce size of growths. It contains some potentially toxic herbs (aconite and phytolacca). Bryonia has been classified by the U.S. government as an endangered species, so the formula has been increasingly difficult to obtain, and variations have also been developed with different herbal combinations.

Dosage
The dose is 5 to 10 drops/day in hot water. Use only under the care of a knowledgeable herbalist.

Precautions
This formula should be used in small amounts. It can be toxic at higher dosage and can cause gastrointestinal distress, peripheral blood cell changes, cardiac toxicity, headache, and double vision.

Chaste Berry (Vitex agnus-castus)
Chaste berry, or *Vitex,* is an herb with a long reputation for balancing progesterone production.[33] It has dopaminergic effects and modulates prolactin secretion from the pituitary gland. Evidence also indicates that it helps reduce growth and shrink small fibroids.

Dosage
The dose is 200 to 500 mg/day.[34]

Precautions
Minor gastrointestinal distress is a rare side effect.

Myomin
Another herbal combination that has a long history of use is Myomin, which contains the following herbs:
200 mg *Smilax glabra* Roxb. (sarsaparilla), a progesterone modulator
160 mg *Curcuma zedaoria*, which has antiinflammatory effects
160 mg *Cyperus rotundus*
160 mg *Aralia dasyphylla* Mig.
120 mg *Pericarpium arecae*

Dosage
The dose is two to three capsules three times/day after meals.

Precautions
Myomin has no significant side effects.

Herbal Therapies for Specific Symptoms

Menorrhagia
Heavy bleeding from fibroids tends to be the symptom that brings most women to the operating room. Menorrhagia is defined as loss of more than 80 mL per menses. Controlling heavy bleeding, or menorrhagia, is probably the most important first step in the fibroid healing program. Severe iron deficiency anemia is one of the most common reasons for surgery. Combinations of herbs that act differently within the uterus can be very effective in reducing blood loss and keeping women out of the operating room. Use of a combination of the following herbal types can significantly reduce menstrual bleeding.

Uterine-toning herbs: These include red raspberry, false unicorn root, and black cohosh.
Astringent herbs: These include yarrow, lady's mantle, beth root, and cinnamon.
Oxytocic herbs: I have only used shepherd's purse for oxytotic effect. It has a long history of use among midwives to help control postpartum bleeding.

These herbs are also used in combination. A combination botanical preparation consisting of tinctures of a tonic herb such as red raspberry and an astringent herb such as yarrow can be used at a dose of 30 drops each twice a day for 2 weeks before the period. This protocol helps the uterus prepare for healthy uterine contractions both to expel the menstrual flow and to optimize effective and nonspasmodic uterine contractions. When bleeding begins, add 30 drops of an oxytotic herbal tincture such as shepherd's purse. The combination of all three herbal tinctures can be taken every 30 minutes for up to 6 doses. No scientific reason exists for using 6 doses as an arbitrary cutoff. I believe that if the patient is still hemorrhaging after 3 hours of using these herbs, something else needs to be considered. However, this protocol has been extremely useful in reducing menorrhagia and reversing iron deficiency anemia. Other herbs in the same categories can be substituted if the patient has a reaction to one of the herbs or if the effect is less than desired. Several botanical companies such as Gaia and Herbpharm standardized herbal tinctures (see Key Web Resources below).

Dosage
See the preceding protocol.

Precautions
These herbs have minor gastrointestinal effects. Yarrow rarely causes rash or sun sensitivity. Shepherd's purse in large doses may interfere with thyroid function. Follow-up with thyroid function testing is suggested.

Antiinflammatory Botanicals
Inflammatory prostanoids, cytokines, and leukotrienes increase the cellular growth factors that support vascularization of the fibroid. Specific botanicals can reduce this inflammation. Botanicals are often found in combination products, such as one containing *Boswellia* (400 mg), ginger (200 mg), turmeric (300 mg), and cayenne (50 mg) in every two tablets.

Dosage
One to two tablets are taken three times/day. The patient may take one to two tablets every 2 hours as needed.

Precautions
Taking such a combination product on an empty stomach can cause abdominal pain in sensitive individuals. These herbal preparations can be taken with food.

Systemic Enzymes
Elimination of excessive inflammation with potent systemic enzyme formulations may reduce the size of fibroids by limiting vascularization of fibroids and by enzymatic myolysis of the fibroid.[35] Such systemic enzymes are Neprinol, Wobenzym, Vitalzyme, and bromelain (from pineapple stems).[36] Other preparations of proteases can also be used. Neprinol[37] has the following ingredients:

- SEBkinase
- Peptizyme SP
- Serrapeptase
- Lipase
- Protease
- Amla
- Papain
- NattoSEB
- Nattokinase
- Bromelain
- Rutin
- Coenzyme Q10
- Magnesium

Dosage
These enzyme formulations should be taken on an empty stomach to avoid action on food rather than on the protein of the fibroid. The dose is gradually built up from 1 tablet three times/day to 15 tablets per day in divided doses.

Precautions
As with any antiinflammatory agent taken on an empty stomach, the clinician must caution the patient about stomach pain. Such enzyme preparations must be used with caution in patients with gastritis and history of gastric ulcer, as well as in patients who take blood thinners.

Antiangiogenesis Factors
The work by Judah Folkman[13] in cancer therapy illustrates the effect of antiangiogenesis on reducing tumor growth. The convolvulus product and other antiangiogenesis factors are used to reduce blood flow to the fibroids.[38] *Convolvulus arvensis* (bindweed) works as an antiangiogenesis factor.[39] Green tea catechins and polyphenols also have antiangiogenic effects.

Dosage
The dose is two tablets three times/day, slowly increased from one tablet twice/day.

Precautions
Headaches are a side effect if the dosage is increased too rapidly. Increase slowly to avoid headaches.

Nutraceuticals
Vitamin C and the Citrus Bioflavonoids (Rutin and Hesperidin)
Vitamin C strengthens capillary desmosomes and can also be helpful in reducing menorrhagia.[40] The citrus bioflavonoids rutin and hesperidin enhance this vitamin C effect and are also mildly estrogenic and as such can have a tonic effect, by reducing the effects of estrogen dominance.

Dosage
The dose is 1000 to 2000 mg/day, but the dosage can be increased up to 75% of bowel tolerance.

Precautions

Vitamin C has been known to cause diarrhea. This is what has been referred to as bowel tolerance. Reducing the dosage to 75% of the amount that causes diarrhea may be the most appropriate individualized approach to that patient. Some question exists about the use of vitamin C in patients with a history of kidney stones.

B Vitamins

Vitamins B_1, B_2, B_3, B_5, and B_6 are important for sugar, fat, and neurotransmitter metabolism, hormone balance, and healthy cortisol production from the adrenal gland.[41] Vitamin B_3 in the form of niacinamide is also a potent antiinflammatory agent. Niacin can be used to reduce menstrual cramping often associated with fibroids.[42] Other B vitamins, such as choline and inositol, support healthy liver function. Vitamins B_2, B_6, B_{12}, and folic acid support the process of methylation, which is necessary for healthy hormone metabolism and for DNA repair. Vitamins B_5 and B_6 also support adrenal function, which is important in healthy hormone balance.

Dosage

A 50-mg B-complex vitamin can supply basic vitamin B needs. Separate additional B vitamins may be necessary. The recommended dose of vitamin B_{12} is 2000 units/day.

The dose of folic acid is 800 mcg or more per day. Doses up to 5 to 10 mg/day have been used for cervical dysplasias. Approximately 35% of the population is estimated to have a mutation of the *MTHFR* gene that decreases their ability to methylate. Most laboratories check for the *MTHFR* C677T gene mutation. I recommend this test, and if a patient is heterozygous or homozygous for the mutation, supplementation, at least in part, with methylfolate seems wise. A reasonable dose of methylfolic acid is 1 to 2 mg/day.

Precautions

When high doses of folic acid are used, attention must be taken to supplying vitamin B_{12} in addition, to avoid masking the signs of pernicious anemia. Peripheral neuropathies have been reported with vitamin B_6 dosages larger than 200 mg/day. Practicing caution when dosing and educating patients to report any tingling in their fingers and toes are important.

For treatment of menstrual cramps, consider having the patient take niacin, 100 mg twice/day throughout the month, then 100 mg every 2 hours while having cramps.

Vitamin D

Vitamin D is very important for the healthy functioning of every cell in the body. It has been found to be useful for the following functions:

- Sugar metabolism
- Programmed cell death (apoptosis)
- Balanced inflammatory reactions
- Reduction in incidence of epithelial cancers
- Bone health
- Healthy thyroid function
- Healthy calcium metabolism

Because of fear of sun exposure and resultant skin cancer, most people use ultraviolet B–blocking, sun protective factor (SPF) 30 or higher sun block.[43] This situation has created almost an epidemic of low levels of vitamin D. Measuring 25-hydroxyvitamin D levels and restoring them to at least 40 ng/dL are imperative. Investigators have estimated that 32 ng/dL will be required to prevent rickets in children. Restoration of vitamin D levels can be accomplished by using 50,000 units/week of vitamin D_2 for 12 weeks and then remeasuring. Supplying at least 1200 mg/day of calcium to a patient being treated with vitamin D is important.[44]

Dosage

If the 25-hydroxyvitamin D blood level is low, give 50,000 units of vitamin D_2 once a week for 12 weeks; then recheck the 25-hydroxyvitamin D level.

Precautions

As with any fat-soluble vitamin, excessive amounts of vitamin D can be toxic. Measuring blood levels again after 12 weeks of supplementation is necessary. Supplying at least 1200 mg/day of calcium in the diet and as a supplement can prevent loss of calcium from bone. Evaluation of parathyroid hormone levels screens for hyperparathyroidism and is important before supplementing. Evidence indicates that supplementation with the other fat-soluble vitamins A, E, and K may be necessary for optimal absorption.

Calcium D Glucarate

Calcium D glucarate reduces the activity of the enzyme beta-glucuronidase, which is produced in patients with intestinal dysbiosis. This enzyme, which is produced by dysbiotic intestinal bacteria, cleaves the glucuronic acid–estrogen bond on estrogens meant to be excreted and instead puts them back into circulation. By the action of beta-glucuronidase, estrogen dominance increases and adds more stress to the already stressed detoxification system.

Dosage

The dose is 500 mg twice/day.

Precautions

No precautions are reported.

Iron

Women with fibroids tend to have heavy menses, or menorrhagia, which is defined as losing more than 80 mL of blood during menstruation. This greater iron loss associated with the blood loss sets up a vicious circle.[45] The lower the iron level becomes, the more weakly the myometrial muscle cells contract, thus contributing to more menstrual blood loss. Evaluation and treatment of low iron stores by measurement of iron levels, total iron-binding capacity, and serum ferritin levels help guide restoration of iron levels and maintain healthy myometrial contractility. A boggy, noncontractile uterus bleeds more than a healthy, well-toned one.

Dosage

The dose is 325 mg/day of ferrous sulfate or its equivalent. Higher doses may be needed during menses.

Precautions
Measuring serum iron levels during supplementation prevents iron overload. Some iron formulas can be constipating.

Selenium
Selenium is a potent antioxidant that supports the action of vitamin E. It also is used in the production of the antioxidant glutathione. Selenium is necessary for the action of thyroid hormone.

Dosages
The dose is 200 to 500 mcg/day.

Precautions
Dosages exceeding 1000 mcg/day can precipitate skin and nail changes. "Garlic breath" may be an early sign of too much selenium.

Magnesium and Zinc
Important for hormone support, magnesium and zinc are responsible for catalyzing approximately 500 different reactions in the body. These minerals are estimated to be deficient in 50% to 75% of the population. One theory for the craving of chocolate in the premenstrual period is the need for magnesium[46]; chocolate is rich in this mineral.

Dosages
The dose of magnesium is 400 to 600 mg/day, and the dose of zinc is 15 to 30 mg/day.

Precautions
Taking too much magnesium can increase diarrhea. Magnesium can also compete with calcium for absorption; if this problem is suspected, magnesium should be taken separately from calcium. Zinc may interfere with copper absorption, and supplementation requires that 2 mg copper be added to the protocol. Red blood cell levels should be checked.

Women who crave chocolate (a rich source of magnesium) before their period may benefit from magnesium replacement therapy.

Omega-3 Fatty Acids (Eicosapentaenoic Acid and Docosahexaenoic Acid)
The omega-3 essential fatty acids (EPA and DHA) help maintain the fluidity of all cell membranes, reduce inflammatory mediators, and are building blocks for hormones. These essential fatty acids are not made in the body and must therefore be consumed. Clinicians have seen time and again how increased and unbalanced inflammation contributes to fibroid tumor problems.

Dosage
The dose is 3 to 6 g/day of EPA and DHA (fish oil).

Precautions
Caution is recommended when prescribing more than 3 to 4 g/day of omega-3 acids to diabetic patients. Reports have noted elevations of blood glucose.

Mind-Body Therapy
Encourage patients to create emotional flexibility by "staying in the moment." Stretching and yoga exercises not only help maintain physical flexibility, but also promote emotional flexibility. Living in the present moment,[47] we modulate stress effects that come from worrying about a possible future that may never come and from fretting about a past that cannot be changed. This chronic stress, which raises cortisol levels and lowers dehydroepiandrosterone (DHEA) levels, contributes to estrogen dominance by "stealing" or shunting progesterone to produce more cortisol.

Body awareness exercises, such as tai chi and qi gong, and meditation and visualization exercises help to reduce blood flow to fibroids and lessen their impact and their growth. Moving and other meditation exercises help to mobilize stagnated energy, as do acupuncture, deep tissue massage, craniosacral work, and psychotherapeutic techniques such as bioenergetics.

Exercise of all kinds has been shown to reduce the harmful effects of stress. Meditation also helps reduce cortisol levels.[48] Many of these techniques focus on chakras or energy centers that correspond to anatomic nerve plexuses or glands of the endocrine system. One such technique is the Freeze Frame technique, developed by The HeartMath Institute: The patient is taught to focus on heart energy or the fourth chakra while breathing into the heart. Thoughts that are stressful are not internalized but instead are blown out with the exhale. This is a simple but powerful way to stay in the moment and reduce the inflammatory effects of stress on the body (see Chapter 94, Enhancing Heart Rate Variability).

Journaling is a technique for ridding the body of stored emotional energy. Removing this stagnating energy is like cleaning out the closet and getting rid of all the clutter in your life. Energy moves again.

While meditating and performing visualization exercises, the patient is instructed to be aware of second chakra issues—relationships, creative blocks, and abuse issues. Journaling has been shown to help reduce the negative effect of these stored emotions (see Chapter 96, Journaling for Health).

Another powerful technique that supports meditation and stress reduction and thereby alleviates symptoms of fibroids and reduces their growth is visualization of the desired results and the intent of bringing healing energy into the area to be healed.

Pharmaceuticals: Gonadotropin Receptor Agonists
The following gonadotropin-releasing hormone (GnRH) receptor agonists may be used.

Leuprolide Acetate
Leuprolide acetate (Lupron) is used to shrink fibroids before surgery to make the tumors easier to remove.[49] This agent can effect a 30% to 60% reduction in fibroid size. Surgeons sometimes complain that using leuprolide decreases their ability to enucleate fibroids easily during myomectomy.

Dosage
The dose is 3.75 to 7.5 mg/month given intramuscularly for 1 to 6 months.

Precautions
Unfortunately, if nothing else is done to prevent regrowth, many fibroids rapidly achieve the same size they were before treatment. This agent causes chemical castration, menopausal symptoms, and osteoporosis.

Danazol
Danazol (Danocrine), which suppresses LH and FSH, can also be used to shrink fibroids.

Dosage
The dose is 600 to 800 mg/day.

Precautions
Precautions are the same as those listed for leuprolide acetate, but they are more intense.

Agents for Menorrhagia Associated With Fibroids

Norethindrone Acetate
Norethindrone acetate is used for menorrhagia associated with fibroids.

Dosage
A dose of 5 to 15 mg/day has been effective in slowing bleeding.

Precautions
The risk of blood clots, fluid retention, breast tenderness, nausea, insomnia, and depression is increased.

Progesterone-Containing Intrauterine Device
Studies have shown that progesterone-containing intrauterine devices (Mirena, Progestasert) reduce menstrual flow.[50]

Precautions
An intrauterine device may be difficult to insert in a woman who has not experienced vaginal delivery, and it may not be effective for a submucous fibroid.

Birth Control Pills
Birth control pills have been shown to reduce menstrual flow.

Dosage
Either daily dosing or the newer 3-month (Seasonal) dosing is effective.

Precautions
All the precautions considered when the pill is prescribed for contraception are relevant here.

Nonsteroidal Antiinflammatory Drugs
Studies have shown that NSAIDs, such as ibuprofen and naproxen (Aleve), reduce menorrhagia by 20% to 50%.

Dosage
The dose of naproxen is one to two 220-mg tablets or capsules every 12 hours. The dose of ibuprofen is 400 mg every 4 to 6 hours.

Precautions
All NSAIDs can increase gastric discomfort and raise the risk of gastrointestinal bleeding.

Tranexamic Acid (an Antifibrinolytic Agent)
Tranexamic acid has been approved for treatment of menorrhagia at doses of 650 mg three times daily during menses. It is very effective and is without serious negative effects.

Natural Hormones

Natural Progesterone
The optimal ratio for progesterone to estradiol during the reproductive years ranges from 100:1 to 300:1. Estrogens are measured in picograms (a trillionth of a gram), and progesterone is measured in nanograms (a billionth of a gram), so the progesterone levels in nanograms per deciliter should be multiplied by 1000 to calculate the ratio.

Preparations of 3% progesterone cream[51] supply 400 mg of progesterone per 2-oz. jar. Vaginal suppositories can contain 100 to 400 mg progesterone per suppository. For heavy menstrual bleeding, vaginal applications of progesterone may be more helpful.[52]

Dosage
The dose of 3% progesterone cream is approximately ¼ teaspoon twice/day for the 2 weeks of the luteal part of the cycle, to supply 20 to 40 mg/day. A 10% cream supplies approximately 100 mg per application and may be necessary to balance estrogens in a patient receiving bioidentical hormone therapy or in cases of severe progesterone need.

Precautions
If excessive amounts of cream are applied to adipose tissue rather than thin skin, sadness or depression may result. Stimulating estrogen receptors can lead to short-term breast cysts or tenderness. Progesterone can exacerbate intestinal yeast problems. In the presence of sugar dysregulation, progesterone can raise insulin-like growth factor-I levels in the breast and may increase atypical breast cell formation. Studies of mifepristone (RU-486), the progesterone receptor antagonist, suggest a role for progesterone in fibroid growth. Clinically, I have witnessed fibroid growth in progesterone-deficient women when progesterone was used therapeutically. This seems to be more of a problem with larger fibroids. High body burdens of lead can also interfere with progesterone effect.

Dehydroepiandrosterone
DHEA reduces IL-6, a potent inflammatory cytokine that can promote the production of estrogens in the body. DHEA stimulates the peroxisome proliferator-activated receptor-gamma receptor, thus reducing inflammation, increasing insulin sensitivity, and reducing estrogen levels by maintaining healthy sugar metabolism and normal insulin levels. It also helps balance the effects of stress on the body by being in equilibrium with cortisol.

Dosage
The dose of DHEA is 5 to 10 mg one or twice/day. The dose of 7-keto DHEA is 25 to 50 mg/day.

Precautions

DHEA can convert to estradiol. Use of the 7-keto form may obviate this issue. Following hormone levels is always necessary when supplementing.

Surgical Treatment

The conventional approach to dealing with uterine fibroids remains largely surgical.[1] Total abdominal hysterectomy—removal of the uterus with cervix, ovaries, and fallopian tubes—is the most common procedure recommended. Subtotal procedures are also performed. These procedures may leave the cervix (supracervical hysterectomy) or the ovaries and fallopian tubes. Hysterectomy can also be performed by the vaginal or laparoscopic route. Robotic laparoscopies are now performed at some centers.

Hysterectomy and other invasive procedures are not without consequence. Postoperative recovery can take up to 4 to 6 weeks. Infectious complications can affect 10% of women. Major injuries to bladder, bowel, ovaries, and ureters happen approximately 1% of the time.

Myomectomy involves removal of the fibroid only, thereby preserving the uterus. Myomectomy can also be performed abdominally or through the laparoscope.

Myolysis techniques require the use of an energy source, which is applied to the fibroid through various instrumentation methods. The energy used may be ultrasound, laser, or electrical. The interior of the fibroid is destroyed, and the fibroid shrinks. The U.S. Food and Drug Administration has approved a myolysis[53] procedure using magnetic resonance imaging guidance and ultrasound as an energy source (ExAblate).

Uterine artery embolization is another procedure that effectively reduces blood flow to the fibroid and hastens shrinkage. Inert polyvinyl alcohol particles are placed in the uterine artery through an artery in the upper thigh.

Except for total hysterectomy, all these procedures have one thing in common: the fibroids grow back. Complications of the procedures include infections, pain, and injuries to major organs in the area, such as ureters, bowel, and bladder.

Other Therapies to Consider

Unblocking the energy of the second chakra is an approach to treatment of uterine fibroids.

Castor Oil Packs

Castor oil packs are hot packs made with wool flannel and hexane-free castor oil. Evidence suggests that they work through the lymphatic system and reduce inflammation. The castor oil pack is applied over the fibroid for 20 to 60 minutes per session. This device is a very effective meditation and visualization tool. The patient meditates on her uterus and visualizes the fibroid shrinking. She also visualizes the blood supply to the fibroids as pipes with turnoff valves and, while doing the meditation, visualizes turning off the valves, thus shutting down the blood supply to the fibroids. The spiritual aspects of healing come into play here.[54]

Through meditation and visualizing the healing of their fibroids, patients are instructed to be aware of any thoughts, feelings, or memories that can be associated with stagnation of second chakra energy and subsequent growth of the fibroid. The classic second chakra issues include relationship issues, not only with people but also with jobs, money, control, and the outside world. Creativity issues may also be expressed here. Abuse issues may come up also and can be related to physical, emotional, or sexual abuse. The idea is to remove these blockages to the healthy flow of energy from the pelvis, where they are creating stagnation and the growth of the fibroid. The release of these issues can be ritualized by having the patient journal everything that comes up and then put the pages into a bowl and burn them—letting them go.

Acupuncture and Deep Pelvic Massage

Acupuncture and deep pelvic massage (Mayan massage is one technique) are other ways of moving or restoring pelvic energy. These modalities are all complementary with the other approaches presented here.

Homeopathy

The following homeopathic remedies can be quite effective in reducing symptoms, as specified:

- Aurum muriaticum: to reduce size of fibroids
- Belladonna: for heavy, red bleeding
- Hydrastinum muriaticum: for large anterior wall fibroids with bladder symptoms
- Ignatia: for grief associated with fibroids
- Medorrhinum 200 C: fibroid: for benign tumors
- Phosphorus 6 C, 200 C: for bright red bleeding with no clots
- Sabina: for bright red bleeding with clots and for severe cramps
- Secale: for almost black blood and for profuse bleeding
- Sepia: for pressure and anger
- Silicea 6 C: for heavy bleeding; for cold, thin, and fatigued patients
- Thlaspi bursa pastoris 6 C (shepherd's purse): for frequent, heavy dark bleeding

See Chapter 111, Therapeutic Homeopathy.

Prevention Prescription

- Consume a hormone-balancing, vegetarian-style, low–saturated fat diet, including soy, green tea, ground flaxseed, omega-3 fatty acid, and cruciferous vegetables.
- Follow a moderate-exercise program (4 to 5 hours/week).
- Reduce xenobiotic (hormone-like) exposures such as pesticides, atrazine (herbicide), and polycyclic aromatic hydrocarbons (found in diesel exhaust), and avoid petroleum-based cosmetics.
- Maintain an appropriate weight.
- Practice stress modification techniques.
- Take a high-potency multivitamin and multimineral supplement.
- Foster healthy digestion and elimination.
- Maintain healthy relationships and have a sense of purpose in life.

Therapeutic Review

This integrative, holistic approach to healing fibroid tumors of the uterus can help avoid some of the more invasive therapies offered. It is very effective in reducing the symptoms associated with these benign tumors. I initially ask patients to commit to a 3-month trial period, during which they will do as much of the program as possible.

At the end of these first 3 months, we assess symptoms, such as menorrhagia and dysmenorrhea, and any growth or shrinkage of the fibroids. The program is considered successful if the patient perceives a reduction in symptoms and no further fibroid growth has occurred. We then continue the program for 3-month periods while continuing to monitor symptoms and uterine size. If at any time symptoms recur or worsen or the fibroids begin to grow, other more aggressive measures must be considered, including surgery.

Lifestyle

- Maintain an appropriate weight.
- Avoid xenoestrogens (dioxins, polychlorinated biphenyls) by eating organic foods.
- Obtain regular aerobic exercise.

Nutrition

- Follow a hormone-balancing diet. The patient should consume a diet that reduces inflammation, acidity, and hormone, pesticide, and antibiotic residues; these foods may encourage the growth of fibroids. High–glycemic index foods similarly should be avoided because of their effects on insulin and sex hormones. Gluten grains also increase estrogens through action of the phase 1 cytochrome P-450 enzyme 3A4 and must be limited. The patient should add foods that will be hormone balancing, such as soy and flaxseed. She should approximate the Asian diet, with 30 to 70 mg/day of isoflavones and 2 tablespoons of ground flaxseed per day. Omega-3 fatty acids, found in foods such as wild Pacific salmon and sardines, should be consumed at approximately 2 to 4 g/day and are also antiinflammatory.
- Reduce intake of saturated fats and trans fatty acids (red meat, dairy, fried foods)
- Increase intake of omega-3 fatty acids (vegetables, nuts, flaxseed, cold-water fish)
- Eat a low–glycemic index diet.
- Avoid gluten as much as possible and completely if gluten sensitive.
- Eat cruciferous vegetables (broccoli, cabbage, cauliflower, Brussels sprouts).
- Drink 3 cups of green tea daily.

Gut and Detoxification Restoration

- The clinician should restore hormone balance and remove sources of inflammation by looking for and healing intestinal dysbiosis and supporting liver detoxification.
- Search for and treat hidden sources of gut dysbiosis, such as heavy metal overload, parasites, and food sensitivities.

Supplements

Add nutrients to support hormone metabolism:

- B-50 complex vitamin daily.
- Magnesium salts are taken at 400 to 600 mg/day.
- Maintain vitamin D_3 levels in the range of 40 to 100 ng/mL.
- Support normal levels of vitamin A to reduce menorrhagia.
- Citrus bioflavonoids, 1000 mg once or twice/day, can also reduce menorrhagia.
- Zinc needs to be at optimal level; consider supplementing if low.
- Indole-3-carbinol or diindolylmethane are taken at 200 to 800 mg/day to reduce estrogen dominance.
- Calcium D glucarate is taken at 500 mg twice/day to reduce increased enterohepatic recirculation of estrogens.

Hormones

- Natural progesterone cream 3% can help restore hormone balance. Use ¼ teaspoon twice/day from day 14 to day 28 of the cycle. If this is not enough, increase to 10% cream, add progesterone as a vaginal suppository, or place a progesterone-containing intrauterine device (IUD). Submucous fibroids may preclude the use of an IUD.
- Insufficiencies in adrenal or thyroid hormones can and have been shown to increase symptoms related to fibroids. Assess and treat low thyroid levels and adrenal insufficiency.
- DHEA has important implications related to the immune system, sugar metabolism, and stress modification. If the DHEA level is low, add 5 to 20 mg of DHEA/day. Watch for conversion to estrogens.

Botanicals

- Add botanicals to reduce heavy bleeding:
  - Red raspberry leaf and yarrow are used for 2 weeks before the period at 30 drops each; once the period starts, add 30 drops of shepherd's purse.
  - Botanicals to support lymphatic drainage from the pelvis are also added. These consist of Gaia herbal combinations such as Scudder's alterative and Echinacea/Red Root formulas. They are taken twice/day at 30 drops each.

Continued

- antiangiogenesis factors such as Convolvulus and green tea extract may reduce blood flow to the fibroids. 
- To reduce inflammation, add antiinflammatory systemic enzymes (Wobenzyme, Vitalzyme, Neprinol) up to 15 tablets/day in divided doses taken on an empty stomach. 

Mind-Body Therapies

- Meditation and visualization exercises using castor oil packs help restore health to the pelvic organs by allowing for the free flow of energy in the second chakra through the corresponding meridians. These activities also help identify stored emotional issues in these energy areas of the body and their impact on the fibroid. 

Conventional Therapies

- Should the less invasive and more natural approaches fail to reduce the symptoms or growth of the fibroid, one can resort to the time-tested, more invasive conventional approaches. These powerful tools should be considered when necessary. The integrative holistic approach can still be used to help prevent any further growth of fibroids after the conventional treatment is performed.
- Surgery (hysterectomy) 
- Strong pharmaceuticals: Leuprolide acetate (Lupron), 3.75 mg intramuscularly once a month for up to 6 months 
- Interventional radiographic procedures 

KEY WEB RESOURCES	
Genova Diagnostics: www.gdx.net Gaia Herb: www.gaiaherbs.com Herbpharm: www.herb-pharm.com	Source for the Comprehensive Digestive Stool Analysis used to diagnose intestinal dysbiosis
Metametrix Clinical Laboratory: www.metametrix.com	Source for the Organix test of protein digestion
Doctor's Data: www.doctorsdata.com	Source for essential and toxic elemental testing. Source for standardized herbal tinctures

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Chapter 56

Vaginal Dryness

Myrtle Wilhite, MD

Pathophysiology and Epidemiology

Vaginal dryness is defined as a reduction in lubrication of the luminal surface of the female vagina. It can occur at any age.

- Dryness alone may cause discomfort; other symptoms may include itch or dyspareunia. See Table 56-1 for risk factors.
- Often, a change in serum estrogen levels is a precipitating factor in vaginal dryness, as can happen with the use of oral contraceptives or loss or blockade of ovarian estrogen production.
- Vaginal dryness prevalence ranges from 13% to 31%,[1] although rates are significantly higher for postmenopausal women (50%),[2] as well as in women treated for breast cancer (63%).[3]
- Vaginal atrophy (also known as atrophic vaginitis or urogenital atrophy) is an inflammation of the vagina (and the outer urinary tract) associated with thinning and shrinking of the tissues, as well as decreased lubrication. The prevalence of vaginal atrophy in postmenopausal women is 43% in the United States, but it varies by nation.[4]

Vaginal dryness can be further classified as *simple* or *complex*.

- Simple vaginal dryness suggests that the vagina and neurovasculature are healthy and functional, and resolution of the dryness solves the problem.
- Complex vaginal dryness indicates multiple factors, and the additional components often interfere with therapeutic resolution of the condition. Complex issues such as diabetes, hypertension, vaginal atrophy, or high-tone pelvic floor dysfunction may complicate therapy. Vaginal stenosis or inflexible pelvic floor muscles may prevent internal massage of the vagina and must be addressed before remediation of vaginal dryness can progress.

Physiology of Vaginal Lubrication

Vaginal lubrication consists of ultrafiltered blood, and thus is reliant on healthy blood flow.

- The vagina contains no glands.
- Blood pressure pushes fluid from the capillaries through intercellular gap junctions between vaginal epithelial cells.[5] The resultant vaginal transudate is mainly composed of water and very small proteins that combine at the vaginal surface with dead epithelial cells.
- Sufficient pelvic blood flow depends on the bioavailability of nitric oxide (NO). Gaseous NO is produced in capillary endothelia in response to shear stress or in response to sexual arousal through parasympathetic nitrergic nerves.[6] Once produced, NO induces vasodilation through a cyclic guanosine monophosphate cascade, which diminishes as phosphodiesterase enzymes break down the cascade.
- Therefore, vaginal lubrication production depends on the synthesis, enzymatic facilitation, and bioavailability of NO (Box 56-1). The enzymatic function of NO synthase is enhanced by steroid hormones, most notably estrogen in a rapid-action nongenomic effect.[7]
- The presence of NO is not sufficient for its effect. Many biologic feedback mechanisms suppress the production of NO, because high production of NO in an inflammatory environment can lead to irreversible free radical production.[8] Metabolic conditions of low inflammation support the bioavailability of NO in facilitating vaginal lubrication.

The vagina's lubrication comes not from glands but from a transudative fluid expressed through vaginal epithelial cells. Transudation requires adequate perfusion and nitric oxide.

TABLE 56-1. Risk Factors for Vaginal Dryness

Reduced Estrogen Availability	Postpartum status, breast-feeding Menopausal transition Premature ovarian failure Oophorectomy Pelvic radiotherapy
Other Medical Conditions	Untreated hypertension Diabetes (types 1 and 2), metabolic syndrome Pituitary disorders Neuropathies, especially autonomic neuropathy Dermatoses (psoriasis, lichen sclerosis, Sjögren syndrome)
Prescription Medications	Antihistamines and decongestants Antidepressants (SSRIs, atypical, TCAs) Antiestrogen therapy for chemoprophylaxis Antiestrogen therapy for endometriosis or fibroids Chemotherapy Diuretics Progesterone predominant oral contraceptives
Unwise Behaviors	Dehydration, including alcohol use Use of douches, extremely hot baths, or strong detergents and dehydrating soaps Use of highly absorptive tampons Use of male condoms with insufficient external lubricant Lack of sufficient arousal before vaginal penetration Smoking

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

BOX 56-1. Manipulation of Nitric Oxide Function

Production of Nitric Oxide
Sufficient L-arginine from Mediterranean diet
- Nuts (peanuts, almonds, walnuts, hazelnuts)
- Fruits (berries, chocolate)
- Beans
- Some meats (fish, chicken)
- Some seeds (sunflower, flaxseed)

Sufficient dietary calcium

Facilitation of the Activity of Nitric Oxide Synthase
Hormones
- Estrogen: rapid nongenomic effect
- Estrogen, soy phytoestrogens, testosterone: genomic effect

Medications and supplements
- Niacin (recouples nitric oxide synthase)
- Angiotensin converting-enzyme inhibitors
- Angiotensin II receptor blockers
- Ginseng

Other
- Presence of high-density lipoprotein
- Reduction of hyperglycemia

Prolonged Activity of Nitric Oxide and Cyclic Guanosine Monophosphate
Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil)

Bioactivity of Nitric Oxide
Medications/supplements
- Aspirin
- Vitamin D (decreases inducible nitric oxide synthase)
- Ginkgo (decreases inducible nitric oxide synthase and nitric oxide scavenger)
- Red wine, plant polyphenols and flavanoids

Other
- Routine moderate exercise

Pathophysiology of Vaginal Epithelium

Mature vaginal epithelial cells produce and store glycogen, which is released during normal cell death and provides nutritional support for *Lactobacillus* species. *Lactobacillus* uniquely releases hydrogen peroxide during metabolism and thereby acidifies the luminal vaginal pH. The vaginal maturation index[9] correlates strongly with noninfected, noninflamed vaginal pH, and both values can be used to assess the health of vaginal tissue.

Changes in the tissue and function of the vagina during the menopausal transition (perimenopause) are highly influenced by declining levels of sex hormones. Waning estrogen levels cause decreased cellular maturation (vaginal maturation index decreases; pH increases), decreased mitotic activity of the basement membrane (reduced cellular renewal), decreased collagen synthesis (weaker dermal structure), and thickened dermoepidermal junctions (making it more difficult for capillary fluid to move through to the surface).[11] All these factors lead to a dry, immature, weakened cellular structure, which is more susceptible to friction damage and decreased repair capacity.

Antiestrogen therapy can lead to moderate to severe vaginal atrophy.[12] Selective estrogen receptor modulators, such as tamoxifen, increase mucin production and maturity of vaginal epithelium[13] while simultaneously reducing blood flow to vaginal tissues in experimental models.[14] Aromatase inhibitors cause severe vaginal dryness resulting from estrogen production suppression.[15]

Integrative Therapy

Topical Vaginal Lubricants

Topical lubricants are inexpensive, easy to use, and highly effective for addressing vaginal dryness.[16] Although all sexual lubricants should reduce friction, some lubricants also increase the *moisture* content of the vaginal surface, whereas others excel at *sealing* the surface effectively and thus holding moisture in place. A successful outcome lies in knowing how to choose the right lubricant, and experimentation is highly encouraged because the specific needs of an individual may not be easily ascertained without home trials. Both the chemical properties and the comfort in use determine the degree of client acceptance and long-term compliance.

TABLE 56-2. Features of Commercially Available Lubricants

PRODUCT	BASE	pH	MOISTURE	SEALS	THICK/THIN	COMMENTS
Astroglide	Water	6.5	No	No	Thin	Glycerin/high osmolality
Astroglide X	Silicone	N/A	No	Yes	Thin	
Carrageenan	Water	4.4	Yes	No	Thick	Normal osmolality
KY Intrigue	Silicone	4.4	No	Yes	Thin	
KY Silk-E	Water	3.8	Yes	Yes	Thin	Aloe
Liquid Silk	Water and silicone	5.2	Yes	Yes	Thin	Medium to high osmolality
Maximus	Water and silicone	5.0	Yes	Yes	Thick	High osmolality
Pre~	Water	7.0	Yes	No	Thin	Normal osmolality
Pink (aka Gun Oil)	Silicone	4.6	Yes	Yes	Thick	Aloe
Replens	Petroleum oil	2.8	Yes	Yes	Thick	Medium to high osmolality
Sliquid Organics Silk	Water and silicone	6.5	Yes	Yes	Thin	Aloe
Surgilube	Water	N/A	No	No	Thick	Glycerin/high osmolality

N/A, not available.

Base ingredients determine function and acceptability of genital lubricants. The two main base ingredients are water or polymers (silicone or oil). In general, the most effective lubricants have the following properties:

1. They incorporate both moisturizing and moisture-sealing qualities.
2. They have a pH compatible with vaginal pH (4.4-6.5).
3. They do not have allergenic or contact irritant components.
4. They meet the physical slip and cushion needs of the user.

Water-based lubricants: Water-based lubricants tend to be the most moisturizing; however, some are formulated at such high osmolality that they actually dehydrate the skin after use. Examples of lubricants that increase skin dehydration include Astroglide17, Surgilube, and KY Jelly.

- Ingredients are often added to increase slip or cushion. Examples include: glycerin, hydroxymethylcellulose, and propylene glycol. Glycols, glycerin, and cellulose are digestible by vaginal bacteria (primarily *Lactobacillus*) and may lead to unwanted bacterial or yeast overgrowth.

Polymer-based lubricants: Silicone-based (inorganic polymers) and oil-based (organic polymers) lubricants have the capacity to seal in moisture, but they are much more difficult to remove from skin. In addition, they can cause falls if they are spilled on tile or smooth surfaces, and they may stain fabrics.

- The type of oil matters. Petroleum-based (aliphatic) oils are strong solvents, highly effective at dissolving latex (an elastic hydrocarbon polymer of *cis*-1,4-polyisoprene), and are not easily cleared from the vaginal lumen. Oils composed of fatty acids (olive, avocado, and coconut) are relatively weak bipolar solvents and do not appear to degrade latex products.[18] However, olive oil goes rancid easily, avocado may stain sheets a green tint, and coconut is difficult to clear over time from the intravaginal lumen.

Preservatives deserve special mention.

- Preservatives are compounds that inhibit or kill unwanted contaminants in solutions. They can be classified into four main categories: detergents (nonoxynol 9, phenoxyethanol), oxidants, chelating (parabens) and metabolic inhibitors (quaternary ammoniums, and organomercurials).
- No perfect preservative for vaginal use exists. Some detergents (nonoxynol 9) have been shown to increase human immunodeficiency virus transmission,[19] whereas others are known to be mild to severe contact allergens (parabens, phenoxyethanol, quaternium compounds).
- Of the available preservatives, methylparaben (which acts as a chelating agent useful against molds and yeasts) has the lowest toxicity. Although parabens are very weakly estrogenic (1000 times less effective at binding estrogen receptors than estrogen),[20] the use of methylparaben has far less impact than using other more harmful preservatives or topical hormonal (estrodiol or estriol) options.

No topical botanical formulation has met utility criteria for vaginal application. Because of the possibility for contact dermatitis, no topical herbal or botanical extract can be recommended at this time.

Table 56-2 gives relevant properties of commonly available sexual lubricants. Although no one lubricant will meet the needs of every person or couple, suggested over-the-counter lubricants with different properties are listed below. Formulations and availability change quickly, however, so check for availability locally or on the Internet.

Liquid Silk Lubricant

Liquid Silk has both moisturizing (water-based) and moisture-sealing (dimethicone) features without glycerin or aloe. It is available in 10-mL sample packets, the pH is 5.2, and it is comfortable for most premenopausal and postmenopausal women.

Dosage
Massage Liquid Silk into the vulva and vagina as needed or after a shower or bath, up to three times daily. Press-release (rather than stroke) is used when skin is fragile or easily torn. This agent is very useful for vulvar dermatoses such as lichen sclerosis and psoriasis.

Precautions
Nonglycerin Liquid Silk is formulated with propylene glycol and parabens, both of which can be skin irritants. Paraben levels are lower in this European product than in U.S. formulations.

Pink Silicone Lubricant
Pink Silicone Lubricant is a combination product, but contains more silicone proportionally than the aloe and water base. It is more useful as a moisture sealer than as a moisturizer, adding cushion during sexual intimacy for premenopausal or postmenopausal women. The pH is 4.5, and it is available in 5-mL sample packets.

Dosage
Pink is more useful than water-based lubricants for reducing friction during vaginal penetration. Some couples massage this onto the partner before penetration.

Precautions
Pink contains aloe, which can cause dermatitis. The pH is fairly acidic, and some women report a burning sensation.

Sliquid Organic Silk Lubricant
Sliquid Organic Silk is a combination product that incorporates a water base with silicone (dimethicone) without glycerin. It is preserved with phenoxyethanol. This partly organic formulation is available in 5-mL sample packets. The pH is 6.5, which is comfortable for some women but irritatingly high for others.

Dosage
This agent is massaged into the vulva and vagina as needed, up to three times daily. Press-release (rather than stroke) when skin is fragile or easily torn.

Precautions
This agent contains aloe, which can cause dermatitis.

Vaginal Renewal Program

Regular vaginal penetration through sexual activity has been associated with enhanced sexual function in postmenopausal women.[21] However, some women lose sexual function rapidly, and experience sudden-onset dyspareunia, which prohibits sexual activity. The Vaginal Renewal (VR) program helps women recondition the health and flexibility of the skin of the vulva and vagina by reducing friction tearing of vulvar skin, as well as increasing blood flow to the vulva and vaginal canal. VR is indicated for women just beginning to feel the effects of hormonal changes, women who have completed pelvic radiation therapy,[22] and women with vaginal atrophy who experience skin tearing and pain when they attempt vaginal penetration.

Dilation is not the goal; blood flow is. During the development of the VR program, we found that vibrating wands were more effective in improving function than static (nonvibrating) dilators. Hard plastic vibrating wands caused less tissue trauma than dilators with soft, textured, or adhesive surfaces tore fragile vaginal epithelium too easily.

VR is completely compatible with topical estrogen therapies, and the combination can be more effective and faster-acting than estrogen or VR alone. Many women experience enough improvement from the combination of estrogen therapy and VR that they are able to discontinue the use of estrogen completely. The VR program does not require the use of estrogen, however, and is preferred by clients and clinicians when topical estrogen is contraindicated.

Precaution
Because comfortable penetration depends on the flexibility of both the skin and the pelvic floor muscles, some women recondition their vaginal skin only to experience uncomfortable or painful penetration because their pelvic floor muscles are inflexible. Referral to a pelvic floor physical therapist is indicated before continuing VR, and no further vaginal penetration should be attempted until a pelvic floor muscle evaluation is completed. VR is contraindicated for persons with vaginismus or an aversion to touching their own genitals.

Specific Situations
Vaginal Dryness Causing Daily Discomfort
1. Choose a moisturizing lubricant, and place it by toilet or use after shower.
2. Dispense a nickel- to quarter-sized amount on the fingers.
3. Use a press-release motion over the entire vulva. Apply additional lubricant as needed if it soaks into skin.
4. Dispense another nickel- to quarter-sized amount on the fingers.
5. Use a press-release motion and a rolling motion and apply to the inner labia, introitus, and perineum.
6. Repeat one or twice daily as needed.
7. If dryness is felt internally, insert 1 mL lubricant using a vaginal applicator at night.

Rehabilitation of Vaginal Dryness With Atrophy
1. Follow the instructions for daily moisturizing.
2. In the clinic, help the client choose an appropriately sized vibrating wand.
   a. The diameter of wand is the most important criterion; choose one that can be inserted comfortably at pelvic examination. A smaller diameter is always better. The client can graduate to a larger size when a finger can be placed beside the wand comfortably during vaginal penetration.
   b. Low-Hertz vibration is more effective than high-Hertz vibration.
3. Instruct the client to do the following:
   a. At home, lubricate the wand.
   b. Turn on the massage wand.
   c. In a reclining position, insert the wand into the vagina to the deepest comfortable depth.
   d. Lie back and let the wand vibrate for 5 to 10 minutes.
   e. Remove the wand and clean with soap and water.
   f. Repeat daily to three times weekly, as needed.

Dryness-Related Dyspareunia

1. Follow the earlier instructions for moisturizing and rehabilitation. Only proceed with sexual intimacy when no pain or discomfort is felt with largest massage wand size.
2. Lubricate penetration object (penis, fingers, glass or steel dildo) with a silicone-based lubricant before penetration.
3. If the penetration object is made of silicone, cover the object with a nonlubricated condom, and apply silicone lubricant to the outside of the condom.

Other Behaviors

Smoking Cessation

Smoking causes functional changes in endothelial health that enhance oxidative stresses.[23] Because smoking is a known risk factor for vaginal dryness,[24] smoking cessation strategies should be pursued as a part of a comprehensive strategy.

Habitual Physical Exercise

Exercise is an effective way to combat vascular aging and enhance the function of small vessel blood flow,[25] including vaginal perfusion.[26] Aerobic exercise positively affects NO (Fig. 56-1),[27] and it is linked to improved endothelial and cardiovascular health.[28]

Dosage

Walk once per day, for 30 to 60 minutes to the level of a gentle sweat. Walking before anticipated sexual activity improves vaginal lubrication as well as subjective symptoms of arousal[29] (see Chapter 88, Writing an Exercise Prescription).

Precautions

Vigorous exercise is not indicated, but exercising to the level of a gentle sweat is sufficient. Walking is ideal.

Nutrition

Dietary reduction in inflammation assists NO -dependent blood flow. For example, despite the increased incidence of sexual dysfunction in women with diabetes,[30] adherence to a Mediterranean diet is associated with a lower prevalence of sexual dysfunction in this patient population.[31]

Mediterranean Diet

A low-glycemic, low-carbohydrate, Mediterranean diet positively manipulates endothelial health and NO bioavailability. Increasing NO bioavailability *before* NO production is beneficial because increasing NO in the presence of inflammatory or oxidized conditions worsens NO bioavailability and damages endothelia directly.

- First, focus consumption on initially increasing both lipid-based and water-based antioxidants, and reduce high–glycemic index foods that spike blood glucose levels and increase insulin resistance (see Chapter 85, The Glycemic Index/Load).
- Second, increase food consumption that targets protein levels of L-arginine (see Box 56-1). Fortunately, these foods are beneficial to satiety, and many incorporate both antioxidants and L-arginine simultaneously.
- Finally, consider whether soy phytoestrogens may be of benefit. Experimentally, fermented soy may also function as a free radical scavenger.[32]

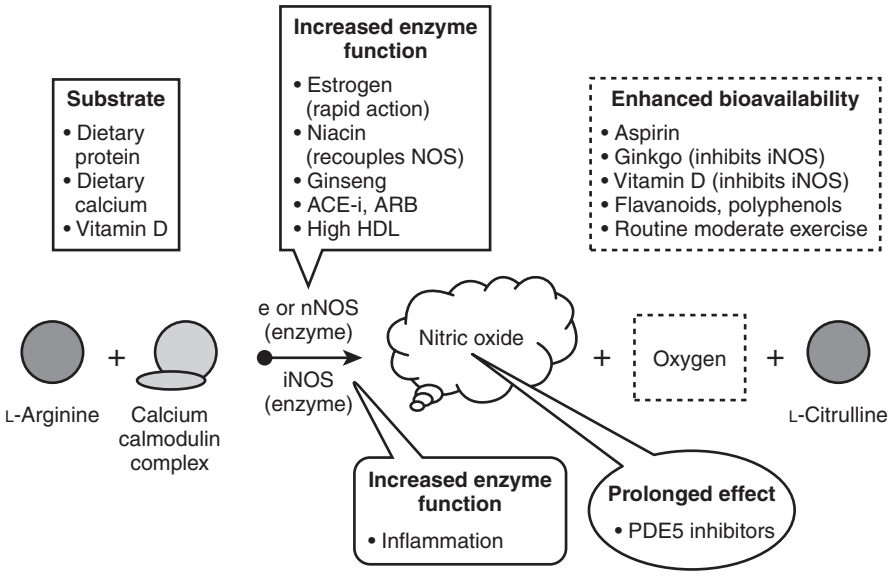
Dosage

Adhere strictly to a Mediterranean diet, with small meal portions and between-meal grazing on nuts and dried berries or cherries (see Chapter 86, The Antiinflammatory Diet).

Precautions

Soy consumption (90 mg isoflavone/day) has shown positive effects on vaginal dryness,[33] but safety is in question,[34] particularly for Western populations.[35]

FIGURE 56-1
Nitric oxide interventions. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; PDE5, phosphodiesterase-5.



Supplements

Vitamin D_3

Vitamin D_3 plays an important role in assisting dietary calcium, manipulating calcium at neural membranes, and in formation of the calmodulin cofactor required for NO production. Vitamin D also independently acts as a free radical scavenger, so increases the bioavailability of NO after production.

Dosage

The initial dose is vitamin D_3, 2000 units orally per day. It is taken with fish oil and calcium citrate. After 1 month, check blood levels of 25(OH)D, and aim for a serum level of 50 ng/mL. For women with more pronounced menopausal symptoms, aim for a serum level of 60 ng/mL.

Precautions

Calcium metabolism and kidney disorders, as well as some inflammatory disorders (sarcoidosis, tuberculosis), are worsened with vitamin D therapy.

Fish Oil (Highly Purified Omega-3 Fatty Acid)

Omega-3 fatty acids assist in the absorption of vitamin D and act as lipid-based antioxidants helping neural function.

Dosage

The dose is 2 to 4 g orally per day. It is taken with vitamin D and calcium. It may be stored in the freezer to reduce "fish burps."

Precautions

Fish oil and omega-3 fatty acids act as anticoagulants, so the dosage must be modified in women taking heparin, warfarin (Coumadin), selective serotonin reuptake inhibitors, aspirin, ginkgo, high-dose garlic, or other potentially blood-thinning regimens.

Calcium Citrate

Sufficient extracellular calcium is required for NO production.

Dosage

The dose is 250 mg orally per day. It is taken with vitamin D and fish oil.

Precautions

Adherence to the Mediterranean diet provides the remainder of calcium needed for vitamin D to use. However, high-dose calcium supplementation (more than 1000 mg/day) is associated with adverse effects,[36] and it is not recommended. Calcium carbonate is not easily absorbable.

Niacin

Reversal of endothelial dysfunction is well addressed with niacin therapy.[37]

Dosage

The dose is 1000 mg two to three times per day.

Precautions

Warn about a flushing reaction. A prolonged incremental increase beginning at 100 mg/day is most successful. Initially, niacin may exacerbate vulvar dermatoses because recoupling of NO production temporarily enhances inflammation.[38]

L-Arginine (as Supplement)

This acts as the protein substrate for NO production.

Dosage

The dose is 500 to 1000 mg daily.

Precautions

Dietary supplementation is more strongly suggested than direct supplementation. L-Arginine may cause hyperglycemia, hypotension, and nausea. It is contraindicated in kidney disease. High serum levels of L-arginine and L-citrulline (byproduct) also act as feedback inhibitors of NO production.

Botanicals

Ginkgo (Ginkgo biloba)

Ginkgo acts on nitric oxide vasodilation in several different ways.[39] It modulates NO second messenger action, scavenges excess NO, inhibits NO production under inflammatory conditions, and inhibits platelet activation.

Dosage

The dose of *Ginkgo biloba* extract 50:1 is 60 mg twice daily. The dose may be increased to 120 mg twice daily.

Precautions

Use ginkgo cautiously with anticoagulants, nonsteroidal antiinflammatory drugs, including aspirin, or high dietary intake of garlic.

Ginseng (Panax ginseng)

Ginseng facilitates endothelial NO release and is a potent antioxidant.

Dosage

The dose is 1 to 2 g root tea infusion three times daily.

Precautions

Ginseng has potential phytoestrogenic activity.[40] It may cause agitation and insomnia.

Not Recommended

Attempts to reverse vaginal dryness with oral black cohosh[41] and topical genistein[42] have been unsuccessful. Damiana *(Turnera diffusa)* blocks progesterone receptors without receptor activation but may boost unopposed estrogen activity.[43]

Pharmaceuticals

Estriol

A 2-week regimen of vaginal daily estriol cream improves vaginal dryness,[44] and it may be indicated as initial therapy in severe cases of vaginal atrophy.[45]

Dosage

The dose of estriol cream is 1 mg intravaginally per day for 2 weeks. It is tapered to three times per week for 2 months, then discontinued. Concurrent use of the VR program may allow earlier taper and prevent recurrence.

Precautions

In breast cancer survivors taking aromatase inhibitors, estriol causes measurable systemic changes suggestive of an estrogen effect.[46]

Estriol is the main estrogen of pregnancy that helps prepare the vagina for delivery. However, estriol does stimulate breast cell proliferation (although less than estradiol) and should be used only as very short-term therapy in cases of severe dysfunction (see the earlier discussion of vaginal renewal for nonhormonal therapy).

Phosphodiesterase-5 Inhibitors

Physiologically, phosphodiesterase-5 inhibitors reduce insulin resistance in endothelial capillaries,[47] in addition to prolonging vasodilation. This produces a beneficial genital perfusion effect in women.[48]

Dosage

Phosphodiesterase-5 inhibitors can be utilized in two different ways. They can be used at a very low dose nightly to increase sleep-related genital perfusion.[49] Alternatively, they can be tried for on-demand sexual activity, taken 30-60 minutes prior to sexual activity. The dose is 12.5 to 100 mg daily. It may be taken at night to reduce symptoms of nausea or hypotension and assist sleep-related perfusion. The client should experiment to determine whether timing before sexual intimacy improves vaginal lubrication.[50]

Precautions

Sildenafil may cause nausea, headache, nasal congestion, renal or hepatic impairment, hypotension, change in vision, and ototoxicity. It is contraindicated with nitrates and alpha$_1$ blockers.

Not Recommended

Oral raloxifene is not recommended for vaginal dryness.[51]

Prevention Prescription

- Maintain regular exercise and movement to enhance blood perfusion to the perineum.
- Consume a Mediterranean diet that is rich in berry fruits, nuts, vegetables, and whole grains, and low in red meat and processed carbohydrates. Focus on foods with high L-arginine levels.
- Favor beverage choices of tea (black, green, red, or white), coffee, or water.
- Maintain therapeutic or sexual vaginal penetration (once a week) to stimulate vaginal lubrication and elasticity.
- Experiment to find a topical sexual lubricant that is comfortable and moisturizes the vulva and vagina.
- Check vitamin D levels and supplement to keep the level higher than 50 ng/mL.
- Take calcium citrate, 250 mg daily with vitamin D.
- Take 2 to 4 g daily of an omega-3 fish oil.
- Avoid tobacco products.

Therapeutic Review

Three main strategies are used for resolving vaginal dryness without hormones, and they are most effective when combined. The first two strategies use the Vaginal Renewal program.

- Use a client-matched topical lubricant (see Table 56-2). B$_1$
- Use massage and vibration to create shear stress on the endothelial capillaries, thus increasing blood flow and vaginal lubrication. C$_1$
- Holistically address diet and lifestyle issues that help facilitate the production and bioavailability of nitric oxide (NO; see Box 56-1 and Fig. 56-1). B$_1$

Nutrition

- First, reduce overall metabolic inflammation with strict adherence to a Mediterranean diet with daily exercise. This approach enhances NO bioavailability and reduces the potential for increasing inflammatory free radical production. B$_1$
- Then, focus the diet more specifically on foods high in L-arginine, and selectively strip high-glycemic foods from the diet. Address satiety with proteins. C$_1$

Supplements

- Consider adding L-arginine, 500 mg daily, to enhance NO production. B$_2$
- Calcium citrate: 250 mg daily, B$_1$
- Vitamin D: 2000 units daily B$_1$
- Omega-3 fish oil: 2 to 4 g daily B$_2$

Botanicals

- *Ginkgo biloba* extract 50:1: 60 mg twice daily C$_2$
- *Panax ginseng:* 1-2 g root tea infusion three times daily C$_2$

Pharmaceuticals

- Use an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for treatment of hypertension (instead of a beta blocker or diuretic). B$_1$
- To increase high-density lipoprotein and recouple NO production, consider niacin, starting at a very low dose and gradually increasing to 1000 mg two to three times a day. B$_2$
- Consider whether phosphodiesterase-5 inhibitors (sildenafil, 12.5 to 100 mg daily) may facilitate daily genital perfusion to increase genital blood flow and vaginal lubrication. B$_2$
- For severe cases, have estriol cream compounded at 1 mg/g of cream, and apply to the vulva and intravaginally daily for 2 weeks. Then reduce to three times per week for 2 months and discontinue. Utilize the Vaginal Renewal program concurrently for faster recovery. B$_2$

KEY WEB RESOURCES

Dietary Fiber Food: http://www.dietaryfiberfood.com/larginine-high.php	List of foods high in L-arginine
A Woman's Touch: http://www.sexualityresources.com	Information on the Vaginal Renewal program (Dr. Wilhite is an owner of this Web site and business.)
University of Michigan Healing Foods Pyramid: http://www.med.umich.edu/umim/food-pyramid/index.htm	Food pyramid of the Mediterranean Diet

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Chapter 57

Benign Prostatic Hyperplasia

David Rakel, MD

Pathophysiology

Even though benign prostatic hyperplasia (BPH) is one of the most common diseases of aging men, its etiology remains relatively unknown. From our current understanding, BPH appears to be related to age, androgens (dihydrotestosterone [DHT]), estrogens, and detrusor dysfunction of the bladder neck. An accumulation of DHT inhibits prostatic cell death, promotes cell proliferation, and thus increases the size of the gland (Fig. 57-1).

As a man passes his fifth decade, serum testosterone levels decrease, and estrogen (as well as prolactin, luteinizing hormone, and follicle-stimulating hormone) levels rise. Estrogen increases the number of androgen (DHT) receptors in the prostate and inhibits androgen metabolism by interfering with hydroxylation. As urinary outflow obstruction develops, the detrusor muscles of the bladder try to compensate by increasing pressure to expel urine, a process that leads to instability of the muscle and worsening symptoms. In summary, factors that promote the accumulation of DHT and estrogens lead to symptoms of BPH and obstruction of the lower urinary tract that, in turn, cause detrusor muscle dysfunction. Stimulation of the alpha-adrenergic system leads to contraction of the smooth muscle fiber that further restricts flow in an enlarged prostate gland. Finally, reason exists to believe that prostaglandins, leukotrienes, and insulin resistance play roles in the inflammatory process of the prostate.

Components of the metabolic syndrome have been shown to cause prostatic enlargement.[1,2] Insulin resistance and truncal obesity appear to be the main culprits.[3] Elevated insulin levels increase sympathetic nerve activity and also bind to insulin-like growth factor (IGF) receptors that stimulate prostate cell growth.[4] Excessive amounts of visceral fat also increase the circulation of estradiol and further stimulate prostate cell growth by increasing DHT levels (Fig. 57-2). Obesity, metabolic syndrome, and insulin resistance also increase systemic inflammation, which is also correlated with the incidence of BPH.[5]

Light to moderate alcohol consumption has been associated with a protective effect on BPH and lower urinary tract symptoms. The association of light to moderate alcohol consumption with an improvement in insulin sensitivity[6] and a decrease in testosterone concentrations[7] may help explain the beneficial influence of alcohol. This positive effect is not seen in men with high alcohol consumption, however.[8] Consuming seven or more alcoholic drinks per week is associated with worsening symptoms.[9]

Integrative Therapy

Table 57-1 gives the mechanism of action of common pharmaceuticals, botanicals, and supplements used for BPH, and Table 57-2 gives information on botanicals and hormones that can worsen symptoms of BPH.

Nutrition

Soy

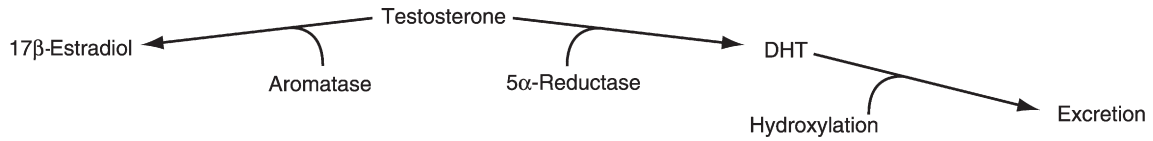
Soy is thought to work in two ways. It is an inhibitor of 5-alpha-reductase, and it is a low-potency estrogen. Soy may block the receptor sites that the stronger estrogens use to increase the accumulation of DHT. Consumption of nonfermented soy products (tofu, soy milk, edamame) has also been found to result in a decreased incidence of prostate cancer.[10,11]

Beta-sitosterol (a major phytosterol found in soy) was found to increase urinary flow and decrease residual volume in the bladder in a double-blind placebo-controlled study using a 20-mg dose.[12] A 3.5-oz serving of soybeans, tofu, or another soy food preparation provides approximately 90 mg of beta-sitosterol.[13] A 1-oz preparation (which is a portion approximately the size of the palm of the hand) equals approximately 25 mg.

Cholesterol

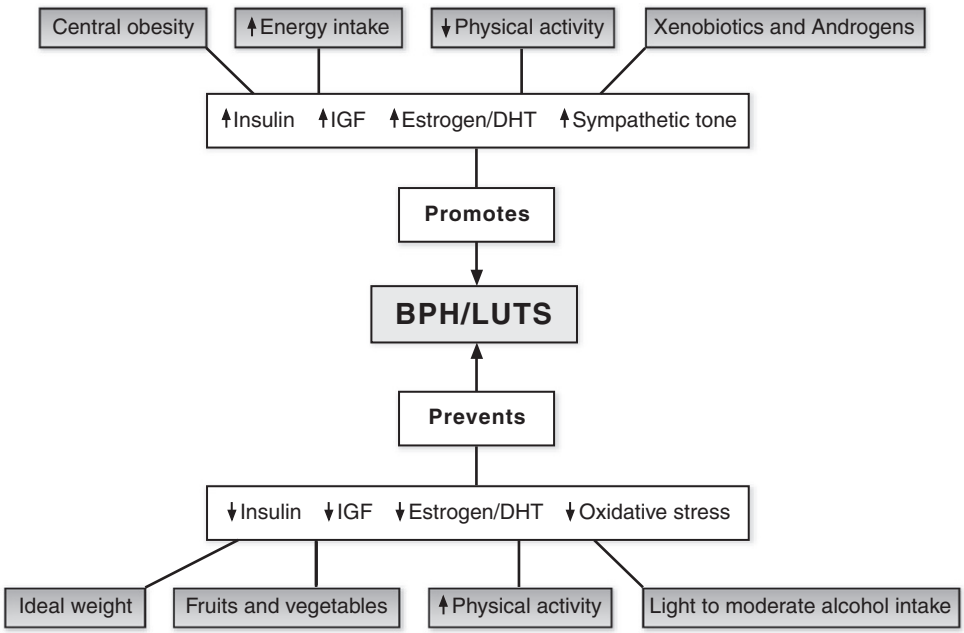
Cholesterol has been associated not only with BPH but also with prostate cancer. Cholesterol metabolites (epoxycholesterols) have been found to accumulate in the hyperplastic

FIGURE 57-1
Inhibitors of aromatase, 5-alpha-reductase, and hydroxylation. BPH, benign prostatic hyperplasia; DHT, dihydrotestosterone.



Inhibitors of Aromatase (↓Estrogen)	Inhibitors of 5α-Reductase (↓DHT)	Inhibitors of Hydroxylation (↑DHT)
Aminoglutethimide (Cytadren)	Finasteride (Proscar, Propecia)	Estrogen
European studies have found no benefit for the treatment of BPH	Saw palmetto *(Serenoa repens)*	
	Zinc	
	Soy	

FIGURE 57-2
Influences affecting the promotion and prevention of benign prostatic hypertrophy (BPH) and lower urinary tract symptoms (LUTS). DHT, dihydrotestosterone; IGF, insulin-like growth factor.



and cancerous prostate gland. For this reason, hypocholesterolemic drugs (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors or "statins") have been associated with a lower risk of BPH and prostate cancer.[14] In addition, treating the dyslipidemia of metabolic syndrome (high triglycerides, low high-density lipoprotein) with exercise and a low–glycemic index/load diet (see Chapter 85, The Glycemic Index/Load) may also prove beneficial because of the association of BPH with metabolic syndrome. Foods high in cholesterol and saturated fat are also rich in arachidonic acid, which is the main precursor of inflammation. Reducing consumption of these foods can benefit BPH by reducing inflammatory triggers.

Omega-3 Fatty Acids

A diet rich in omega-3 fatty acids helps reduce the influence of prostaglandins and leukotrienes on the inflammatory component of BPH (see Chapter 86, The Antiinflammatory Diet). Recommend foods rich in omega-3 fatty acids such as cold-water fish (salmon, mackerel, and sardines), vegetables, and ground flaxseed or flaxseed oil. Flaxseed oil can be taken in capsule form. Recommend lignan-rich flaxseed oil, two to four 500-mg capsules twice a day. Patients can also buy whole flaxseeds, grind 2 tablespoons (approximately 30 g) of the seeds, and sprinkle the ground flaxseed on salads or yogurt or add it to a smoothie. Flaxseed has the added benefit of lignan fiber, which helps bind estrogen in the gut and thus promotes estrogen removal.

TABLE 57-1. Mechanism of Action of Common Pharmaceuticals, Botanicals, and Supplements Used for Benign Prostatic Hyperplasia

MECHANISM OF ACTION	THERAPY
Alpha$_1$-Adrenergic Blockade	Alfuzosin (Uroxatral) Doxazosin (Cardura) Prazosin (Minipress) Tamsulosin (Flomax) Terazosin (Hytrin)
5-Alpha-Reductase Inhibition	Finasteride (Proscar) Dutasteride (Avodart) Saw palmetto *(Serenoa repens)*
Antiproliferative Action	African wild potato *(Hypoxis hemerocallidea)* Beta-Sitosterol Lycopene Pumpkin seed *(Cucurbita pepo)* Pygeum *(Prunus africana)* Red clover *(Trifolium pratense)* Soy Stinging nettle root *(Urtica dioica)*
Antiinflammatory Action	Rye grass pollen *(Secale cereale)* (Cernilton)

Modified from http://naturaldatabase.com.

TABLE 57-2. Products That Can Worsen Symptoms of Benign Prostatic Hyperplasia

MECHANISM OF ACTION	PRODUCT
Sympathetic stimulation: Increases tone of prostatic stroma, causes constriction of urethra, and can also stimulate bladder spasm	Bitter orange Ephedra Country mallow Yohimbe
Anticholinergic stimulation: Makes urination more difficult by inhibiting bladder contraction and causing urinary retention	Henbane Scopolia Jimson weed Wild lettuce
Hormonal stimulation: Accelerates growth of the prostate	Androstenediol Dehydroepiandrosterone (DHEA) Androstenedione Pregnenolone

Adapted from Lee M. Management of benign prostatic hyperplasia. In: *Pharmacotherapy: A Pathophysiological Approach*. 5th ed. New York: McGraw-Hill; 1999.

Supplements

Beta-Sitosterol

Beta-sitosterol is a sterol found in almost all plants. It is one of the main subcomponents of a group of plant sterols known as phytosterols that are very similar in composition to cholesterol. These plant sterols are the active ingredients in popular margarine spreads (Take Control, Benecol) used to lower cholesterol. Beta-sitosterol is found in rice bran, wheat germ, peanuts, corn oils, and soybeans. High levels are also found in botanicals such as saw palmetto, rye grass pollen, pygeum, and stinging nettles, which have been found to be beneficial for BPH. Unlike cholesterol, beta-sitosterol cannot be converted to testosterone. It is also inhibits aromatase and 5-alpha-reductase. Beta-sitosterol is likely one of the many reasons that eating vegetables is good for health. Encourage adequate consumption of these plants in the diet.

Two randomized studies showed a benefit of beta-sitosterol in treating BPH, with little potential harm.[15,16] This benefit persisted for up to 18 months of use.[17] A Cochrane Review found beta-sitosterol to improve urinary symptoms and flow measures. This supplement does not appear to reduce the size of the prostate gland.[18]

Dosage

The dose is 60 mg twice daily. This dose can be reduced to 30 mg twice daily after symptoms improve.

Precautions

Beta-sitosterol is well tolerated. Gastrointestinal side effects are the most common. This supplement can enhance the cholesterol-lowering effects of antihyperlipidemic medications.

Zinc

Intestinal uptake of zinc is inhibited by estrogen. Because estrogen levels increase in aging men, men with BPH may have low zinc levels. In fact, marginal zinc deficiency is common in older adults, and in men it may worsen the symptoms of BPH. In the 1970s, research showed that supplementing with zinc resulted in a reduction in the size of the prostate gland and in symptoms of BPH.[19] Further research showed that zinc inhibits 5-alpha-reductase,[20] and it also inhibits the binding of androgens to their receptors in the prostate.[21] This effect on androgens is thought to result from zinc's ability to inhibit prolactin, which, like estrogen, increases the receptors for DHT in the prostate. Therefore, zinc not only decreases the production of DHT, but it also inhibits DHT binding to its receptors.

Coffee can decrease zinc absorption by 50%. Because caffeine stimulates the adrenergic nervous system (smooth muscle of the prostate), encourage patients with BPH to limit their intake.

Prescription drugs that can result in low serum zinc levels include thiazide diuretics, steroids, methotrexate, tetracyclines, and fluoroquinolones. Consider zinc supplementation in those patients with BPH who are taking these medications. Do not give zinc to patients taking tetracycline or fluoroquinolone antibiotics, however, because zinc can affect the absorption of these drugs. Pumpkin seeds are a rich source of zinc, and this may explain their potential therapeutic benefit for BPH.

Dosage

The dose of zinc is 30 mg per day.

In prescribing zinc supplementation, be aware that zinc competes with copper, calcium, and iron absorption. Make sure that the patient does not take more than the recommended dose and does not take calcium and iron supplements with zinc.

Botanicals

Saw Palmetto (Serenoa repens)

Saw palmetto has been found to be a weak inhibitor of 5-alpha-reductase, but it may have a more active role in reducing the number of estrogen and androgen (DHT) receptors, as well as an antiinflammatory effect on the prostate. Saw palmetto inhibits fibroblast growth factor and epidermal growth factor and stimulates apoptosis, thus further slowing prostate cell proliferation. Its principal ingredient, the sterol beta-sitosterol, is also found in soy products (see earlier), as well as in other herbs used to treat diseases of the prostate including pygeum bark, stinging nettle root, and pumpkin seed extract.

Saw palmetto reduces the inner prostatic epithelium but does not reduce the size of the gland. Nonetheless, saw palmetto has been found to improve symptom scores, nocturia, residual urine volume, and urinary flow in patients with BPH. It does not affect prostate-specific antigen (PSA) levels.[22] In a large randomized study, saw palmetto was found to be as effective as finasteride (Proscar) but without the drug's side effects, and the International Prostate Symptom Score (IPSS) was reduced by 37%.[23] However, a more complete evaluation of 30 randomized trials by a 2009 Cochrane Review of 5222 subjects concluded that no significant difference existed between *Serenoa repens* (saw palmetto) and placebo for the treatment of urinary symptoms related to BPH.[24]

Although the evidence for BPH improvement is marginal, saw palmetto has three positive influences on the prostate gland: it is antiandrogenic, antiproliferative, and antiinflammatory.

Dosage

The dose is 160 mg twice daily. Allow 8 weeks before seeing therapeutic benefit.

Precautions

Mild adverse effects have included headache, nausea, diarrhea, and dizziness. Saw palmetto does not influence the cytochrome P-450 enzyme system of the liver, and drug interactions are rare.

> The most beneficial saw palmetto extract is composed of at least 85% fatty acids and 0.2% sterols. For example, a 160-mg pill should have a minimum of 136 mg fatty acids and 0.32 mg sterols.

Product lines that have been proven to be composed of at least 85% fatty acids and 0.2% sterols include the following: Nature's Way, CVS, Centrum, Natrol, Bayer, Quanterra, Sundown Herbals, NaturPharma (Walmart), and Walgreens.

Rye Grass Pollen (Secale cereale)

Rye grass pollen is also known as grass pollen and grass pollen extract. Clinical studies used a form called Cernilton (flower pollen), a brand manufactured by Cernitin. This has been bought by the company Graminex and is now marketed under the name of PollenAid.

This extract has been used in Europe for BPH since the 1970s. Double-blind clinical studies found it to be effective, with an overall response rate near 70%.[25] Rye grass contains a substance that has been found to inhibit prostatic cell growth[26] and reduce inflammation of the prostate by inhibiting prostaglandins and leukotrienes.[27]

Studies have shown the greatest improvement in nocturia, urinary frequency, and residual urine volume.[28] Rye grass and flower pollen are also used for symptomatic relief of prostatitis and prostatodynia.

Dosage

The typical dose of rye grass pollen is 126 mg three times daily. A standardized extract 20:1 of *Secale cereale* can be obtained through the following companies: Graminex PollenAid, 500 mg three times daily, or Pure Encapsulations ProstaFlo, 320 mg three to five capsules per day in divided doses.

Precautions

Abdominal distention, heartburn, and nausea may occur. This product is not likely to cause allergy because allergenic proteins are removed in the manufacturing process.

Pygeum africanum (*synonym:* Prunus africana)

Pygeum is obtained from the bark of the African plum tree. As with saw palmetto, its benefits are thought to come from fatty acids (sterols) that reduce inflammation through the inhibition of prostaglandins, as well as prostatic cholesterol levels that are precursors to testosterone production. Pygeum also increases prostatic and seminal fluid secretions.

A meta-analysis revealed that men taking pygeum had a 19% reduction in nocturia and a 24% reduction in residual urine volume. Peak urine flow was increased by 23%, and side effects were mild and similar to those reported with placebo.[29] The TRIUMPH study included treatment outcomes of BPH from six European countries. After 1 year of therapy, participants who received either *Pygeum africanum* or *Serenoa repens* (saw palmetto) showed a 43% improvement in IPSS scores and improvement in quality of life compared with no treatment.[30]

Pygeum is more expensive than saw palmetto, and overharvesting of the bark is threatening the survival of the species.

Dosage

The dose is 100 to 200 mg each day.

Precautions

Nausea and abdominal pain may occur.

Pharmaceuticals

Alpha-Adrenergic Blocking Agents

The TRIUMPH study mentioned earlier followed 2351 men with BPH.[30] After 1 year, those therapies that showed the most benefit in IPSS scores were, in descending order; alpha blockers (68%), finasteride (57%), and *Serenoa repens* or *Pygeum africanum* (43%) compared with watchful waiting. Of the therapies discussed, the alpha blockers are likely to give the most subjective improvement. Blocking the alpha-adrenergic system results in relaxation of the smooth muscle fibers of the prostate gland, with reduction of symptoms and improved urinary flow. The response is rapid (within hours), and studies have shown long-term efficacy.

The most commonly used drugs, terazosin (Hytrin) and doxazosin (Cardura), require dose titration to avoid postural hypotension. The newer and more expensive alpha$_1$-adrenergic antagonist tamsulosin (Flomax) is more specific for the prostatic tissue, thus reducing the incidence of hypotension and the need to titrate the dose.

Dosage

For terazosin (Hytrin), start at 1 mg nightly and titrate every week to effect, up to a maximum of 20 mg. Terazosin is available in 1-, 2-, 5-, and 10-mg formulations. For doxazosin (Cardura), start at 1 mg nightly and titrate every week to effect, up to a maximum of 8 mg. Doxazosin comes in 1-, 2-, 4-, and 8-mg formulations. The dose of tamsulosin (Flomax) is 0.4 mg 30 minutes after a meal every day, up to a maximum of 0.8 mg per day. Tamsulosin is available in a 0.4-mg formulation.

Precautions

Postural hypotension, dizziness, fatigue, headache, nasal stuffiness, and retrograde ejaculation may occur.

5-Alpha-Reductase Inhibition

Finasteride prevents the conversion of testosterone to DHT and lowers DHT serum levels. This drug can take as long as 6 months to work, but it appears to halt the progression of prostate growth. In terms of patient satisfaction and symptom reduction, finasteride is not a great drug unless the goal includes treatment of male-pattern baldness. Finasteride causes a 50% reduction of PSA.

Dosage

The dose of finasteride is 5 mg once a day, and it comes in 5-mg tablets. The dose of dutasteride is 0.5 mg once daily, and it is available in 0.5-mg tablets.

Precautions

Decreased ejaculatory volume (2.8%), impotence (3.7%), and decreased libido (3.3%) have been reported. These drugs can take up to 6 months to show benefit.

Surgery

When severe symptoms are not controlled with the previously discussed therapies, consider urologic referral for minimally invasive therapy or surgical resection, as follows:

- Transurethral microwave thermotherapy (TUMT) uses a microwave antenna that generates heat in the transition zone and results in coagulation necrosis. This procedure is performed on an outpatient basis.
- Transurethral needle ablation (TUNA) involves the placement of small needles in the prostate via cystoscopy that emit radiofrequency energy resulting in necrosis of prostatic tissue.

The minimally invasive procedures described here have decreased morbidity compared with transurethral resection of the prostate but are not as effective in reducing symptoms, and no tissue is obtained for pathologic evaluation.

- Transurethral resection of the prostate (TURP) is the gold standard and will likely result in the greatest symptomatic improvement (95% of patients have improved symptoms). Complications such as incontinence (1%), blood transfusion (3% to 5%), retrograde ejaculation (20% to 75%), and stricture formation (5%) are becoming less severe with the use of laser prostatectomy that reduces bleeding. TURP is the most invasive procedure (except for open prostatectomy) and requires a hospital stay.
- Transurethral incision of the prostate (TUIP) involves endoscopic placement of one to two incisions along the prostatic capsule to reduce urethral constriction. This procedure has been found to be effective (83% of patients have improved symptoms) and safe for men with smaller glands (smaller than 30 g) who may not need TURP.

Prevention Prescription

- Avoid excessive amounts of saturated fat, such as those found in red meet, fried foods, and dairy.
- Replace vegetable oils with olive or canola oil for cooking.
- Consume omega-3–rich fats found in cold-water fish, nuts, greens, and ground flaxseed.
- Consider light to moderate (1 glass or less daily) alcohol consumption.
- Eat plenty of natural plants, particularly those rich in beta-sitosterol, such as green leafy vegetables, rice bran, wheat germ, peanuts, corn oils, nuts, and soybeans.
- Encourage soy-based foods such as soy milk, edamame, soy nuts, and tofu. Try to eat 1 to 2 oz per day, and consider substituting soy milk for dairy milk.
- Avoid dietary supplements or environmental exposures that may increase circulating hormone levels such as pesticides, herbicides, and recombinant bovine growth hormone (rBGH)-rich dairy products. Also avoid drugs that include dehydroepiandrosterone (DHEA), androstenedione, testosterone, and human growth hormone.
- Maintain appropriate weight, and perform regular aerobic exercise.
- Treat metabolic syndrome with exercise, weight loss, and a low–glycemic index/load diet to reduce inflammation of the prostate (see Chapter 85, The Glycemic Index/Load, and Chapter 31, Insulin Resistance and the Metabolic Syndrome).

Therapeutic Review

This is a summary of therapeutic options for benign prostatic hyperplasia (BPH). A patient presenting with severe symptoms (BPH Symptom Index Score or International Prostate Symptom Score [IPSS] greater than 19) will benefit by jumping ahead to a more aggressive therapy such as alpha blockers or referral to a surgeon. For the patient who has mild to moderate symptoms, however, this ladder approach is appropriate (see Tables 57–1 and 57-2).

Removal of Exacerbating Factors

- Ask the patient to stop taking over-the-counter cold remedies or diet aids (phenylpropanolamine [PPA]), nasal decongestants (pseudoephedrine), herbs (ma huang, Ephedra), or caffeinated products that contain sympathomimetics, which increase prostatic muscle tone.
- Consider asking the patient to stop taking pharmaceutical products that have anticholinergic effects leading to urinary retention. These agents include antihistamines, bowel antispasmodics, bladder antispasmodics, tricyclic antidepressants, and antipsychotics.

Nutrition

- Increase soy-rich foods in diet. A 1-oz serving each day (approximately the size of the palm of the hand) provides approximately 25 mg. B1
- Encourage a low-fat and cholesterol-free diet. B1
- Encourage foods rich in omega-3 fatty acids (salmon, nuts, or flax), or take 1 tablespoon of lignan-rich flaxseed oil twice daily or 1 to 2 tablespoons of ground flaxseed twice daily. B1

Supplements

- Beta-sitosterol: 60 mg twice daily A1
- Zinc: 30–40 mg daily B2

Botanicals

- Start with Saw palmetto: 160 mg twice daily A1
- Or pygeum: 100 to 200 mg daily B1
- If no improvement occurs after 8 weeks, consider adding the following:
  - Rye grass pollen: 126 mg three times daily B1
    - Rye grass pollen has more of an antiinflammatory effect, which may act synergistically with saw palmetto or pygeum.
  - Other herbal products that have potential benefit include stinging nettles and pumpkin seed extract.

Pharmaceuticals

- If no improvement occurs with the use of botanicals, discontinue them and start an alpha-adrenergic blocker (see text for doses). A2
- If the patient is unable to tolerate an alpha blocker, consider finasteride, at 5 mg daily. A2

Surgical Therapy

- If the patient's symptoms persist or worsen despite the foregoing measures, refer for urologic evaluation and treatment, with the following options:
  - Transurethral microwave thermotherapy (TUMT) B2
  - Transurethral incision of the prostate (TUIP) B2
  - Transurethral resection of the prostate (TURP) A3

KEY WEB RESOURCES

American College of Physicians: BPH Symptom Index Calculator: http://cpsc.acponline.org/enhancements/238BPHSymptomCalc.html
Tool for calculating the BPH (Benign Pprostatic Hyperplasia) Symptom Index Score (also known as the International Prostate Symptom Score [IPSS])

AUA (American Urological Association) Foundation: Management of Benign Prostatic Hyperplasia: http://www.urologyhealth.org/urology/index.cfm?article=144
Patient Education on BPH

Mayo Clinic: Benign Prostatic Hyperplasia: http://www.mayoclinic.org/bph/treatment.html
Surgical Options for BPH

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References are available online at expertconsult.com.

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Chapter 58

Urolithiasis

Jimmy Wu, MD

Pathophysiology

Over the past few decades, an increasing percentage of the U.S. population has had the misfortune of experiencing the disabling pain that accompanies urolithiasis. The National Health and Nutrition Examination Survey (NHANES) reported that approximately 5% of persons in the United States will have experienced at least one symptomatic stone in their lifetime.[1] Notable epidemiologic risks include being white, male, and living in hot, arid regions.[2] As evidenced by Hippocrates' reference to "…persons laboring under the stone,…" in his famous oath, this common medical problem has challenged even history's most renowned healers.[3]

In addition to being responsible for so much morbidity in individual patients, kidney stones were estimated by a retrospective study to cost more than $5.3 billion in lost work hours and direct health care expenses in the year 2000.[4] Because most patients with idiopathic kidney stones have some underlying urine metabolic abnormality, the risk of recurrence is 40% at 5 years and 75% at 20 years.[5] This tendency for urologic stones to reemerge within the same people presents an opportunity for health care providers to promote a preventive and integrative approach in protecting against stone recurrence.

Data demonstrate certain epidemiologic disparities in gender, location, and race. For reasons that are still unclear, men consistently have a higher risk of developing kidney stones than do women. Geographically, the "stone belt," consisting of the southeastern U.S. region, also tends to have higher prevalence of renal lithiasis, likely because of its hotter climate. Finally, black U.S. residents appear to suffer less from this disease than do their white counterparts.[6]

To provide the most appropriate counseling, the clinician must understand how kidney stones form and what elements are commonly present in stones. Kidney stones are a product of normally soluble material (e.g., calcium, oxalate) supersaturating in urine to a level that facilitates crystallization of that very material (Fig. 58-1).[7] With this origin in mind, any approach that discourages urinary crystallization or promotes crystallization inhibition forms the basis for the preventive recommendations described in this chapter.

More than 80% of kidney stones primarily consist of calcium, usually calcium oxalate. These oxalate stones may also contain phosphate or uric acid. The remainder of kidney stones can be divided into stones that have uric acid, struvite (magnesium ammonium phosphate or infection stone), or cystine as their primary constituents. Most calcium stone formers possess some sort of urinary metabolic abnormality that can be detected with a 24-hour urine sample[7] (Table 58-1).

> Patients with recurring stones or with a stone manifesting before they are 30 years old should have a 24-hour urine test to check for high levels of calcium, oxalate, and uric acid or low levels of citrate.

Many patients (33% to 66%) who suffer from calcium-based kidney stones have hypercalciuria, which is mostly idiopathic but can be familial. The urine is supersaturated with a high enough level of calcium that calcium renal calculi begin to form. When patients also have accompanying hypercalcemia, other disorders must be ruled out (e.g., hyperparathyroidism, sarcoidosis, cancer).[8]

Similarly, patients who are found to have high urinary oxalate levels are predisposed to passing calcium oxalate stones. Hyperoxaluria has two main causes. A rare primary form is inherited as an autosomal recessive trait. The more common acquired form involves increased oxalate absorption secondary to ileal compromise and fat malabsorption (enteric fat does not absorb but rather binds to dietary calcium and thus allows for higher levels of absorbed oxalate).[9]

FIGURE 58-1
Kidney stones in the kidney, ureter, and bladder. (From National Kidney and Urologic Diseases Information Clearinghouse: <http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm>; Accessed 26.09.11.)

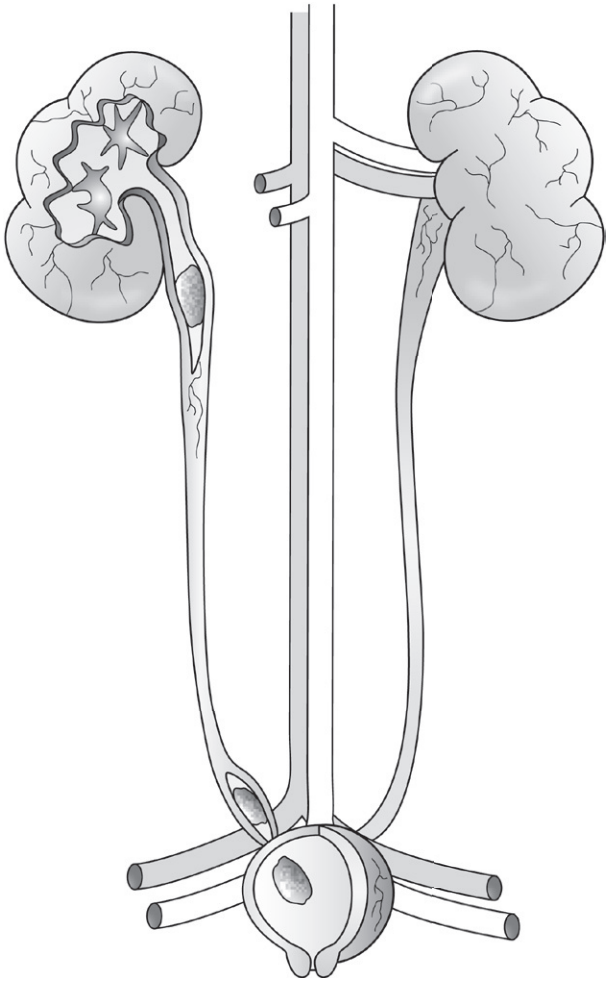


TABLE 58-1. Lithogenic Values of Urinary Biochemical Factors With Dietary Prescription

URINE FACTOR	24-HR URINE VALUE	DIETARY PRESCRIPTION
Fluid volume	Less than 2 L	Maintain total fluid intake at more than 2 L/day Reduce caffeine Stay more hydrated if strenuous physical activity
Calcium	Female: more than 250 mg Male: more than 300 mg	Maintain adequate dietary calcium intake Reduce sodium and animal protein intake Reduce calcium supplements Reduce carbohydrate intake
Oxalate	More than 40 mg	Maintain adequate dietary calcium intake Reduce dietary oxalate intake Avoid vitamin C supplements Increase magnesium-rich foods
Citrate	Female: less than 550 mg Male: less than 450 mg	Increase fruit and vegetable intake Reduce sodium and animal protein
Uric acid	Female: more than 600 mg Male: more than 800 mg	Reduce purine-high foods Reduce animal protein intake Reduce alcohol intake

Data from Graces F, Costa-Bauza A, Prieto RM. Renal lithiasis and nutrition. *Nutr J.* 2006;5:1-7; and Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. *Kidney Int.* 2006;70:835-839.

The third metabolic disorder found in patients with calcium stones is hypocitraturia. Citrate serves as a protective factor against calcium stone formation because it can chelate calcium in urine, thereby forming a soluble complex that is harmlessly excreted. Therefore, people with low levels of citrate in their urine are at risk for calcium stone formation.[9]

Of the disorders related to stones that are not composed of calcium, primary uric acid nephrolithiasis is the next most common (10%). Any factor that acidifies the urine pH (e.g., protein intake, insulin resistance) creates an environment more susceptible to stone formation. The other two factors that contribute to uric acid stone formation include low urinary volume (e.g., dehydration, diarrhea) and hyperuricosuria (e.g., enzymatic deficiency syndromes, drugs, gout).[10]

Struvite stones typically form in patients who have chronic urinary tract infections with urease-producing bacteria such as *Proteus* or *Klebsiella*. These patients classically develop staghorn calculi found in the renal pelvis. The stones consist of multiple magnesium ammonium phosphate crystals and calcium carbonate-apatite.[11]

Finally, cystine stones (1%) are the result of cystinuria, which is a rare genetic autosomal recessive metabolic disorder. Cystine stones should be considered in patients who have their first stone during childhood (median age, 12 years).[12]

Integrative Therapy

Nutrition and Supplementation

Any recommendation that limits lithogenic ingredients and promotes lithoprotective factors serves as the basis for the nutritional and supplemental suggestions given here (see Table 58-1; Table 58-2). The literature on the role of nutrition and supplements in kidney stone prevention is abundant, but solid evidence to support the dietary recommendations given here is lacking.

In general, people who have unhealthy lifestyles and develop qualities of the increasingly common metabolic syndrome are at increased risk for stone formation. A study that used NHANES data found strong associations between people who had various features of metabolic syndrome

TABLE 58-2. Foods High in Bioelements Related to Kidney Stone Formation

Lithoprotective		
CALCIUM (DIETARY)	**MAGNESIUM**	**CITRATE**
Milk	Almonds	Orange
Yogurt	Cashews	Lemon
Cheese	Soybean	Cranberry
Broccoli	Potato	Pineapple
Salmon	Nuts	High-citrate juices and sodas

Lithogenic		
SODIUM	**OXALATE**	**PURINE**
Potato chips	Rhubarb	Legumes
Canned foods	Spinach	Spinach
Frozen dinners	Chocolate	Red meat
Soy sauce	Peanuts	Alcohol
Table salt	Cashews	Sardines

Data from Office of Dietary Supplements, National institutes of Health: http://ods.od.nih.gov/factsheets/list-all/; Accessed 26.09.11; and Graces F, Costa-Bauza A, Prieto RM. Renal lithiasis and nutrition. *Nutr J.* 2006;5:1–7.

(e.g., obesity, hypertension, diabetes, hyperlipidemia) and stone formation. This finding underlines the overall importance of promoting healthy nutrition and physical activity in the prevention of kidney stones.[13–15]

Water

The dietary recommendation to increase fluid intake has strong scientific support for preventing recurrent renal lithiasis. Several observational studies dating to 1966 postulated that increased fluid intake is beneficial, and one randomized controlled trial in 1996 actually showed that fluid intake achieving a urinary volume of 2 L reduced the stone recurrence rate from 27% to 12%.[13,14,16,17]

A safe recommendation is to ask patients to drink 2 to 3 L of water per day. One approach is to tailor the fluid recommendation to the calculated urine volume from the 24-hour urine test. For example, if the 24-hour urine volume is 1.5 L, it will be best to advise the patient to drink two more 8-ounce ($2 \times 240 = 480$ mL) cups of water to achieve 2 L total.[18] Although no evidence exists for the following, some practitioners recommend that their patients maintain urine at a very light color. Some clinicians have also advocated drinking water at bedtime because urinary concentration usually occurs during sleep.[19] Endurance athletes with stones must be especially aware of their fluid loss through sweat. Furthermore, caution should be used when ingesting mineral water because it may contain calcium or other lithogenic material.

Beverages

A few studies examined the efficacy of encouraging or discouraging different types of beverages for the prevention of stones. In particular, fruit-based juices were studied because of their citrate (lithoprotective) content. However, vitamin C was shown to increase urine oxalate (lithogenic); not surprisingly, evidence for fruit-based juices remains ambiguous.[13] Several studies showed that grapefruit juice increases the risk for stones; conversely, lemon juice, orange juice, and cranberry juice have mostly been viewed as protective against renal stones.[6,13,20–23]

Not much is discussed about the role of soft drinks in stone formation, but the general recommendation is to limit soda consumption, possibly because of the caffeine content.[23,24] Caffeine, through a dilution effect, can increase the risk of calcium oxalate stone formation.[23] However, sodas with higher citrate content may theoretically neutralize any lithogenic effect.[21] Other caffeinated beverages such as coffee and tea (especially black tea) should also be avoided.[13]

Calcium (Dietary and Supplement)

Contrary to conventional wisdom, limiting dietary intake of calcium is not recommended. This conclusion was proven several times with strong evidence. Two prospective observational studies from the 1990s concluded that kidney stone formation was inversely associated with dietary calcium intake.[25–27] In addition, a 5-year randomized controlled trial comparing groups that differed by the calcium load in their diet proved that decreasing dietary calcium was a risk factor for symptomatic stone recurrence.[25,28]

The theory behind this conclusion is that dietary calcium protects against stone formation by binding with oxalate and thereby reducing urinary oxalate levels. It takes a smaller increase of urinary oxalate than of urinary calcium to precipitate stone formation. Therefore, a high urinary oxalate level is a larger risk factor in calcium oxalate stone formation. This finding explains why dietary calcium is actually lithoprotective.[26]

In contrast, investigators have suggested that the effect of calcium supplements is different. A 1997 study showed that calcium supplements in women resulted in a higher risk of calcium stone formation. The rationale for this finding was that the supplements were not taken with food, and calcium's function in reducing dietary oxalate absorption was thereby nullified. However, other data showed a neutral effect of calcium supplements in men and younger women.[18,25,27,29]

Oxalate

Despite several studies, no consensus exists regarding the effect of dietary oxalate on stone formation, even in patients with hyperoxaluria.[13] Because of its low bioavailability, dietary oxalate may not be readily absorbed.[6,18] Therefore, no firm recommendation can be made about limiting dietary oxalate, although such advice is not harmful. Oxalate-rich foods include nuts (almonds, peanuts, pecans, walnuts, cashews), vegetables (rhubarb, spinach), and chocolate.[13,18]

Vitamin C

Vitamin C can be metabolized to oxalate and therefore could increase risk of stone formation. One trial showed that supplemental vitamin C increased urinary oxalate excretion; however, no evidence indicates that vitamin C actually causes an increase in symptomatic stone formation. Therefore, recurrent stone formers should not be instructed to limit their dietary vitamin C intake, especially because foods high in vitamin C are also high in citrate. A reasonable approach is to suggest limiting supplemental vitamin C.[6,13,18,30]

Sodium
Studies showed that increased dietary sodium results in elevated calcium in the urine and reduced urinary excretion of citrate. This combination effect makes high sodium intake a potential risk factor for higher stone recurrence. One recommendation is that, especially for patients with hypercalciuria, sodium intake should be restricted to less than 3 to 6 g per day.[6,13,18]

Protein
An increase in dietary protein intake appears to raise urinary calcium and uric acid levels and decreases urinary citrate levels.[6,13,18] Therefore, reducing protein intake can also benefit patients with calcium and uric acid stones. Some studies examined combination diets, and participants who followed diets with a low-protein component had a lower stone recurrence rate.[31]

Carbohydrates
Some investigators postulated that a possible relationship between higher intake of carbohydrates or refined sugar and increased urinary calcium may be partially responsible for the higher rates of kidney stones in wealthier countries.[6] However, the association is too weak to recommend carbohydrate cessation to protect against stone recurrence.

Omega-3 Fatty Acid
Increased intake of dietary omega-3 fatty acids does not reduce the risk of kidney stone formation. However, using fish oil supplements as prevention is promising because small studies showed that these supplements reduced urinary excretion of calcium and oxalate.[25,32,33]

Purines
People with uric acid stones are generally advised to avoid a high-purine diet. Purine-containing foods include organ meats, legumes, mushrooms, spinach, alcohol, sardines, and poultry.[10]

Magnesium
In theory, magnesium binds to oxalate and thus potentially decreases the risk of calcium oxalate stones. Sparse data suggest that dietary and supplemental magnesium can lower the risk of stone formation in men.[25,20,34] Dietary magnesium can be mostly found in dairy products, meat, seafood, avocados, dark green vegetables, and cocoa.[13]

Botanicals and Other Herbal Medicines

Many studies have examined the potential use of various botanicals and herbs for prevention of stone formation. However, most studies have used in vitro or animal models. Only a few trials have demonstrated some promise within human models.[35]

Phyllanthus niruri (e.g., stonebreaker, chanca piedra) is a plant that has been studied and used in Brazil; it has been studied in the human population and has shown efficacy in preventing stone recurrence.[35] Other studied herbals include *Andrographis paniculata, Hibiscus sabdariffa,* and *Orthosiphon grandiflorus.*[35] Most of these are frequently taken as teas.

Phyllanthus niruri may potentiate insulin and other antidiabetic medications, as well as antihypertensive medications. Do not take during pregnancy.

Probiotics

Oxalobacter formigenes is an anaerobic bacterium responsible for degrading oxalate in the body. Investigators have postulated that a probiotic containing this species would be useful for preventing stone formation in patients with hyperoxaluria. There have not been many studies that have shown actual benefit in decreasing symptomatic stone incidents, but several have demonstrated the physiologic significance of this bacterium in decreasing urinary oxalate levels.[36,37]

Traditional Chinese Medicine

Acupuncture
Although data on acupuncture as a preventive measure for kidney stones are scant, this technique has been used extensively as an analgesic for both the acute renal colic presentation and for patients receiving a planned extracorporeal shock wave lithotripsy (ESWL) procedure.[38]

Some anecdotal evidence indicates that acupuncture using techniques that facilitate energy manipulation of the kidney and bladder can help with acute stone-related pain and with stone recurrence.[39]

Herbals
Limited data from the Kampo traditional Japanese herbal medicine tradition indicate that some herbal mixtures, including Chorei-to, Wullingsan, Jin Qian Cao, and Niao Shi mixture, have been helpful, mostly as diuretics, in stone prevention.[38,40]

Ayurvedic Medicine

Including *P. niruri* as described earlier, several Ayurvedic medicines are commonly used for nephrolithiasis management. These include *Tribulus terrestris, Orthospihon stamineus/grandiflorus* (Java tea), and *Dolichos biflorus* (horse gram).[40]

Pharmaceuticals

This discussion includes medications that have demonstrated efficacy for the prevention of stone recurrence. Management of acute nephrolithiasis-related symptoms (e.g., pain, nausea) is not discussed in this chapter.

Alkalinizers
This drug class primarily works to increase urine pH. Because uric acid stones tend to supersaturate in acidic urine, alkalinizers such as potassium citrate and sodium bicarbonate are mostly used to prevent documented uric acid stones. Potassium citrate is preferred because it can also reduce urinary calcium, and it provides citrate as a lithoprotective element.[41]

Dosage
The dose of potassium citrate is 10 mEq three times a day (if $U_{citrate}$ is greater than 150 mg/day) or 20 mEq three times a day (if $U_{citrate}$ is less than 150 mg/day) with meals, up to 100 mEq/day. It comes in 5- and 10-mEq pills.

The dose of sodium bicarbonate is 650 mg three times a day. It is available in 325-and 650-mg tablets, as well as in powder form.

Precautions

Potassium citrate may cause nausea or hyperkalemia (especially when it is taken with other medications that may cause hyperkalemia). Sodium bicarbonate may cause bloating.

Calcium Channel Blockers

This drug class has some data supporting its use as an "expulsive" medication that assists with stone passage. Nifedipine has as an antispasmodic effect on the ureter and eliminates the fast uncoordinated component of ureteral smooth muscle contraction. Most studies have examined its use with a steroid (25 mg/day of methylprednisolone), which has demonstrated a higher stone-expulsion rate, shorter expulsion time, and reduced need for analgesia.[41]

Dosage

The dose of nifedipine is 30 mg daily extended release (ER) for 20 to 30 days. It comes in 30-mg ER tablets.

Precautions

Nifedipine may cause flushing, peripheral edema, lightheadedness/dizziness, headache, and gastrointestinal upset.

Alpha$_1$ Channel Blockers

Alpha$_1$ channel blockers also work as antispasmodics, especially on the distal ureter. Several studies, especially of distal ureteral stones, demonstrated efficacy, with a higher stone-expulsion rate.[41]

Dosage

For doxazosin, start 1 mg at night and titrate every week to effect, to a maximum of 8 mg/day. It comes in 1-, 2-, 4-, and 8-mg tablets.

The dose of tamsulosin is 0.4 mg, taken 30 minutes after a meal daily, to a maximum of 0.8 mg daily. It comes in 0.4-mg tablets.

The dose of alfuzosin is 10 mg ER daily. It is available in 10-mg ER tablets only.

Precautions

Postural hypotension, dizziness, fatigue, headache, nasal stuffiness, and retrograde ejaculation may occur.

Medical expulsive therapy is recommended for stones up to 10 mm. Alpha blockers appear to perform better with stones 5 to 10 mm.[42]

Thiazide Diuretics

Because thiazides can lower calcium excretion by as much as 50%, they benefit patients with recurrent stones resulting from hypercalciuria. This drug class should be considered if recurrence persists despite appropriate dietary changes. Studies showed a 90% reduction in the incidence of new stones with thiazide therapy. Chlorthalidone can be given just once a day because of its lower half-life. However, the clinician should be wary of hypokalemia because low potassium can reduce urinary citrate excretion. To avoid hypokalemia, adding potassium citrate is advisable.[41]

Dosage

Hydrochlorothiazide is taken at 25 mg daily, but higher doses may be needed to achieve an adequate calcium-lowering effect. It comes in 12.5-, 25-, and 50-mg tablets.

Chlorthalidone is taken at 25 mg daily. It comes in 25-mg tablets.

Precautions

Hypokalemia, hyperuricemia, hyponatremia, dizziness, and headache may occur.

Xanthine Inhibitors

Frequently used in patients with gout, these medications can also be used for stone formers with hyperuricosuria (with either uric acid or calcium stones). Xanthine inhibitors interfere with the conversion of xanthine into uric acid.[10]

Dosage

The dose of allopurinol is 200 to 300 mg per day in divided doses once to three times a day.

Precautions

Be cautious in patients with renal failure.

Surgery

Most stones smaller than 4 mm are generally watched conservatively and are believed to have a 90% chance of passing by themselves, especially if they are found in the distal ureter. Stones between 4 and 6 mm have a dramatically smaller chance of passing (50%), whereas stones between 7 and 10 mm have only a 20% chance of passing spontaneously. Besides larger stones, stones that are located more proximally in the ureter have greater difficulty for spontaneous resolution.[42]

Surgery is considered for kidney stones that are believed to have a low chance of self-resolution. Surgical treatment includes lithotripsy, ureteroscopy, and percutaneous nephrostomy, and the choice of therapy depends on several factors, including position and size.

Extracorporeal Shock Wave Lithotripsy

Of the three surgical options, ESWL is the least invasive and considered to be first-line therapy in the appropriate context. Lithotripsy has been considered to be just as effective as ureteroscopy for stones that are smaller than 10 mm (86% versus 90% stone-free rate), regardless of location in the ureter. If the stone is larger, lithotripsy may have to be performed several times (Fig. 58-2).[43]

Serious complications of ESWL are not common, but the procedure can cause transient pain, hematuria, nausea, and vomiting. More life-threatening complications have been common in patients who have required multiple treatments for larger stones. Pregnancy, uncontrolled hypertension, uncontrolled coagulopathy, and distal obstruction to the stone are absolute contraindications.[43]

FIGURE 58-2
Extracorporeal shockwave lithotripsy. (From National Kidney and Urologic Diseases Information Clearinghouse: <http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm>; Accessed 26.09.11.)

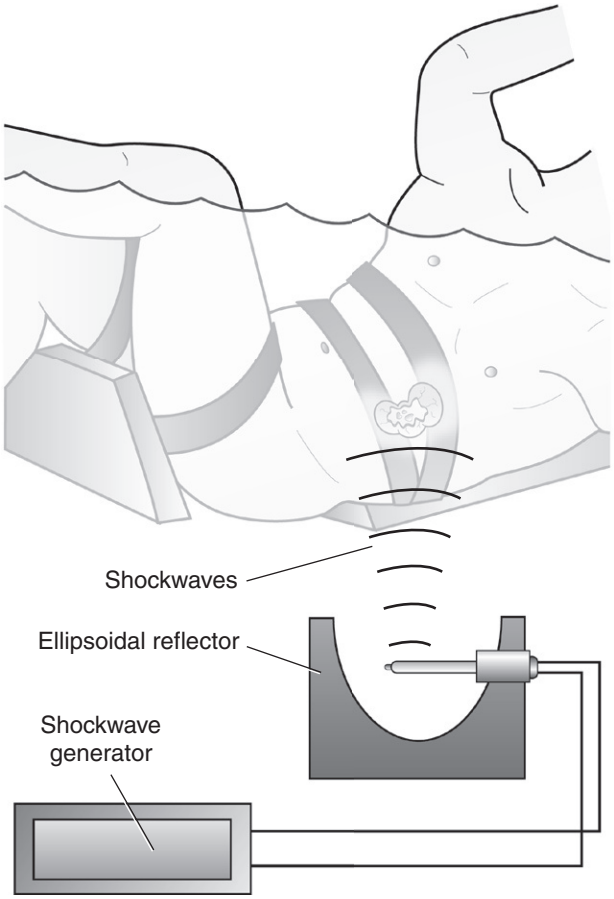
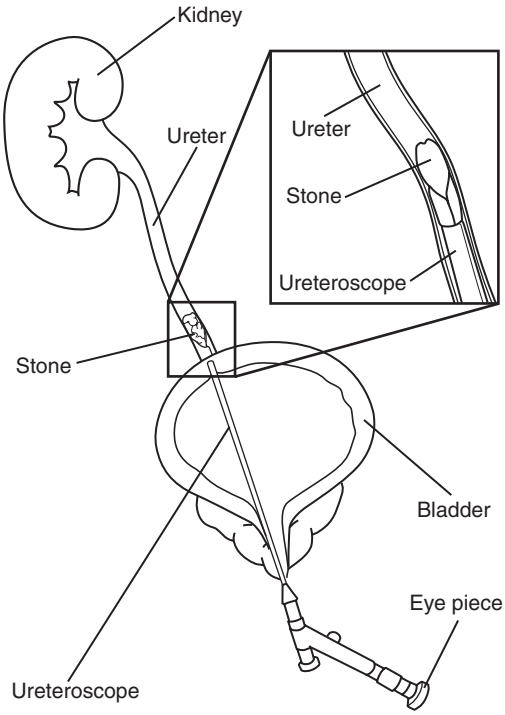


FIGURE 58-3
Ureteroscopic stone removal. (From National Kidney and Urologic Diseases Information Clearinghouse: <http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm>; Accessed 26.09.11.)



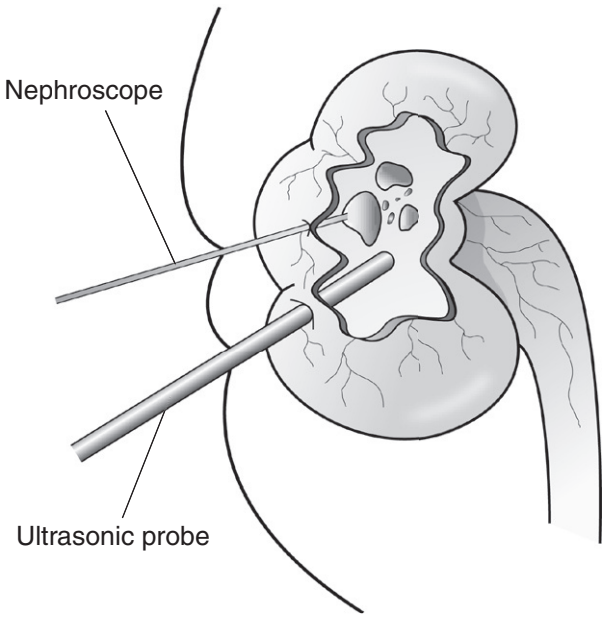
Rigid and Flexible Ureteroscopy

Although ESWL can be considered for stones that are larger than 10 mm, ureteroscopy has greater success (73% versus 67%). Ureteroscopy involves passing a scope through the ureter to remove the stone physically, sometimes with the help of laser (Fig. 58-3). Especially with larger, proximal, and impacted stones, this technique is preferred. In patients who have absolute contraindications to ESWL therapy, ureteroscopy is an acceptable alternative.[43,44] With the development of more advanced technology (flexible and smaller-caliber scopes) and techniques, complications such as ureteral perforation or stricture formation have become much less common.[43,44]

Percutaneous Nephrolithotomy

Because of a larger side effect profile, percutaneous nephrolithotomy is reserved for patients with renal calculi (especially staghorn struvite stones) and large impacted proximal ureteral stones. Patients in whom ureteroscopy fails are also candidates for percutaneous nephrolithotomy. This technique involves inserting a needle through the skin into the kidney's collecting system and dilating the tract to 1 cm, to allow the urologist to break up and remove the stones (Fig. 58-4).[43,44] Just like any other invasive procedure, percutaneous nephrolithotomy has complications such as bleeding, injury to other organs, and infection.[44,45]

FIGURE 58-4
Percutaneous nephrolithotomy. (From National Kidney and Urologic Diseases Information Clearinghouse: <http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm>; Accessed 26.09.11.)



Prevention Prescription

- Maintain a daily fluid intake of 2 to 3 L (approximately 8 to 10 glasses of water). Try to limit situations that exacerbate dehydration (e.g., hot weather, endurance exercise).
- Do *not* limit your dietary calcium intake. A low-sodium, low-protein diet can be helpful.
- Drink lemonade, orange juice, and cranberry juice, but limit grapefruit juice and sodas.
- Develop a healthy lifestyle that maintains a normal body mass index.
- For patients with hyperoxaluria, limit intake of foods with high oxalate levels, including nuts (almonds, peanuts, pecans, walnuts, cashews), vegetables (rhubarb, spinach), and chocolate.

Therapeutic Review

The purpose behind these suggested therapeutic options for kidney stones is to prevent recurrence of symptomatic stones. Regardless of stone composition, all patients with kidney stones should be advised to increase their water intake. Depending on the type of stone and results of metabolic evaluation, additional dietary, supplemental, and medical recommendations can also be made. Surgery is reserved for patients with large stones, recalcitrant disease, obstructing disease, and stones located in certain positions along the urologic tract that are difficult to access.

Removal of Exacerbating Factors

- Avoid excessive exposure to any environment or activity that promotes dehydration (warmer climates or strenuous physical activity).
- Maintain general healthy eating and physical activity habits that prevent development of metabolic syndrome conditions (e.g., obesity, hypertension, hyperlipidemia).

Nutrition

- Drink lots of water, with 2 to 3 L per day recommended (8 to 10 glasses of water). A1
- Do not limit dietary calcium intake. A1
- Limit caffeine, soda, grapefruit juice, protein, carbohydrate, and salt intake (less than 2.5 g daily). B1
- Drink lemonade, orange juice, and cranberry juice. B1
- Decrease consumption of oxalate-containing foods, especially if you have hyperoxaluria. B1
- Decrease intake of purine-rich foods, especially if you have uric acid stones. B1
- Tailor your diet based on the type of metabolic abnormality. A1

Supplements

- Limit supplemental calcium, but if needed for bone fortification, take with food. B2
- Limit supplemental vitamin C. B1
- Take supplemental omega-3 fatty acids. C1
- Take supplemental magnesium. B1
- Probiotics containing *Oxalobacter formigenes* can be used, especially if you have hyperoxaluria. C1

Botanicals

- *Phyllanthus niruri* (stonebreaker, chanca piedra): take 250 mg daily to twice a day before meals. B2
- Other Chinese herbs can be tried (Chorei-to, Wullingsan, Jin Qian Cao, and Niao Shi). C2
- Other herbs frequently used in Ayurvedic medicine (*Tribulus terrestris, Orthospihon stamineus/grandiflorus* [Java tea], and *Dolichos biflorus)* can be considered. C2

Energy Medicine

- Acupuncture can be used for pain after extracorporeal shock wave lithotripsy (ESWL) and possibly as a kidney or bladder energy-modifying treatment. B2 C2

Pharmaceuticals

- Diuretics, especially thiazides (hydrochlorothiazide, 25 mg daily) can be used for their hypocalciuric effect. A2
- Potassium citrate is useful as an alkalinizer and citrate promoter, at 10 mEq three times a day (if $U_{citrate}$ greater than 150 mg/day) or 20 mEq three times a day (if $U_{citrate}$ less than 150 mg/day) with meals, up to 100 mEq/day. A1
- $Alpha_1$ blockers (tamsulosin, 0.4 mg 30 minutes after a meal daily; maximum, 0.8 mg daily) and calcium channel blockers (nifedipine, 30 mg daily extended release) can facilitate stone expulsion. A2
- Allopurinol, at 200 to 300 mg daily, can help prevent uric acid stones. A2

Surgical Therapy

- ESWL is very successful for smaller stones (less than 1 cm) located in the distal ureter. A2
- Ureteroscopy can be used for larger stones that are located more proximally or are impacted. A2
- Percutaneous nephrolithotomy is reserved for recalcitrant stones and for staghorn calculi. A3

KEY WEB RESOURCES

National Kidney & Urologic Diseases Information Clearinghouse: http://kidney.niddk.nih.gov/kudiseases/topics/stones.asp
Medline Plus Interactive Patient Module on Kidney Stones: http://www.nlm.nih.gov/medlineplus/tutorials/kidneystones/htm/index.htm
WebMD: Kidney Stones—Prevention: http://www.webmd.com/kidney-stones/kidney-stones-prevention

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Chapter 59

Chronic Prostatitis

Mark W. McClure, MD

Pathophysiology

Prostatitis is the most common reason that men younger than age 50 years, and the third most common reason that men older than age 50 years, see a urologist. Nevertheless, most new diagnoses of prostatitis are made by primary care physicians.[1] Investigators estimate that one in every two men will experience prostatitis symptoms during their lifetime.[2] Although the term prostatitis literally means prostatic inflammation, inflammation is not always present, and neither is infection. In fact, patients are often diagnosed with prostatitis simply because they experience pain during a rectal examination.[3] In an effort to standardize the terminology used to describe the different types of prostatitis, the National Institutes of Health proposed the four categories listed in Table 59-1.[4]

Only 5% of men with prostatitis have bacterial prostatitis.[5]

Bacterial prostatitis is usually caused by manipulation of the urinary tract, unsafe sexual practices, and spasms of the muscular tissue in the bladder neck, prostatic urethra, and external urethral sphincter. Muscular spasms induce prostatitis by interrupting the smooth flow of urine and thereby causing reflux of urine into ducts that permeate the prostate. Chronic bacterial prostatitis, which is characterized by prostatic calculi, ductal obstruction, and chronic inflammation, is more common than acute bacterial prostatitis.[6]

One reason that bacterial prostatitis is rare can be traced to a substance called antibacterial factor. Secreted by cells that line the prostatic ducts, antibacterial factor kills bacteria on contact. In the 1970s, researchers discovered that zinc was the active component of antibacterial factor. Although the prostate has the highest zinc concentration of any tissue in the body, men with chronic bacterial prostatitis have extremely low concentrations of zinc within their prostates, even though their blood zinc levels are usually normal.

Most men (95%) have nonbacterial prostatitis.[7] Chronic abacterial prostatitis is subdivided into two categories, depending on the number of inflammatory white blood cells (WBCs) in the expressed prostatic secretions (EPS): An amount of 10 or more WBCs per high-power field in the EPS is labeled chronic inflammatory abacterial prostatitis (category IIIa); a lesser amount is labeled chronic noninflammatory abacterial prostatitis (category IIIb). From a practical standpoint, however, commonly measured parameters such as WBCs in EPS, WBCs in urine, and urine cultures fail to distinguish patients with chronic prostatitis from controls.[1]

Although controversial, the origin of chronic inflammatory abacterial prostatitis has been linked with occult bacterial infection, nanobacteria, genetic factors, hormonal imbalance, aging, chemical irritants, fungal infections, and autoimmunity.[2,8,9] Researchers theorize that noninflammatory abacterial prostatitis is caused by spasms of the pelvic floor musculature, stress, and intraprostatic urinary reflux.[2,10] Cytokines produced by leukocytes and prostate epithelial cells can also produce prostatic inflammation in the absence of bacteria.[7] Although provocative, none of these theories provides a unified mechanism for the cause of chronic prostatitis.

In contrast to the inflammation or infection theory, current research suggests that chronic prostatitis is an aspect of chronic pelvic pain resulting from a complex, interrelated cascade of events unique to each individual.[11] The condition is initiated by a trigger such as trauma, infection, irritation, or dysfunctional voiding. The condition may abate spontaneously or in response to therapeutic interventions. Conversely, if the condition persists, especially in an individual who is anatomically or genetically susceptible, it can lead to local tissue damage and inflammation, as well as peripheral and central nervous system sensitization. With continued stimulation, the nervous system becomes up-regulated, and the response to pain becomes extenuated locally and in adjacent areas even if the involved tissue response remains stable or lessens.[12] In addition, persistent pelvic and perineal

TABLE 59-1. Categories of Prostatitis

I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis
	IIIa: Inflammatory (more than 10 WBC/hpf in expressed secretions)
	IIIb: Noninflammatory (less than 10 WBC/hpf in expressed secretions)
IV	Asymptomatic inflammatory prostatitis

Data from Krieger JN, Nyberg LJ, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282:236–237.
WBC/hpf, white blood cells per high-power field.

pain induces chronic pelvic muscle tension, which begets more pain in a feed-forward cycle. Anxiety, depression, fear, and maladaptive coping mechanisms can further exacerbate the situation.[8]

Although treatment guidelines can help steer physicians in the right direction, physicians in clinical practice use a process of elimination, based on the results of trial-and-error therapies, to diagnose and treat patients with prostatitis.[13] For both the patient and the physician, the hallmark of successful treatment is the resolution of symptoms. Fortunately, according to data from the Chronic Prostatitis Collaborative Research Network, after 2 years of follow-up, men with chronic prostatitis or chronic pelvic pain rarely experienced clinically significant progression of symptoms, and nearly one third considered themselves significantly improved.[14]

Integrative Therapy

Physicians routinely treat prostatitis with a combination of art and science. Just the same, before integrative therapies are instituted, proper medical evaluation is mandatory because other conditions (e.g., bladder cancer, prostate cancer, and interstitial cystitis) can mimic prostatitis symptoms. Once a proper diagnosis has been established, it is safe to proceed with the measures described here.

Lifestyle

Lifestyle—daily choices that are under our control—can either improve or worsen prostatitis symptoms. Healthful choices such as regular exercise, sufficient rest, nutritious food, and stress reduction improve symptoms.[6,15] Unhealthful choices have the opposite effect.

Nutrition

Although foods are taken for granted, they are potent medicine that can either increase or decrease prostatitis symptoms.

Do's

The following measures, which can improve prostatitis symptoms, should be encouraged:

- Fruits and vegetables: Five to nine daily servings of brightly colored fruits and vegetables should be eaten. Rich in antioxidant vitamins and minerals, fruits and vegetables may improve prostatitis symptoms by reducing inflammation.[16]
- Flaxseed: Flaxseeds are a rich source of antiinflammatory omega-3 essential fatty acids and a nutritious phytoestrogen-containing fiber called lignan. Flaxseeds should be ground in a coffee grinder, and 1 teaspoon should be sprinkled over cereal or vegetables twice daily. The unused portion should be stored in the refrigerator.
- Soy: Encourage two servings of soy protein daily. Soy protein reduces not only prostatic inflammation, but also the risk of prostate cancer.[17]
- Water: Drink at least 64 oz of water daily. Water dilutes noxious urinary irritants.

Don'ts

The following substances can worsen prostatitis symptoms. Therefore, patients should be encouraged to avoid them.

- Hot spicy foods
- Alcohol or caffeinated beverages
- Refined sugar
- Junk food or foods high in saturated fat

Sugar and saturated fats aggravate prostatitis by inducing the production of arachidonic acid and associated inflammatory prostaglandin and leukotriene molecules.

Supplements

Zinc

Zinc is essential for proper immune function, and this may explain why men with depressed prostate zinc concentrations are more susceptible to chronic bacterial prostatitis. Unfortunately, supplemental zinc is unable to normalize depressed prostate zinc concentrations. However, taking oral zinc supplements can normalize seminal fluid zinc levels and reverse prostatitis-induced infertility.

Dosage

The dose is 40 mg zinc gluconate (less expensive) or zinc picolinate (better absorbed) daily.

Precautions

Taking more than 40 mg of zinc daily can depress serum copper levels and impair immunity. Zinc supplements should be taken 2 hours before or 4 to 6 hours after taking quinolone antibiotics.[18]

Quercetin

A naturally occurring plant flavonoid, quercetin reduces prostatic inflammation and inhibits bacterial infection.[19] Onions, parsley, sage, tomatoes, and citrus fruits are rich natural sources of quercetin.

Dosage

Fruit and vegetable consumption can provide between 15 and 40 mg of quercetin daily. Quercetin is available in capsules (250, 300, and 500 mg) and tablets (50, 250, and 500 mg).

Take between 250 and 500 mg of quercetin 20 minutes before meals three times daily. Bromelain derived from the stem of pineapple plants *(Ananas comosus)* improves the absorption of quercetin; therefore, an equivalent amount of bromelain should be taken daily along with quercetin three times daily.

Precautions
Quercetin may increase the blood level of digoxin, felodipine, cyclosporine, estrogen, and doxorubicin, and it can theoretically interfere with the activity of quinolone antibiotics. Patients taking cisplatin chemotherapy should not take quercetin.[20]

Botanicals: Overview

Although herbs are effective for various prostate disorders, in contrast to prescription drugs, herbs take 4 to 6 weeks to achieve their maximum effect. Just the same, herbs are less expensive, have fewer adverse effects, and often work when prescription drugs have failed. Herbs can be taken singly or in combination.

Herbs That Decrease Prostatic Inflammation

Prostatic inflammation causes pain and swelling. Referred pain radiates along the nerves that supply the prostate. The herbs discussed here can reduce prostatic inflammation.

Saw Palmetto (Serenoa repens)
Derived from the berries of the dwarf palmetto palm tree, saw palmetto induces apoptosis in prostate epithelial cells and inhibits two enzymes that convert arachidonic acid to prostaglandin E_2 and leukotriene molecules, thus inhibiting the inflammatory cascade.[21]

Dosage
Take two capsules of a solid extract containing 160 mg of saw palmetto standardized to contain 85% to 95% fatty acids and sterols once daily or in divided doses.

Precautions
Occasional upset stomach may occur.

Rye Grass Pollen (Secale cereale)
European and Scandinavian physicians routinely use a proprietary brand of rye pollen extract (Cernilton, now marketed as PollenAid) to treat men with nonbacterial prostatitis successfully. Rich in phytosterols, *Secale cereale* blocks the formation of inflammatory prostaglandin and leukotriene molecules.[22]

Dosage
The typical dose of PollenAid is one capsule or two tablets three times daily before meals with a glass of water.

Precautions
Occasional upset stomach may occur.

South African Star Grass (Hypoxis rooperi)
Commonly used by European physicians to treat benign prostatic hyperplasia, South African star grass is rich in phytosterols, especially beta-sitosterol.[23] Beta-sitosterol not only reduces prostatic inflammation, but it also lowers serum cholesterol.

Dosage
Dosage depends on the formulation. Select a product that contains at least 50% beta-sitosterol and take as directed.

Precautions
Occasional gastrointestinal adverse effects can occur.

Clivers (Galium aparine)
Rich in antioxidant flavonoids, clivers is a nonirritating diuretic herb that reduces prostatic inflammation.

Dosage
Drink 1 glass of water containing 30 to 40 drops of liquid extract three times daily.

Precautions
None are noted.

Agrimony (Agrimonia eupatoria)
The flowering portion of agrimony is rich in antioxidants known as catechins that can inhibit inflammation.

Dosage
The daily dose is 3 g of herb. Drink 1 glass of water containing 30 drops of liquid extract three times daily.

Precautions
None are noted.

Stinging Nettle (Urtica dioica)
Nettle root is packed with polysaccharides that inhibit inflammatory prostaglandin and leukotriene molecules, thereby reducing prostatic pain and swelling and improving urinary flow.[24]

Dosage
The normal daily dose is 4 to 6 g. For tea, add 1.5 g of coarse powdered herb (1 teaspoon = 1.3 g) to cold water, heat to boiling for 1 minute, steep covered for 10 minutes, and then strain. For dry extract, take one 120-mg capsule twice daily.

Precautions
Occasional stomach upset can occur.

Herbs That Decrease Painful Urination

In addition to drinking plenty of water and avoiding urinary tract irritants, the patient seeking to alleviate dysuria can use the herbs discussed in this section.

Marshmallow Root (Althaea officinalis)
Marshmallow root soothes inflamed mucous membranes and stimulates immune function.[25]

Dosage
Marshmallow root is available as a tea, liquid tincture, or capsule. Drink several cups of tea daily, drink 1 glass of water containing 30 to 40 drops of tincture daily, or take capsules containing an equivalent of 6 g of powdered root daily in divided doses.

Precautions
Marshmallow root can delay the absorption of drugs taken simultaneously.

Eryngo (Eryngium campestre)
The dried leaves, flowers, and roots of eryngo are used to make an herbal tincture that assuages dysuria.

Dosage
Drink 1 glass of water containing 60 drops of liquid tincture three or four times daily.

Precautions
None are noted.

Herbs That Prevent Recurrent Urinary Tract Infections

A urinary tract infection can cause bacterial prostatitis because urine can reflux into prostatic ducts during voiding.[5] Scientific research suggests that the herbs discussed in this section may help prevent recurrent urinary tract infections.

Cranberry (Vaccinium macrocarpon)
Although not specific for prostatitis, proanthocyanidins contained in cranberries can prevent *Escherichia coli, Klebsiella pneumonia, Proteus* species, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* from adhering to urothelial mucosa.[26] This finding is relevant because *Escherichia coli* is the most common cause of bacterial prostatitis.

Dosage
Drink 8 oz of *unsweetened* cranberry juice daily, or take a standardized solid cranberry extract, one capsule three times daily for prevention or two capsules three times daily if infection is present.

Precautions
None are noted.

Uva ursi (Arctostaphylos uva-ursi)
Approved by the German Commission E for inflammatory disorders of the urinary tract, uva ursi leaves contain a potent urinary antiseptic called arbutin. Arbutin is hydrolyzed in alkaline urine to hydroquinone. Hydroquinone inhibits bacteria that commonly cause prostatitis.

> Owing to its high tannin content, uva ursi should not be taken for more than 1 week. Uva ursi is contraindicated in pregnant women, patients with renal disease, nursing mothers, and children younger than 12 years old.

Dosage
Uva ursi is available as a tea (steep 3 g of ground herb [1 heaping teaspoon] in 150 mL cold water for 12 to 24 hours and then strain; drink 1 cup four times daily), as a solid extract (the hydroquinone derivative, calculated as water-free arbutin, is dosed at 100 to 210 mg four times daily), and as a 1:1 fluid extract (drink 1.5 to 4 mL in water three times daily).[27]

Precautions
Uva ursi is safe when taken as directed. Avoid medications or foods that acidify the urine (e.g., cranberries) while taking uva ursi because it works best in alkaline urine.

Pharmaceuticals

Antiinflammatory Medications
Although antiinflammatory medications cannot cure prostatitis, they can reduce prostatic inflammation and pain.[5]

Dosage
One can prescribe 200 mg of celecoxib daily for 2 to 4 weeks.

Precautions
If taken long term, most nonsteroidal antiinflammatory drugs can cause gastrointestinal bleeding and renal impairment. Selective cyclooxygenase-2 inhibitors may increase the risk of heart attack and stroke, especially at higher doses.

Alpha-Adrenergic Blockers
Routinely used to treat benign prostatic hyperplasia, alpha-adrenergic blockers relax smooth muscle tissue in the prostatic urethra and bladder neck. Although data are conflicting, alpha-adrenergic blockers may improve prostatitis symptoms, especially in men without long-standing disease and in men with symptomatic bladder outlet obstruction.[28]

Dosage
Doxazosin and terazosin must be titrated to the maximum effective dosage. Alfuzosin, silodosin, and tamsulosin do not require titration. Take 10 mg of alfuzosin or 8 mg of silodosin with the same meal daily or 0.4 mg of tamsulosin 30 minutes after the same meal daily. If the medication has not improved prostatitis symptoms within 4 to 6 weeks, further medication is rarely helpful.

Caution
Patients planning cataract surgery should inform their ophthalmologist that they are taking an alpha-adrenergic blocker.

Precautions
Alpha-adrenergic blockers can cause postural hypotension, asthenia, dizziness, nasal congestion, and delayed or retrograde ejaculation. Alfuzosin and silodosin should not be taken in patients with moderate or severe hepatic insufficiency or severe renal insufficiency. The potential exists for syncope with all alpha-adrenergic blockers.

Antibiotics
Ideally, antibiotics should be reserved for culture-proven bacterial infection. Nevertheless, clinical investigators at the National Institutes of Health reported that clinicians routinely prescribe antibiotics in more than 95% of patients with prostatitis.[13] Researchers found that bacterial count, leukocyte count, and antibiotic levels could not predict a favorable response to antibiotics.[29] Furthermore, antibiotics may improve prostatitis symptoms because they suppress inflammation caused by cytokines, not because they eradicate infection.[7]

> Approximately one third of patients with nonbacterial prostatitis respond to antibiotics, the same proportion that responds to placebo.[30,31]

Pending the results of a post–prostatic massage urine culture, prescribing quinolone antibiotics is a reasonable approach. If patients are allergic to quinolone antibiotics, alternate choices include trimethoprim-sulfamethoxazole, tetracycline, macrolide (azithromycin or clarithromycin), or erythromycin. If the culture results are negative, the antibiotics may be stopped. Conversely, if the patient shows clinical improvement, antibiotic therapy may be continued.

Dosage

A 1-month course of antibiotics usually suffices; however, men with chronic bacterial prostatitis may require protracted antibiotic therapy.

Precautions

Probiotics should be taken in addition to antibiotics, but separate from them, to minimize antibiotic-related gastrointestinal adverse effects.

Biomechanical Techniques

Sitz Bath

Taking a hot sitz bath for 15 minutes twice daily increases blood flow to the prostate, reduces prostatic inflammation, and enhances immune function.

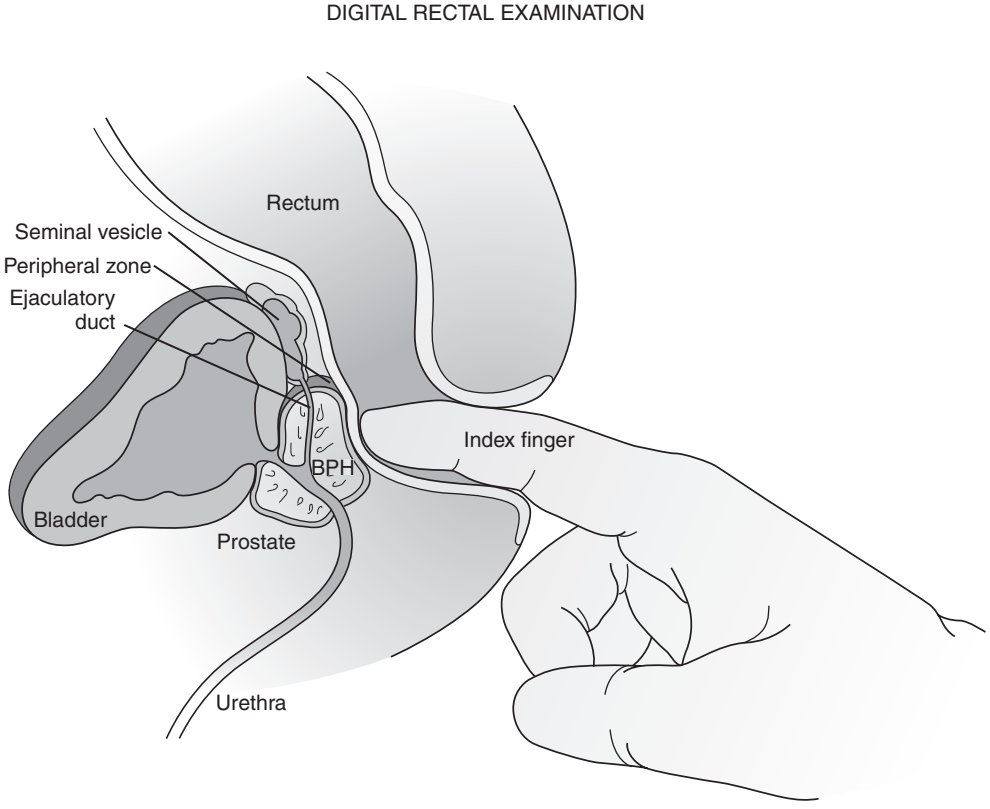
Prostatic Massage

A time-honored treatment for prostatitis, prostate massage forces secretions laden with dead bacteria and cellular debris into the prostatic urethra. To perform prostate massage, insert the dominant gloved index finger into the patient's rectum to the base (deepest aspect) of the prostate (Fig. 59-1). Next, slide the pad of the index finger to the lateral aspect of the prostate. Inform the patient that the following procedure may be uncomfortable. Maintain constant firm pressure against the surface of the prostate while sweeping the finger horizontally to the midline. Continue this process in a stepwise fashion by moving from the base of the prostate to the apex (closest aspect) of the prostate. Repeat the same maneuver on the opposite side of the prostate. If fluid is discharged from the tip of urethra, a drop can be dabbed on a glass slide for microscopic examination. To obtain a specimen for culture, instruct the patient to wipe the tip of the penis with an antiseptic wipe and then void directly into a culture container (not the toilet). Prostate massage works best in combination with antibiotic therapy for treating chronic bacterial prostatitis.[32]

Physical Therapy

Research has shown that men with chronic pelvic pain syndrome often develop guarding behavior in their pelvic musculature that results in a feed-forward pain cycle in which repeated tensing of pelvic muscles causes an accumulation of noxious chemicals producing pain that causes additional muscle contractions. Techniques that decrease muscle tension (e.g., trigger point release, pelvic floor reeducation, biofeedback, and relaxation techniques) can improve symptoms of chronic pelvic pain syndrome.[33]

FIGURE 59-1
Digital rectal examination. BPH, benign prostatic hyperplasia.



Transurethral Microwave Therapy

Three sham-controlled trials showed that transurethral microwave therapy is an effective, safe, and durable treatment for resistant nonbacterial prostatitis. This technique can also kill bacteria that cause chronic bacterial prostatitis.[5]

Mind-Body Therapy

Chronic prostatitis exacts a heavy emotional toll on men. According to one survey, the quality of life for these men was on par with men suffering from chronic low back pain, heart disease, or inflammatory bowel disease.[34] Furthermore, the mental consequences of chronic prostatitis were deemed worse than those associated with congestive heart failure and diabetes.[35] The following mind-body modalities can help alleviate the pain and suffering that accompany chronic prostatitis by providing men with new coping skills:

- Relaxation Techniques (see Chapter 93, Relaxation Techniques)
- Guided imagery (see Chapter 95, Guided Imagery)
- Meditation (see Chapter 98, Recommending Meditation)
- Yoga
- Psychological counseling

Stress Reduction

Although stress is a part of everyday life, heightened levels of stress worsen the symptoms of prostatitis. Mediated through the sympathetic nervous system, prolonged stress increases the incidence of urinary tract infections, depresses the immune system, and increases spasms of the bladder, urethra, and pelvic musculature. Although stress cannot be eliminated, it can be controlled (see Chapter 93, Relaxation Techniques).

Therapies to Consider

Homeopathy

Safe and effective homeopathic remedies for nonbacterial prostatitis deserve further consideration. Consult a licensed homeopathic physician, if one is available. Otherwise, the authors of *Everybody's Guide to Homeopathic Medicines* recommended trying one of the following homeopathic medications, according to the predominant symptom[36]:

- Pulsatilla: Pain in the prostate after urination
- Chimaphila umbellata: Prostate soreness made worse with pressure, especially sitting
- Kali bichromium: Prostate pain worsened by walking and improved by standing
- Causticum: Pressure and pulsations in the prostate with pain radiation into the urethra and bladder after voiding a few drops
- Sabal serrulata: Prostatism symptoms and dysuria
- Lycopodium: Pressure in the prostate accentuated during and after voiding

Dosage

These remedies are available at many health food stores. A common starting dose is a 1:100 dilution with 30 cycles of succussion that is known as 30 C, taken two to three times daily for up to 5 days during acute symptoms and less frequently as the symptoms improve. For chronic cases, take a low potency twice daily for up to 2 weeks (see Chapter 111, Therapeutic Homeopathy, for additional information).

Traditional Chinese Medicine

Chinese herbal therapies and acupuncture can improve annoying prostatitis symptoms.[37] Consult a qualified traditional Chinese medicine practitioner. For a list of certified practitioners, contact the National Certification Commission for Acupuncture and Oriental Medicine (see Key Web Resources box).

Prevention Prescription

- Exercise at least 30 minutes three times weekly.
- Obtain at least 7 hours of sleep daily.
- Practice stress reduction and relaxation techniques daily.
- Eat two servings of soy products and at least five to nine servings of fruits and vegetables daily.
- Drink at least 64 oz of water daily.
- Avoid junk food, hot and spicy foods, alcohol, and caffeine.

Therapeutic Review

Unless symptomatic patients are allergic, start them on a quinolone antibiotic pending results of a post–prostatic massage urine culture. If the culture result is positive, further treatment should be based on culture results. If the culture result is negative, the antibiotics can be stopped unless symptoms improve, in which case antibiotic therapy may be continued. Antibiotics should be taken for 1 month along with a probiotic (but not at the same time of day). Patients who fail to respond, and those who have recurrent prostatitis, should be referred to a urologist for further evaluation. Other measures that are helpful for bacterial and nonbacterial prostatitis are listed here.

Nutrition

- Eat fresh fruits and vegetables.
- Add soy and ground flaxseed to the diet.
- Drink plenty of water.
- Avoid urinary irritants such as caffeinated beverages, junk food, tobacco products, alcohol, and spicy food.

Continued

Mind-Body Therapy

- Encourage stress reduction techniques.
- Consider meditation, counseling, and biofeedback. B1

Supplements

- Take a high-potency multivitamin daily.
- Also take additional zinc gluconate or picolinate 40 mg daily, plus quercetin 250 to 500 mg and an equal amount of bromelain 20 minutes before meals three times daily. B2

Botanicals

- Depending on symptoms, a 6-week trial of one or more of the following herbs should be tried:
  - Saw palmetto *(Serenoa repens):* 160 mg twice daily B1
  - PollenAid *(Secale cereale):* one capsule or two tablets three times daily before meals A1
  - Stinging nettle *(Urtica dioica):* dry extract, 120 mg twice daily B1
- If no improvement occurs, consider trying a different herbal combination. C1

Pharmaceuticals

- Try a 2- to 4-week course of a cyclooxygenase-2 inhibitor to alleviate painful prostatitis symptoms.
- If muscle spasms are suspected, try a 4- to 6-week trial of an alpha-adrenergic blocker.
- If improvement occurs, continue the medication; otherwise, stop. B2

Biomechanical Techniques

- Recommend daily sitz baths as needed.
- Consider physical therapy and regular prostatic massage. B1

Prostatitis Symptom Index

- Monitor therapeutic response by asking patients to fill out a prostate symptom index form before initiating therapy and monthly thereafter as long as symptoms persist (Fig. 59-2).[38]

FIGURE 59-2
National Institutes of Health prostatitis symptom index. (From Litwin MW, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. *J Urol.* 1999;162:374)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas:

	Yes	No
a. Areas between rectum and testicles (perineum)	○ 1	○ 0
b. Testicles	○ 1	○ 0
c. Tip of the penis (not related to urination)	○ 1	○ 0
d. Below your waist (in your pubic or bladder area)	○ 1	○ 0

2. In the last week, have you experienced:

a. Pain or burning during urination	○ 1	○ 0
b. Pain or discomfort during or after ejaculation	○ 1	○ 0

3. How often have you had pain or discomfort in any of these areas over the last week?
- ○ 0 Never
- ○ 1 Rarely
- ○ 2 Sometimes
- ○ 3 Often
- ○ 4 Usually
- ○ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you have had it over the past week?

○ 0 (No pain) ○ 1 ○ 2 ○ 3 ○ 4 ○ 5

○ 6 ○ 7 ○ 8 ○ 9 ○ 10 (Extreme pain)

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?
- ○ 0 Not at all
- ○ 1 Less than 1 time in 5
- ○ 2 Less than half the time
- ○ 3 About half the time
- ○ 4 More than half the time
- ○ 5 Almost always

6. How often have you had to urinate less than two hours after you finished urinating, over the last week?
- ○ 0 Not at all
- ○ 1 Less than 1 time in 5
- ○ 2 Less than half the time
- ○ 3 About half the time
- ○ 4 More than half the time
- ○ 5 Almost always

Impact of symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?
- ○ 0 None
- ○ 1 Only a little
- ○ 2 Some
- ○ 3 A lot

8. How much did you think about your symptoms, over the last week?
- ○ 0 None
- ○ 1 Only a little
- ○ 2 Some
- ○ 3 A lot

Quality of life

9. If you were to spend the rest of your life with your symptoms just the way they have been over the last week, how would you feel about it?
- ○ 0 Delighted
- ○ 1 Pleased
- ○ 2 Mostly satisfied
- ○ 3 Mixed (about equally satisfied and dissatisfied)
- ○ 4 Mostly dissatisfied
- ○ 5 Unhappy
- ○ 6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3 and 4 _____

Urinary symptoms: Total of items 5 and 6 _____

Quality of Life Impact: Total of items 7, 8 and 9 _____

KEY WEB RESOURCES	
Prostatitis Foundation: www.prostatitis.org	A comprehensive and reliable resource for additional information about prostatitis
National Kidney and Urologic Diseases Information Clearinghouse, National Institutes of Health prostatitis information: http://kidney.niddk.nih.gov/kudiseases/pubs/prostatitis	A patient-oriented overview of prostatitis
National Certification Commission for Acupuncture and Oriental Medicine: http://www.nccaom.org	Maintains a list of certified practitioners of traditional Chinese medicine

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Chapter 60

Erectile Dysfunction

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Pathophysiology

Erectile dysfunction (ED), the most common sexual problem in men, affects up to one third of men at some point in their lives. ED is defined as the inability to achieve or maintain a sufficient erection for satisfactory sex. The prevalence of ED increases with age,[1] and ED is associated with poor cardiovascular health, psychosocial factors, hormonal disorders, recreational drug abuse, and adverse effects from prescribed medications. Less common are anatomic, traumatic, or infectious causes.[2] Normally, an erection is stimulated by a combination of neurovascular, hormonal, and environmental factors beginning with sexual interest and desire. Through parasympathetic activation, endothelial cells are directly activated to produce nitric oxide (NO), which is the major hormonal mediator needed to initiate and maintain an erection. With NO present, the corpus cavernosum is engorged with arterial blood as a result of smooth muscle endothelial relaxation while venous return is simultaneously restricted.[3]

Evaluation

The World Health Organization and the American Urological Association recommend a limited ED evaluation,[4] starting with the five-item International Index of Erectile Function Questionnaire (IIEF-5) (Table 60-1).[5] A careful review of medications that contribute to ED (Table 60-2) is recommended, as is substance abuse screening for alcohol, tobacco, or marijuana.[6] Risk factors should be assessed in all patients presenting with ED (Box 60-1).[7,8] Blood pressure and weight or abdominal girth measurements are useful initial assessments of cardiovascular health, which is the main risk factor for ED. Testicular, prostate, penis, and breast inspection should also be considered, to rule out hypogonadism, hypertrophy or mass, Peyronie's disease, and gynecomastia, respectively.[9] Nocturnal penile tumescence can be assessed by patient self-report or use of the "stamp test,"[10] Rigiscan, or Snap-Gauge cuff testing.[7,11] The presence of nocturnal erections in a patient with ED suggests a psychogenic origin such as stress, fatigue, or mood disorders.[7,12] Advanced imaging such as penile duplex ultrasonography is not recommended for the diagnosis of ED.[7,13]

Further workup includes laboratory fasting glucose and lipids, thyroid-stimulating hormone, complete blood count, prostate-specific antigen, urinalysis, creatinine, and electrolytes.[4,7] Serum total testosterone levels should be considered for men older than 50 years or men with signs of hypogonadism who are younger than 50 years old. In addition to positive physical examination findings, hypogonadism is defined as a morning serum total testosterone level less than 300 ng/dL (10.4 nmol/L).[2,4,7,14]

> Presentation of erectile dysfunction is a window of opportunity to improve health and reverse the development of cardiovascular disease.

Integrative Therapy

Pharmaceuticals

Phosphodiesterase Inhibitors

Phosphodiesterase type 5 (PDE5) inhibitors (Table 60-3) such as sildenafil, vardenafil, and tadalafil remain first-line therapy options for ED.[7,15] These drugs are very effective, are used as needed, and are generally well tolerated and safe.[16,17] Common side effects include headache, nasal congestion, flushing, abnormal vision, and dyspepsia. Evidence supports equal effectiveness of these agents.[18–20] However, approximately one third of men do not respond to PDE5 inhibitors, and these agents are not considered effective for improving libido.[21] PDE5 activity is testosterone dependent, and the prevalence of hypogonadism in men is 5% to 15%.[22,23]

Dosage

Doses are provided in Table 60-3.

TABLE 60-1. International Index of Erectile Function Questionnaire (IIEF-5)

Over the Past 6 Months:	**SCORE**				
	1	2	3	4	5
1. How do you rate your **confidence** that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always

IIEF-5 Scoring:
The IIEF-5 score is the sum of the ordinal responses to the five items.
22–25: No erectile dysfunction
17–21: Mild erectile dysfunction
12–16: Mild to moderate erectile dysfunction
8–11: Moderate erectile dysfunction
5–7: Severe erectile dysfunction

From Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res.* 1999;11:319–326.

Testosterone

Testosterone supplementation in hypogonadism is superior to placebo in improving erections, sexual function, and libido.[22,24] Testosterone supplementation with either compounded bio-identical testosterone or pharmaceutical brands should be monitored regularly with complete blood count, liver function tests, and annual prostate-specific antigen with digital rectal examination.[25]

Dosage

Pharmaceutical testosterone (e.g., Androderm, AndroGel, Striant, Testim) is prescribed at 12.5 to 100 mg applied topically every morning and titrated to normal serum total testosterone laboratory levels that are checked monthly.[25] Compounded bio-identical testosterone preparations are available through reputable compounding pharmacies[26] (see Chapter 34, Hormone Replacement in Men).

Prostaglandin E_1 Injection

In comparison, the prostaglandin E_1 agent alprostadil is self-administered as an intracavernosal injection (e.g., Caverject, Edex) or urethral suppository (e.g., Muse). Alprostadil is considered the gold standard of ED therapy, but is still second-line therapy to oral PDE5 inhibitors.[7,27,28] However, alprostadil is expensive, requires training and comfort with self-administration, may rely on urology consultation, and can be uncomfortable or inconvenient. Dosing for alprostadil intracavernosal injection ranges from 2.5 to 7.5 mcg three times a week as needed. Alprostadil intraurethral suppository treatment ranges from 125 to 1000 mcg daily as needed.

Gene Therapy

Gene therapy involves local injection of a plasmid containing the Maxi-K protein gene *(MKPG),* which is expressed through cellular transcription and translation into a potassium channel needed for an erection. Although *MKPG* injection therapy appears safe, it is invasive, relatively new, expensive, often not covered by insurance, and unavailable in most locations, and the long-term effects have not been established. Advantages include enabling sexual spontaneity, twice-yearly injection therapy, and synergistic activity with PDE5 inhibitor medications, and it can be used by men taking nitrates.[7,29–31]

Vacuum Erection or Constriction Device

For those men who are comfortable, motivated, and open-minded, vacuum erection or constriction devices (e.g., Erec-Tech, Firma) have shown promise for postsurgical, structural (e.g., Peyronie's disease), and prostate cancer radiation rehabilitation.[32–34] Satisfaction rates are higher than 80%, but these devices should be avoided in men with sickle cell disease or other bleeding disorders.[35,36] Patients should be counseled by a health care worker experienced with these devices.

Surgery

Penile prosthesis surgery (e.g., Coloplast) emerged in the 1970s, and many men who are managed with medication or supplements are likely to require penile prosthesis implantation as ED progresses.[7,37] However, this surgical procedure is invasive, has increased risk for complications, is expensive, and is not typically covered by insurance.

TABLE 60-2. Medications That May Contribute to Erectile Dysfunction

MEDICATION CLASS	EXAMPLES
Alcohol and Drugs of Abuse	Alcohol, amphetamines, barbiturates, cocaine, heroin, marijuana, tobacco
Analgesics	Opiates
Anticholinergics	Tricyclic antidepressants
Anticonvulsants	Phenytoin, phenobarbital
Antidepressants	Lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants
Antihistamines	Dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, promethazine
Antihypertensives	Alpha blockers, beta blockers, calcium channel blockers, clonidine, methyldopa, reserpine
Antiparkinsonian agents	Bromocriptine, levodopa, trihexyphenidyl
Cardiovascular agents	Digoxin, disopyramide, gemfibrozil
Cytotoxic agents	Methotrexate
Diuretics	Spironolactone, thiazides
Hormones	5-Alpha-reductase inhibitors, corticosteroids, estrogens, LH-releasing hormone agonists, progesterone
Immunomodulators	Interferon-alfa
Sedatives	Benzodiazepines, butyrophenones, phenothiazines

Data from references 2, 6, and 7.

Pharmaceutical medications work better and do not share the risk of contaminated or adulterated products. Dependable nutraceuticals should be considered in appropriate patients who are intolerant of pharmaceuticals or who are more philosophically in line with nonpharmaceutical agents.

Nutraceuticals

In general, supplements are much less effective than pharmaceuticals for treating ED.[38] In 2007, the U.S. Food and Drug Administration issued a statement warning

BOX 60-1. Risk Factors for Erectile Dysfunction

- Advancing age
- Alcohol abuse or alcoholism
- Cardiovascular disease
- Diabetes mellitus
- Drug abuse (e.g., marijuana, cocaine, methamphetamine)
- Dyslipidemia or hypercholesterolemia
- History of pelvic/prostate irradiation or surgery
- Hormonal disorders (e.g., hypogonadism, hypothyroidism, hyperprolactinemia)
- Hypertension
- Medications (e.g., antihistamines, benzodiazepines, selective serotonin reuptake inhibitors)
- Neurologic disorders (e.g., dementia, multiple sclerosis, parkinsonism, paraplegia or quadriplegia, stroke)
- Obesity
- Penile venous leakage
- Peyronie's disease
- Psychological conditions (e.g., anxiety, depression, guilt, history of sexual abuse, marital or relationship strain, stress)
- Sedentary lifestyle
- Tobacco use

Data from references 2, 4, and 7.

TABLE 60-3. First-line Pharmaceutical Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction

MEDICATION	DOSE	ONSET	DURATION	PRECAUTIONS	SOR/HARM
Sildenafil (Viagra)	25–100 mg	15–60 min	4 hr	Avoid with nitrates and alpha blockers	A1
Vardenafil (Levitra)	5–20 mg	30 min	4 hr	Avoid with nitrates and alpha blockers	A1
Tadalafil (Cialis)	5–20 mg	15–45 min	36 hr	Avoid with nitrates and alpha blockers	A1

Data from Brant WO, Bella AJ, Lue TF. Treatment options for erectile dysfunction. *Endocrinol Metab Clin North Am.* 2007;36:465–479; and Palit V, Eardley I. An update on new oral PDE5 inhibitors for the treatment of erectile dysfunction. *Nat Rev Urol.* 2010;7:603–609.
SOR, strength of recommendation.

BOX 60-2. Products That Are Not Safe or Reliable for Use According to the Food and Drug Administration[39,40]

- Aziffa
- Enzyte
- Erex
- Erexis
- Eyeful
- Hard Drive
- Libidinal
- Man Up
- Maxyte
- Mojo
- Monster Excyte
- OMG/OMG45
- Prolatis
- Red Magic
- Rockhard Weekend
- Size Matters
- Stiff Nights
- Straight Up
- Stud Capsules
- Verect
- WOW
- Xaitrex
- Xytamax
- Zilex
- Zotrex

Data from U.S. Food and Drug Administration (FDA). FDA Warns Consumers Not to Use Super Shangai, Strong Testis, Shangai Ultra, Shangai Ultra X, Lady Shangai, and Shangai Regular (also known as Shangai Chaojimengnan). <www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/default.htm>; Accessed 22.03.11; Natural Standard. Erectile Dysfunction Products Recalled. <http://naturalstandard.com/news/news201008010.asp>; 2010 Accessed 22.03.11.

BOX 60-3. Supplements With Insufficient Evidence

- 5-Hydroxytryptophan (5-HTP)
- Ambra grisea (ambrein)
- Androstenediol
- Ashwagandha
- Brazilian wandering spider venom (peptide Tx2-6)
- *Bufo* toad (bufotenine, Chan Su)
- *Butea superba*
- Chaste tree berry
- Clove
- Coleus
- Creatine
- Deer velvet
- Ephedra
- Maca *(Lepidium meyenii)*
- Melatonin
- *Muira puama* (potency wood)
- Niacin
- Pomegranate
- Pygeum
- Rhinoceros horn
- Rhodiola
- Saw palmetto
- Spanish fly (cantharides)
- *Tribulus terrestris* (TT)
- Wild yam

Data from references 38, 42, and 43.

consumers to avoid use of impotence supplements.[39,40] Patients should be counseled to avoid email promotions and Internet advertisements for these and other products that falsely claim to enhance male libido and sexual function. Further, many of these products are contaminated or adulterated,[41] and they are not considered reliable or safe for use (Box 60-2). Other products may be commonly used but are ineffective (Box 60-3).[38,42,43] However, some evidence indicates that the judicious use of high-quality nutraceuticals may be considered in appropriate situations (Table 60-4).[44–65]

Bioenergetics

Evidence is generally lacking for acupuncture and massage in treating ED.[66] Further, massage therapy may be socially inappropriate in this context. Evidence is also lacking for osteopathic and chiropractic manipulation.[42] Further, evidence for yoga, energy medicine, physical therapy, and the Alexander technique for the specific treatment of ED is insufficient.[42] However, these and other methods should be individually adapted and encouraged as part of overall health management as appropriate.[67]

Mind-Body Therapy

Sexual desire, arousal, and climax are mediated through complex psychoneurological mechanisms. Psychological interventions are recommended as a strength of recommendation taxonomy category 1B for ED resulting from anxiety, depression, posttraumatic stress disorder, guilt, sex abuse history, relationship strain, performance anxiety, postsurgical adjustment disorder, and general stress.[7,42,68–73] Evidence is insufficient to recommend art therapy, hypnosis, aromatherapy, meditation, or guided imagery.[42] However, appropriate relaxation methods should be individually adapted and encouraged as needed.[67,72]

Lifestyle

A strong association exists between chronic diseases of lifestyle and ED (see Box 60-1), and treatment must include weight loss, healthy nutrition, and regular exercise.[2,6,7,74,75] First-line therapy also involves a review of medications that can contribute to ED (see Table 60-2). Research shows that men with ED are at significant risk for cardiovascular disease.[75–77] One study found that ED symptoms manifest on average 3 years earlier than symptoms of CAD.[78] Conversely, blood pressure control is associated with a lower prevalence of ED, particularly in older patients.[79] Similarly, metabolic syndrome seems to play an important role in the etiopathogenesis of ED.[74,80,81] For men diagnosed with diabetes mellitus, the prevalence of ED is as high as 89%.[78,79] Further, obesity nearly doubles the risk of ED.[1,80] Investigators have also noted a possible association between

TABLE 60-4. Common Supplements for Erectile Dysfunction

SUPPLEMENT/HERB	MECHANISM	DOSE	PRECAUTIONS	TIP	SOR/HARM
Panax ginseng[38,45–47]	Ginsenosides, increased NO	900 mg tid	Insomnia, mania, dysrhythmias	SS-cream[46] may help premature ejaculation	B 1
Dehydroepiandrosterone[48,49]	Testosterone precursor, increased NO	50 mg daily	Insomnia, mania, acne, gynecomastia	May take up to 24 wk; best in HTN, least helpful in DM	B 2
Yohimbine[38,50–53] (Yocon)	MAO inhibition, calcium and alpha blockade, NO	5–10 mg tid	HTN, CAD, DM, mood disorders, renal/liver disease, BPH	Use very cautiously, monitor closely	A 2
L-Arginine[54,55] (Prelox, Sargenor, R-Gene-10 Solution)	Precursor to NO	1000–2000 mg tid	Gout, asthma, GI upset	Additive effect with pycnogenol[54]	B 1
Pycnogenol[54,56] (Prelox, Sargenor)	Pine bark extract, activates NO synthase	40 mg tid	GI upset, vertigo, warfarin use	Alone may take up to 12 wk; additive effect with 500 mg L-arginine tid	B 1
Propionyl-L-carnitine[57,58]	Antiinflammatory, mediates NO	1000 mg bid	GI upset	Improves sildenafil effectiveness after prostate surgery and DM	C 1
Horny goat weed/*Epimedium*[59–61] (Etana)	Icariin, PDE5 inhibition	2000 mg daily/200 mg daily	Prolonged QT, HTN, GI upset, mania	May also help osteoporosis	C 2
Ginkgo biloba[62,63]	Flavonoids, terpenoids	60–120 mg bid	ASA, warfarin use, GI upset	May help ED due to SSRIs	B 2
Saffron[64,65]	Crocins increase plasma oxygen	200 mg daily	Dry mouth, allergy (rare)	May help ED due to depression; expensive	C 1

From Natural Medicines Comprehensive Database. *Erectile Dysfunction*. <http://naturaldatabase.therapeuticresearch.com/nd/Search.aspx?cs=&s=ND&pt=&sh=6&fs=ND&id=331&r=3&searchid=26261145&txt=erectile+dysfunction#selected>; Accessed 22.03.11 (subscription required).
ASA, acetylsalicylic acid; bid, twice daily; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; DM, diabetes mellitus; ED, erectile dysfunction; GI, gastrointestinal; HTN, hypertension; MAO, monoamine oxidase; NO, nitric oxide; PDE5, phosphodiesterase type 5; SOR, strength of recommendation; SSRIs, selective serotonin reuptake inhibitors; tid, three times daily.

ED and periodontal disease.[82] The risk of ED is nearly double in men who smoke,[83] and alcoholism is known to affect sexual function in men.[83] ED therefore presents a window of opportunity to motivate lifestyle changes toward greater health.[80] One study found that men who seek treatment for ED may prefer alternatives to pharmaceutical intervention, such as lifestyle change.[70]

The most important recommendation to prevent erectile dysfunction is to encourage overall healthy behaviors to improve well-being and reduce the incidence of chronic disease.

No exercise or nutrition regimen is specifically favored for treatment of ED. However, exercise and nutrition should be tailored to each patient's specific needs. Other lifestyle recommendations include regular dental care such as flossing, which may be beneficial for cardiovascular disease and ED.[84] In addition, prolonged or frequent bicycle riding may inhibit neurovascular flow to the perineum and thereby negatively influence ED. In these patients, a trial of rest, change in exercise routine, or cycling adaptations (e.g., split seat or recumbent posture) can be tried.

Therapies to Consider

Comprehensive treatment plans based in Ayurveda, traditional Chinese medicine, and homeopathy may have value in facilitating greater overall health in the context of ED. However, evidence is insufficient to recommend specific treatments within these traditions for ED. Detoxification may be a beneficial jump-start to a healthy lifestyle and can be considered for some patients (see Chapter 104, Detoxification).

Prevention Prescription

- Obtain regular vigorous exercise most days of the week for 30 to 60 continuous minutes.
- Follow a healthy calorie-controlled antiinflammatory or Mediterranean diet rich in phytonutrients and antioxidants (organic fruits and vegetables), omega-3 fatty acids, whole grains, nuts, seeds, legumes, filtered water, green or rooibos tea, and lean or organic meats.
- Reduce stress through rest, vacation, meditation, breathing exercises, yoga, journaling, sauna, and selected manual therapies.
- Maintain healthy sexual relationships, good communication, and regular erections and ejaculations (three times/week).
- Avoid tobacco, marijuana, and other illegal or recreational drugs.
- Be moderate with alcohol consumption (2 drinks or less per day on average).
- Avoid antinutrients such as high-fructose corn syrup, trans fats, artificial sweeteners, colors, or preservatives, and processed foods.
- Avoid pesticides, herbicides, and overuse of chemical or cleaning products.
- Avoid heating or storing food in plastics (e.g., bisphenol-A endocrine and hormone disruptor).

Therapeutic Review

Workup and Evaluation

- History with International Index of Erectile Function-5 (IIEF-5) short survey and medication review
- Physical examination with blood pressure, body mass index, and genitourinary examination
- Laboratory tests (complete blood count, fasting glucose and lipids, electrolytes, creatinine, liver function tests, thyroid-stimulating hormone, prostate-specific antigen, morning total serum testosterone)

Lifestyle

- Antiinflammatory diet
- Weight loss
- Regular exercise 30 to 60 minutes daily
- Stress reduction
- Smoking cessation[83]
- Alcohol reduction

First-Line Pharmaceuticals

- Trial of phosphodiesterase type 5 inhibitor A1
  - Sildenafil (Viagra): 25 to 100 mg orally daily as needed or
  - Vardenafil (Levitra): 5 to 20 mg orally daily as needed or
  - Tadalafil (Cialis): 5 to 20 mg orally every 72 hours as needed

Nutraceuticals

- Yohimbine: 5 to 10 mg three times daily A2
- *Panax ginseng*: 900 mg three times daily B1
- Pycnogenol: 40 mg three times daily with or without 500 to 1000 mg of L-arginine three times daily B1
- L-Arginine: 1000 to 2000 mg three times daily B1
- Saffron: 200 mg daily (particularly in erectile dysfunction with depression) C1
- Propionyl-L-carnitine: 1000 mg twice daily (to improve sildenafil response) C1
- Avoidance of proprietary or low-quality brands

Mind-Body Therapy

- Psychotherapy for patients with mood disorder, posttraumatic stress disorder, sex abuse history, relationship strain, or performance anxiety B1
- Stress reduction through yoga, meditation, breathing, massage, journaling, psychotherapy, and rest B1

Second- and Third-Line Therapies

- Vacuum erection or constriction devices with training or A1
- Alprostadil (Muse) urethral suppositories: 125- to 1000-mcg pellet intraurethrally daily as needed or A2
- Alprostadil (Caverject) injections: 2.5 to 7.5 mcg intracavernosal injection three times weekly as needed or A2
- Surgery with urology referral B3

Continued

Hormone Replacement

- Hypogonadism or testosterone deficiency diagnosis, low total serum testosterone less than 300 ng/dL.
- Topical testosterone: 12.5 to 100 mg every morning titrated to normal laboratory levels checked every 4 weeks until stable 
- Compounded bioidentical testosterone 
- Serum total testosterone laboratory test every 4 weeks until stable and then every 6 to 12 months
- Initial and annual serum total testosterone, complete blood count, liver function tests, and prostate-specific antigen laboratory tests with genitourinary examination

KEY WEB RESOURCES

Cornell University Medical College: http://www.cornellurology.com/sexualmedicine/ed	Academic resource for the evaluation of erectile dysfunction (ED)
Titan Healthcare: http://www.titanhealthcare.co.uk/index.cfm/go/home	Information on vacuum erection devices and options for purchase
MedlinePlus, National Institutes of Health: http://www.nlm.nih.gov/medlineplus/erectiledysfunction.html	Patient education tutorial on ED
American Association of Sexuality Educators, Counselors, and Therapists: http://www.aasect.org	Information and resource to help find a certified therapist
Mayo Clinic: http://www.mayoclinic.com/health/erectile-dysfunction-herbs/MC00064/METHOD=print	Patient handout on herbs for ED
Penn Medicine, University of Pennsylvania: http://www.pennmedicine.org/encyclopedia/em_PrintArticle.aspx?gcid=003339&ptid=1	Information about the ED stamp test

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Chapter 61

Osteoarthritis

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Osteoarthritis (OA) is a slowly progressive degenerative disease of the joints that afflicts approximately 27 million people in the United States.[1–6] OA is already the most frequently reported chronic condition in older adults, and with the aging of the baby boom population and increased rates of obesity, investigators estimate that by 2030, more than 67 million people in the United States (25% of the population) will have OA.[6–8] The costs of OA in terms of human suffering are extremely high.

Because conventional therapies for OA have limited effectiveness, and toxicities associated with suitable drugs often limit use, many patients are left to face surgery or chronic pain, muscle weakness, lack of stamina, or loss of function.[2,9–15] OA of the hip or knee is particularly disabling because it limits ambulation, but OA also strikes the hands, spine, feet, and other joints with the same destructive process (Fig. 61-1).[1,3,11–13] The end point of the OA disease process is total loss of joint cartilage in the affected area with the need for joint replacement.[12,13]

OA is a disease with multiple causes. It should be considered not a consequence of wear and tear but, rather, a breakdown of normal physiologic pathways. The whole joint is affected in OA, with pathologic changes in bone, cartilage, and synovium.[16,17] Imbalances within the joint occur between metabolic and degradative processes facilitated by cytokines, inflammatory meditators, and chondrocyte activity.[16–18] OA is broadly broken down into two categories: primary OA, in which no specific risk factors, except for age, can be identified; and secondary OA, in which changes can be related to systemic or local factors. Figure 61-2 shows the systemic and local factors that increase susceptibility to OA.

Pathophysiology

Normal Joints

The major constituents of cartilage are water, proteoglycans (composed of protein cores in addition to chondroitin sulfate and keratin sulfate side chains), and collagen (predominantly type II). Collectively, these constituents form the extracellular matrix (ECM). Chondrocytes are metabolically active cells that are responsible for synthesis of the ECM. Proteoglycans provide elasticity of cartilage, and collagen supplies tensile strength. Muscles and ligaments provide support and protection, whereas nerve endings supply proprioceptive information. Cartilage health and function depend on compression (pumping fluid from the cartilage into the joint space and into capillaries and venules) and release (allowing cartilage to reexpand, hyperhydrate, and absorb nutrients).

Early Changes of Osteoarthritis

Early in OA, the articular cartilage surface becomes irregular, with superficial clefts in the tissue and increased chondrocyte proliferation and cluster formation.[17] Increased hydration of the ECM leads to a failure of the elastic restraint of collagen (i.e., weakening of the collagen network); in addition, proteoglycan distribution becomes altered.[16,17] Progression of OA leads to a net decrease in proteoglycans and an increase in the permeability of water. Loss of elasticity and greater permeability of water lead to higher chondrocyte stress and more exposure to degradative enzymes. As the process continues, the articular cartilage undergoes deepening of the clefts and irregularities that eventually result in ulceration and exposure of the bone.[16–18]

Late Changes of Osteoarthritis

In late OA, subchondral osteoblasts increase bone formation, thus leading to stiffer and less compliant bones. This process, in turn, results in microfractures, followed by callus formation, more stiffness, and more microfractures. The osteophytes (outgrowths of bone) that form are the hallmarks of OA. They ultimately restrict motion. Subchondral cysts are formed in an attempt to equalize pressure. Gross ulceration of articular cartilage produces focal and then diffuse areas of complete loss of cartilage. In later stages, ECM levels of proteoglycans and keratan sulfate decrease, as does the length of chondroitin

FIGURE 61-1
Degenerative joint disease. Anteroposterior (**A**) and lateral (**B**) views of the knee show the characteristic finding of osteoarthritis. Joint space narrowing and osteophyte formation at the medial and patellofemoral compartments with varus alignment at the knee are visible. A large suprapatellar joint effusion is also apparent. (From Scott NW. *Insall and Scott Surgery of the Knee*. 4th ed. Philadelphia: Churchill Livingstone; 2005.)

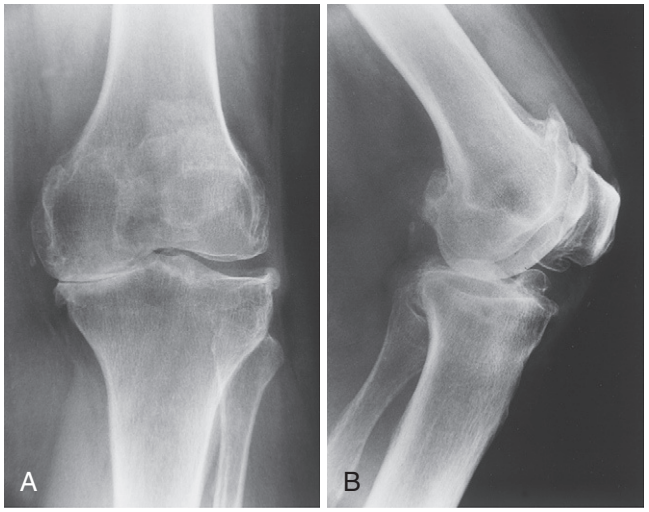
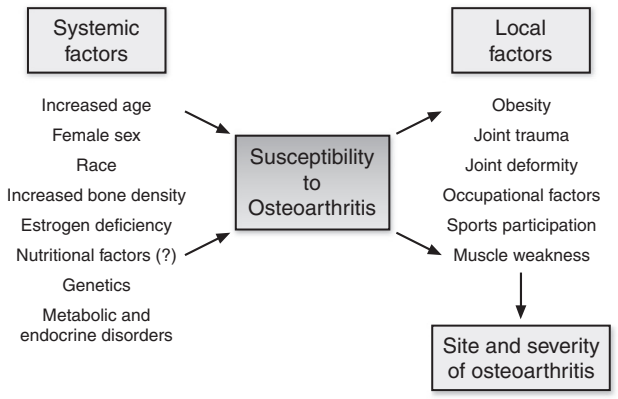


FIGURE 61-2
Systemic and local factors that increase susceptibility to arthritis. (Modified from Dieppe P. The classification and diagnosis of arthritis. In: Kuettner K, Goldberg V, eds. *Osteoarthritic Disorders*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1995:7.)



sulfate chains. These changes in concentrations of components within the ECM lead to cartilage resembling the composition of immature cartilage.[17] Soft tissues around the joint are also affected, leading to inflammatory infiltrates in the synovium, greater laxity of ligaments, and weakened muscles.

Other factors in the inflammatory and destructive processes in the joint include the matrix metalloproteinase (MMP) family of proteinases, which degrade proteoglycans and collagen,[17,18] and the cytokines interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), which upregulate MMP gene expression, facilitate damage to the joint, and inhibit reparative pathways that would restore joint integrity.[19] Other cytokines involved in OA processes include the proinflammatory cytokines IL-6, IL-8, IL-11, IL-17, and leukemia inhibitory factor (LIF), as well as the antiinflammatory cytokines IL-4, IL-10, and IL-13.[19]

Integrative Therapy

Integrative therapy in OA is aimed at reducing pain, improving joint functionality, and reducing further progression of the disease. Some complementary therapies have potential disease-modifying effects, such as glucosamine and chondroitin sulfates, whereas other treatments provide symptomatic relief.

Nutrition

Antiinflammatory Diet

An antiinflammatory diet is characterized by emphasizing omega-3 fatty acids (found primarily in deep-water fish), minimizing omega-6 fatty acids, and emphasizing unprocessed whole grains, beans, and fruits and vegetables. Fish oil, especially eicosapentaenoic acid, is often added as a supplementary measure. Significant overlap exists between the antiinflammatory diet and the Mediterranean diet that can reduce risk of cardiovascular disease.[20,21]

Antiinflammatory diets have demonstrated clinical benefits in persons with inflammatory diseases such as rheumatoid arthritis.[20,22] More extensive antiinflammatory dietary measures such as a gluten-free vegan diet have been shown to reduce inflammatory markers in patients with rheumatoid arthritis,[23] as well as improving symptoms.[24]

Williams et al[25] found that a diet high in fruits and vegetables, independent of lifestyle effects and body mass index, was likely protective against radiographic hip OA (see Chapter 86, The Antiinflammatory Diet).

Weight Loss

Weight is directly related to the development of OA; overweight persons are at a higher risk.[26] In patients who already have symptomatic OA, weight loss may decrease pain and slow progression of the disease.[27] In one study, a 10% reduction in weight led to a 28% improvement in function.[28] Messier et al[29] found that a combination of moderate exercise with modest weight loss provided better overall improvements in self-reported measures of function and pain, as well as in performance measures of mobility in a population of older overweight and obese adults with OA of the knee, than did either intervention alone. In a 2010 study,[30] investigators found that a 10% weight loss in obese and overweight patients with OA was associated with a reduction in biomechanical pathologic features of OA of the knee by decreasing knee joint compressive loads during walking compared with low to no weight loss (see Chapter 38, An Integrative Approach to Obesity).

A 10% reduction in weight in obese individuals can lead to a 28% improvement in function.

Exercise

Three types of exercise should be incorporated into a program for OA sufferers: aerobic training, resistance training and muscle strengthening, and flexibility and range of motion. Because both group-based and home-based programs may be effective, the patient's preference is an important consideration.[31]

The Fitness and Arthritis in Seniors Trial (FAST) assessed the effectiveness of aerobic and resistance exercise on pain, disability, and disease progress in patients with knee OA. Positive effects were found for both types of exercise.[32,33] In addition, aerobic training can reduce risk factors associated with disease states, such as heart disease and diabetes, and thereby improve overall health status. Recommended exercises are walking, biking, swimming, aerobic dance, and aerobic pool exercises. For patients with symptomatic hip OA, aquatic exercises can be effective.[33]

Exercise is the most effective nonpharmacologic treatment for reducing pain and improving function. Some form of physical activity should be done on most days, with a more formal exercise routine at least three days per week.

Muscles are important shock absorbers and help stabilize the joint. Therefore, periarticular muscle weakness may result in progression of structural damage to the joint in OA. In addition, insufficient loading of a joint leads to atrophy of both articular cartilage and subchondral bone.[34] Strength training generally helps offset the loss of muscle mass and strength typically associated with normal aging. Strength training has been found beneficial for older adults, especially those with OA because it not only improves muscle strength but also increases function and reduces pain.[35] Clinicians should reassure patients with OA that strengthening exercises will not exacerbate their symptoms if the exercises are done in the appropriate manner and dose.[35]

Flexibility is a general term that encompasses the range of motion of single or multiple joints and the ability to perform certain tasks. The range of motion of a given joint depends primarily on the structure and function of bone, muscle, and connective tissue. Cartilage needs regular compression and decompression to enable it to remodel and repair damage, as well as to receive appropriate nutrients. OA affects the structure of these tissues such that range of motion and flexibility are reduced. The basis of exercise interventions to improve flexibility is that the muscle and connective tissue properties can be improved, thereby enhancing function.[36]

General Recommendations

Although doses vary, patients should consider 20 minutes of exercise, three times a week, building up to at least 180 minutes of mild to moderate exercise per week. The exercise recommendations given here are based on studies assessing exercise for the treatment of OA. The regimens are only guidelines and should be modified according to a patient's current health status and severity of OA. These regimens can also be appropriate for those attempting a weight loss program.

Aerobic Exercise

This form of exercise has three phases: (1) the warmup phase (slow walking, calisthenics: arm circles, trunk rotation, shoulder and chest stretches and side stretches), for 10 minutes; (2) the stimulus phase (walking at 50% to 70% of heart rate reserve), for 40 minutes; and (3) the cool down phase (slow walking and flexibility exercises: shoulder stretch, hamstring and lower back stretch), for 10 minutes.

Dosage

Patients should exercise for 1 hour per session, three times weekly.[32]

Resistance Training and Muscle Strengthening

A strength training program that provides progressive overload to maintain intensity throughout the exercise program has been found to be most beneficial for improvements in strength, function, and pain reduction in older adults with OA.[35]

A resistance program also has three phases: (1) the warmup phase, for 10 minutes; (2) the stimulus phase, for 40 minutes; and (3) the cool down phase, for 10 minutes. During the stimulus phase, exercises should improve the overall muscular fitness of the person and strengthen the major muscle groups of both the upper and lower extremities. Each exercise should be done in 2 sets of 12 repetitions. Exercises can include leg extension, leg curl, step-up, heel raise, chest fly, upright row, military press, biceps curl, and pelvic tilt. These exercises can be performed with dumbbells, cuff weights, or resistance machines.[32]

Dosage

Patients should exercise for 1 hour per session, three times weekly.

Flexibility and Range of Motion

Exercises that develop and improve range of motion also aid in maintaining flexibility. These exercises involve static movements and maintained stretching of the major muscle groups. The exercises should be performed two to three times/week and be of moderate intensity (5 to 6 out of 10, with 10 the most intense).[36,37]

General Precautions

Two precautions should be considered before implementation of an exercise program in patients with OA: (1) exercise of an acutely inflamed or swollen joint should be deferred until the acute process subsides and (2) an exercise stress test should be performed to identify cardiac disease in those at risk.[38]

Precautions With Resistance and Strength Training

When beginning a resistance and strength training program, patients should start with the lowest possible resistance (1.3 kg for upper body and 1.1 kg for lower body). Weight

should be increased in a stepwise fashion guided by the patient's tolerance. If a patient is able to complete 2 sets of 10 repetitions, then the weight is tolerable. If a patient establishes a plateau in weight tolerance, then it is appropriate to increase the weight when the patient is able to perform 2 sets of 12 repetitions for 3 consecutive days.[32]

Mind-Body Therapy

Telephone Interventions

Telephone-based strategies can be an integral part of the management of chronic disease. A randomized controlled trial evaluated whether telephone-based or office-based interventions, or both, improved the functional status of patients with OA.[39] Subjects in the intervention groups were contacted monthly by telephone or scheduled clinic visits by trained people who were not health care professionals. At each contact, the following items were discussed: (1) joint pain, (2) medications, (3) gastrointestinal and other medication-related symptoms, (4) date of the next scheduled outpatient visit, (5) an established mechanism by which patients could telephone a physician during weekends and evenings, and (6) barriers to keeping appointments. At 1 year, in comparison with the control group, persons receiving telephone calls reported less physical disability and pain and tended to have better psychological status.[40] The Internet may be used in the future to improve patient outcomes.

Dosage

Telephone calls are made to patients twice weekly for 6 months[39] or monthly.[40]

Precautions

A good patient-provider relationship ensuring effective communication and the ability to understand and implement medical guidance over the telephone should exist before patients are counseled by telephone.

Group Programs

The Arthritis Self-Management Program (ASMP) is a community-taught, peer-led intervention in which patients gain the confidence and the necessary tools to manage their disease. Participants attend 2-hour weekly sessions for 6 weeks. These sessions include education about pathophysiology and pharmacotherapy, as well as the design of individualized exercise and relaxation programs, appropriate use of injured joints, aspects of patient-physician communications, and methods for solving problems that arise from illness. The sessions are taught from an interactive model, which promotes individual participation and self-management techniques.[41] A 4-year follow-up study found that participants had reduced pain and fewer physician visits, and they spent fewer days in the hospital.[41]

Dosage

Patients attend a group course with an experienced teacher twice weekly for at least 12 weeks.

Precautions

This approach may not work for patients who need more attention or individual face-to-face education.

Yoga

One small randomized controlled trial demonstrated that weekly yoga for 8 weeks, in addition to patient education, group discussion, and support, improved pain and tenderness symptoms in patients with OA of the hand.[42] Yoga may also help patients in pain to become more aware of pain, as well as cognitive and behavioral responses associated with pain.[43,44]

Dosage

Although the dose is variable, patients should consider Hatha yoga, at 1 hour per week for 8 weeks.

Precautions

Several types of yoga practices exist; it is important to begin with gentle, easy exercises.

Physical Modalities

Reduction of Joint Loading

Patients with OA of the knee or hip should avoid prolonged periods of standing, kneeling, or squatting. In patients with unilateral OA of the hip or knee, a cane, when held in the contralateral hand, may diminish joint pain by reducing joint contact force. Bilateral disease may necessitate the use of crutches or a walker.[45] A Cochrane Review on the use of braces or orthoses for knee OA indicated only limited evidence to support the effectiveness of these devices.[46] However, the trials that have been undertaken indicate good symptom relief from the use of wedged insoles in patients with OA of the medial knee compartment.[47] The 2008 Osteoarthritis Research Society International (OARSI) guidelines indicated that patients with knee OA and mild to moderate varus or valgus instability may benefit from knee bracing because bracing can reduce pain, improve stability, and reduce the risk of falling.[33]

Heat Therapy

Application of heat can raise the pain threshold and produce muscle relaxation. Moist heat produces greater elevation of the subcutaneous temperature than dry heat and is often preferable for relief of pain. A randomized placebo-controlled double-blind clinical trial examining the effects of local hyperthermia induced by 433.92-MHz microwave diathermy in OA of the knee found that three 30-minutes sessions per week for 4 weeks produced significant improvements in pain reduction and physical function.[48]

Superficial heat penetrates the skin only a few millimeters and does not reach deeper joints such as the hip and knee. In contrast, a heat mitten may raise the temperature of the small joints of the hand.[49]

Dosage

For commercial hot packs (temperature, 165°F to 170°F), treatment time is 15 to 30 minutes, and the temperature is adjusted to the patient's tolerance by using commercial covers or increasing towel thickness between the patient and the hot pack. For diathermy, patients undergo 30-minute sessions three times weekly for 4 weeks.

Precautions

The risk of thermal injury is higher in patients with poor circulation or impaired sensation.[45] Use heat therapy with caution in patients who have reduced peripheral circulation or severe cardiac insufficiency. Be aware of superficial metal implants and open or closed wounds in skin.

Cold Therapy

Cold applications are often recommended after strenuous exercise to relieve muscle aching. They may be delivered by ice packs, ice massage, or local spray. Superficial cooling can decrease muscle spasm and raise the pain threshold. A Cochrane Review of three randomized controlled trials showed that ice treatment may improve range of motion and reduce edema in knee OA.[50]

Dosage

Most cold applications are for 20 to 30 minutes and are reapplied in 2 hours. Rewarming times should be at least twice as long as cooling times, to avoid excessive cooling.

A classic ice pack (23°F to 32°F) is a mixture of crushed ice and cold water wrapped in terry cloth or enclosed in a plastic bag. These packs usually maintain a surface temperature above freezing and thus do not require an insulator between the patient's skin and the pack.

Cold packs (33°F to 50°F) are a mixture of water and antifreeze that forms a gel mixture in a vinyl cover. These gel packs may induce frostbite because of their low temperature, so a layer between the skin and the pack is warranted. Treatment should be limited to less than 30 minutes with these cold packs.

Precautions

Cold applications should not be used in patients with Raynaud's phenomenon, cold hypersensitivity, cryoglobulinemia, or paroxysmal cold hemoglobinuria.[45]

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) has been considered as a treatment modality for OA of the knee or hip. It can help with short-term pain relief, and no serious side effects have been reported.[33]

Dosage

For conventional TENS, the frequency is 85 pps, the pulse width is 75 μsec. The intensity is sensory, with placement of pads over the target tissue, dermatome, or nerve distribution. The duration of application is 15 to 30 minutes to 4 hours (until relief is obtained). The frequency of application is one to six times daily, depending on the patient's response and the intensity of pain.

Precautions

Use TENS with caution in patients who have cardiac pacemakers, implanted cardioverter defibrillators, ECG monitors, other electronic implants, skin allergic reactions, and impaired skin sensation, as well as in patients who drive or operate hazardous machinery and are currently taking pain medications.

Stimulation over the intercostal muscles should be avoided or closely monitored because, in one case report of a patient with cardiac disease, this stimulation led to respiratory failure. In addition, caffeine intake higher than 200 mg/day (approximately 3 cups of coffee/day) decreased the ability of the TENS to modulate pain.[51]

Massage

Massage may lead to improvement in pain and function. A randomized control trial of Swedish massage therapy in patients with OA found significant improvements in pain, stiffness and physical function, pain perception, knee range of motion, and time to walk 50 ft.[52] Research to replicate these findings and further define the role of massage in the treatment of OA of the knee is ongoing. Research evaluating the role of massage in the treatment of other joints afflicted with OA is also needed.

Dosage

The dose of Swedish massage is 60 minutes per week.

Precautions

Although the risk of local pain from excessive pressure or bruising does exist, massage is commonly performed and is generally not harmful. Massage likely has no serious risks.

Acupuncture

Acupuncture-associated analgesia is believed to work through the release of opioid peptides.[53] Numerous randomized controlled trials have been undertaken to assess the efficacy of acupuncture for treatment of pain associated with OA. In a 1975 study, 40 patients were randomly allocated to receive acupuncture either at standard points or at placebo or sham points.[18] Analysis before and after treatment showed a statistically significant improvement in tenderness and subjective report of pain in both groups.[54] In a 1982 study, 32 patients with OA of the hip, knee, or humeroscapular joint were randomly allocated either to receive weekly acupuncture or to take piroxicam, with checkup visits at 2, 4, 6, 12, and 16 weeks. The extent of improvement was equal in both groups at 2 weeks (30%); after that, however, the acupuncture group showed greater pain relief than the piroxicam group.[55] A systematic review of 11 randomized controlled trials of acupuncture for OA concluded that the most rigorously conducted studies showed that acupuncture is not superior to sham needling in reducing pain from OA.[56] The most recent Cochrane Review of acupuncture reported that although sham-controlled trials do have statistically significant benefits, the benefits do not meet the predefined thresholds for clinical relevance, and the benefits are small.[57] The investigators also noted that the benefits are likely the result of placebo effect or participant expectations.[57]

Another randomized controlled trial, however, suggested that acupuncture may indeed provide relief for OA pain, unlike sham acupuncture.[58] In this trial, 570 patients with knee OA were randomly allocated to receive 23 sessions of either true or sham acupuncture over 26 weeks or to participate in 6 2-hour education sessions over 12 weeks (control). Persons in the true acupuncture group showed an improvement in function at 8 weeks and a significant improvement in pain at 26 weeks compared with the sham and control groups, as evidenced by scores on

the Western Ontario and McMaster Universities Arthritis Index (WOMAC).[58]

Acupuncture may serve as an adjunct to a conventional medical regimen by allowing a reduction in dosage of nonsteroidal antiinflammatory drugs (NSAIDs) and therefore potentially reducing the side effects occasionally seen with long-term NSAID use.[59] Each state has its own requirements for acupuncture licensure and certification. Patients should be referred only to a licensed or certified practitioner.

The 2008 OARSI recommendations for managing OA of the knee noted that acupuncture may be of symptomatic benefit in patients with knee OA.[33] In addition, although multiple sham-controlled trials showed minimal benefit over sham, acupuncture may still provide symptomatic relief for patients with OA who are wary of or unable to use pharmaceutical interventions.[60]

Dosage

Acupuncture treatments vary depending on the patient's underlining conditions, the severity and location of pain, and the practitioner's assessment. However, most acupuncture treatments last between 15 and 30 minutes with needles inserted. A common acupuncture regimen consists of treatment once to three times weekly.

Precautions

Acupuncture may cause bleeding or bruising at the site of needle insertion. Therefore, patients taking blood thinning medications may have a higher incidence of this side effect.

Acupuncture has been shown to improve both pain and function in osteoarthritis of the knee. Six or more treatments are often required before efficacy can truly be assessed.

Supplements

Glucosamine Sulfate and Chondroitin Sulfate

Glucosamine's primary role is as a substrate for glycosaminoglycans and the hyaluronic acid backbone used in the formation of proteoglycans found in the structural matrix of joints.[61] Chondroitins are the main glycosaminoglycans in human joints and connective tissue, and they play a role in cartilage formation through the stimulation of chondrocyte metabolism and synthesis of collagen and proteoglycans.[62] Destructive synovial enzymes are inhibited by chondroitin.[63] Unlike other therapies used as symptom modifiers, such as NSAIDs, these supplements are potentially structure modifying.[33] Glucosamine sulfate and chondroitin sulfate are sulfate derivatives of glucosamine and chondroitin, and doubts regarding their absorption and metabolic fate have fueled skepticism about their therapeutic potential.[64] This dilemma has stimulated numerous studies.

In a 2001 double-blind randomized controlled trial,[65] 212 patients with knee OA were randomly assigned to receive either 1500 mg of glucosamine sulfate or placebo once daily for 3 years. Seventy-one of 106 patients receiving placebo completed the trial, and radiographs of their knees showed progressive joint space narrowing. Sixty-eight of 106 patients receiving glucosamine sulfate completed the trial, and they had no radiographic evidence of joint space narrowing. This study concluded that oral administration of glucosamine sulfate over the long term could prevent joint structure changes in patients with OA of the knee, as well as improve symptoms.[65]

Two randomized controlled trials looked at the effectiveness of chondroitin sulfate in OA.[66,67] In one trial, 300 patients with knee OA were randomly assigned to receive either 800 mg of chondroitin or placebo once daily for 2 years.[66] Although the study found no significant symptomatic effect, results suggested that long-term chondroitin sulfate use may retard radiographic progression of the disease. A 2004 study of 120 patients receiving either the same dosage of chondroitin sulfate or placebo for 1 year provided some evidence that chondroitin sulfate may reduce pain and improve function associated with knee OA.[67]

To evaluate the benefit of glucosamine sulfate and chondroitin sulfate for OA, a meta-analysis combined with systematic quality assessment was performed.[68] Fifteen double-blind randomized placebo-controlled trials were included in the analysis. The knee was the joint studied in all the trials, and in one study the hip was also evaluated. Glucosamine or chondroitin sulfate was taken orally in 12 of the studies, intramuscularly in 2 of the studies, and intraarterially in 1 of the studies. Glucosamine sulfate or chondroitin sulfate demonstrated a moderate to large effect on OA symptoms. However, methodologic problems may have led to exaggerated estimates of benefit. Overall, these compounds do appear to have efficacy in treating OA symptoms, and they are safe.[68] Glucosamine may not be as effective in patients who are obese compared with patients of normal weight.

The Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) compared 1500 mg of glucosamine hydrochloride alone and in combination with chondroitin in 1500 people with mild knee pain from OA. Using an end point of 20% reduction in pain, no significant benefit of each supplement individually or in combination was noted. Those individuals with more severe symptoms (moderate to severe OA) reported a 22% reduction in pain. Glucosamine hydrochloride was used in this trial. Most over-the-counter products contain glucosamine sulfate.[69]

Glucosamine and chondroitin are sold as dietary supplements in most health food stores, as well as in many pharmacies. They are often sold in combination; however, it is unclear whether the combination is superior to either treatment alone.[70] In December 1999 and January 2000, a health consultant firm purchased 25 brands of glucosamine, chondroitin, and combination products to test whether the products contained the amounts listed on their respective labels. Nearly one third of the products did not contain the stated amounts of the supplements.[71] According to Vangsness et al,[72] glucosamine and chondroitin sulfate have shown inconsistent but overall positive efficacy in decreasing OA pain and improving joint function. The safety of these compounds was equivalent to that of placebo. In addition, although the literature suggests that individual use of glucosamine sulfate, chondroitin sulfate, or glucosamine hydrochloride has therapeutic value, the effectiveness of monotherapy with these agents has not been proven.[72]

Dosage
The dose of glucosamine sulfate is 500 mg three times daily, and the dose of chondroitin sulfate is 300 mg three times daily, both for a minimum of 6 weeks.

Precautions
Potential adverse effects include dyspepsia, nausea, and headache.

S-Adenosylmethionine
S-Adenosylmethionine (SAMe) is a physiologic molecule formed in the body from the essential amino acid methionine. It functions in a wide variety of anabolic and catabolic reactions in all living cells. Although the mechanism of action on the symptoms of OA is not fully understood, it may be related to the agent's ability to stimulate proteoglycan synthesis in OA cartilage.[73] The U.S. Food and Drug Administration approved SAMe for sale as a dietary supplement in 1999; however, it has been used since the mid-1970s, primarily in Europe to treat depression and arthritis.[74]

To encourage production of *S*-adenosylmethionine in the body, patients with osteoarthritis who have low folic acid levels should consider increasing these levels through higher consumption of dark green leafy vegetables or supplementation.

A 1987 double-blind randomized controlled trial compared 1200 mg of SAMe with 1200 mg of ibuprofen taken by 36 patients with OA of the knee, hip, or spine, or a combination, for 4 weeks.[75] Morning stiffness, pain at rest and during motion, crepitus, swelling, and limitation of motion in the affected joints were assessed before and after treatment. The study found that both treatments were well tolerated and equally effective in lessening symptoms. The investigators thus concluded that SAMe exerted a beneficial effect on the symptoms of OA.[75] Similar results were found in a trial comparing 1200 mg of SAMe and 150 mg of indomethacin; SAMe was better tolerated.[76] A later randomized double-blind crossover study comparing celecoxib with SAMe in 56 patients with knee OA suggested that SAMe may be as effective as celecoxib at reducing symptoms but may have a slower onset of action.[77] *The Arthritis Foundation's Guide to Alternative Therapies* noted that SAMe is a promising treatment worth trying for pain relief, but that more scientific evidence is needed to prove that it supports cartilage repair.[78]

Dosage
The dose is 400 to 1600 mg daily; a common regimen is 600 mg twice daily.

Precautions
Watch for nausea and gastrointestinal distress. Ensure adequate intake of vitamin B_{12} and folate through diet (green leafy vegetables) or supplementation to optimize SAMe supplementation.[79,80] Do not take close to bedtime because of the risk of insomnia.

Methylsulfonylmethane
Methylsulfonylmethane (MSM) is a dietary supplement commonly sold for the treatment of OA. The MSM metabolite dimethyl sulfoxide is found naturally in the human body. Because sulfur is necessary for the formation of connective tissue, MSM is thought to be useful in the treatment of OA. Animal studies have suggested that MSM may help decrease inflammatory joint disease,[81] but unfortunately, no published human trials are available. Overall, the literature on the sulfur-containing compounds SAMe and MSM, in OA appears to be limited. However, the literature shows trends toward decreased pain and increased function with consistent use of these compounds. The therapeutic benefit and safety of these compounds for long- and short-term use needs to be further researched, especially through randomized clinical trials.[72,82]

Dosage
The dose is 1000 to 3000 mg three times daily.

Precautions
Watch for nausea, diarrhea, and headache. Although MSM is promoted as being nontoxic, clinical data are lacking, and further scientific study is needed to define the efficacy and safety of this supplement.

Pharmaceuticals: Nonopioid Analgesics

Acetaminophen
Acetaminophen acts by inhibiting prostaglandin synthesis in the central nervous system. It may relieve mild to moderate joint pain and may be used as initial therapy on the basis of its overall cost, efficacy, and toxicity profile.[83]

Dosage
The dose is 325 to 1000 mg every 4 to 6 hours, up to a maximum of 4 g/day.

Precautions
Reactions are uncommon with normal therapeutic doses of acetaminophen but include nausea, rash, and minor allergic reactions, transient drop in white blood cell count, liver toxicity, and prolongation of the half-life of warfarin. Patients with hepatic impairment or active hepatic disease must be monitored when acetaminophen is prescribed for the long term. Patients with viral hepatitis, alcoholism, or alcoholic hepatic disease are at greater risk for acetaminophen-induced hepatotoxicity.[84] Long-term acetaminophen use should be avoided in patients with underlying renal disease. Tobacco smoking may also potentially increase the risk for acetaminophen-induced hepatotoxicity.[84]

Tramadol
Tramadol is a synthetic opioid agonist that inhibits reuptake of norepinephrine and serotonin. It should be considered for patients with moderate to severe pain in whom acetaminophen therapy has failed and who have contraindications to NSAIDs.[75]

Dosage
The dose is 50 to 100 mg every 4 to 6 hours, up to a maximum of 400 mg/day.

Precautions
Watch for nausea, constipation, drowsiness, and, rarely, seizures.

Pharmaceuticals: Nonsteroidal Antiinflammatory Drugs

Nonselective Cyclooxygenase Inhibitors
Nonselective NSAIDs are a group of chemically dissimilar agents that act primarily by inhibiting the cyclooxygenase (COX) enzymes and thus inhibit the production of prostaglandins in peripheral tissues. Examples are aspirin, ibuprofen, naproxen, indomethacin, sulindac, and piroxicam.

Dosage
- Aspirin: 2.6 to 5.4 g in divided doses daily
- Ibuprofen: 300 to 800 mg three or four times daily; maximum, 3200 mg/day
- Naproxen: 250 to 500 mg twice daily; maximum, 1500 mg/day
- Indomethacin: 25 mg two or three times daily; maximum, 200 mg/day
- Sulindac: 150 to 200 mg twice daily; maximum, 400 mg/day
- Piroxicam: 20 mg daily or 10 mg twice daily

Cyclooxygenase-2 Inhibitor
COX-2–specific inhibitors act in the same manner as nonselective COX inhibitors, but their action is confined to inflamed tissues. Celecoxib (Celebrex) is the only COX-2 inhibitor currently available on the market.

Dosage
The dose of celecoxib (Celebrex) is 200 mg daily or 100 mg twice daily.

Precautions for All Nonsteroidal Antiinflammatory Drugs
Precautions vary with specific agent and include epigastric distress, nausea, vomiting, gastrointestinal bleeding (nonselective NSAIDs more than COX-2 inhibitors), prolonged bleeding (aspirin), headache, dizziness, and renal toxicity. Epidemiologic studies have shown that COX-2 inhibitors may increase the risk of myocardial infarction.[85]

The choice between nonselective NSAIDs and COX-2–specific NSAIDs should be based on the risk of upper gastrointestinal bleeding.

> Data from epidemiologic studies demonstrate that among persons 65 years old and older, 20% to 30% of all hospitalizations and deaths resulting from peptic ulcer disease are attributable to NSAID use.[86]

Persons at increased risk of gastrointestinal bleeding are those 65 years of age or older, as well as those with a history of peptic ulcer disease, previous upper gastrointestinal bleeding, concomitant use of oral corticosteroids or anticoagulants, and, possibly, smoking and alcohol consumption.[87] Patients in this category may benefit from a COX-2–specific inhibitor or a nonselective NSAID with gastroprotective therapy (e.g., misoprostol, omeprazole, or high-dose famotidine).

Pharmaceuticals: Opioid Analgesics

Patients with OA who have tried acetaminophen, tramadol, and NSAIDs without success may consider opiates. Opiates bind to receptors in the central nervous system to produce effects that mimic the action of endogenous peptide neurotransmitters—specifically, the relief of intense pain. These agents should usually be avoided for long-term use, but their short-term use helps in the treatment of acute exacerbations of pain.[88] Commonly used opiates are fentanyl, meperidine, propoxyphene, acetaminophen plus propoxyphene, hydromorphone, long-acting morphine, oxycodone plus acetaminophen, and acetaminophen plus hydrocodone.

Dosage
Doses and routes vary.

Precautions
In addition to the potential for addiction to these agents, side effects include constipation, nausea, vomiting, sedation, urinary retention, and respiratory depression.

Pharmaceuticals: Topical Analgesics

In patients with OA of the hands or knees, topical analgesics may relieve mild to moderate pain.[89] A cream may be used alone or in combination with an oral agent.

Capsaicin Cream
Capsaicin cream (Zostrix) is a commonly used topical agent. It exerts its pharmacologic effect by depleting local sensory nerve endings of substance P, a neuropeptide mediator of pain.

Dosage
A thin film of capsaicin cream (0.025%, 0.075%) should be applied to the symptomatic joint four times daily.

Precautions
A local burning sensation is common but rarely leads to the discontinuation of therapy.

Diclofenac
Aside from capsaicin cream, diclofenac sodium is available as a topical solution. This product (Pennsaid) combines diclofenac with dimethylsulfoxide (DMSO). Pennsaid is indicated for the treatment of signs and symptoms of OA of the knee. Most studies have shown topical diclofenac to be equivalent to oral diclofenac in the treatment of OA of the knee.[90–94] Pennsaid, in particular, has also shown similar effectiveness in treatment of OA of the knee, although further studies to compare Pennsaid with other formulations of diclofenac have yet to be done.[90]

Dosage
Diclofenac topical (Pennsaid 1.5% topical solution plus DMSO, Solaraze 3% gel, Voltaren topical 1% gel) is applied to the knee four times daily. It may also be used for other areas of body or joint pain. The Flector patch is applied directly to the area of pain. The skin patch can be worn for up to

12 hours and then removed. Apply a new patch at that time if pain continues. Do not wear a skin patch while taking a bath or shower or while swimming.

Precautions

Although diclofenac is applied topically, it is absorbed systemically and has possible side effects. Aside from local irritation at the site of application, diclofenac topical solutions, like other NSAIDS, may the increase risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke or increased gastrointestinal events such as bleeding, ulceration, and perforation of stomach or intestines.

Intra-Articular Steroid Injections

Injections are useful in treating a joint effusion or local inflammation that is limited to a few joints. Injections should be limited to three or four per year because of concern about the possible development of progressive cartilage damage through repeated injections in weight-bearing joints.[95]

Other Pharmaceuticals: Diacerein

Diacerein (INN), also known as diacetylrhein, is a drug used in the treatment of OA. It works by inhibiting IL-1. A 2006 Cochrane Review found no significant difference between diacerein and NSAIDS.[96] Although diacerein may have a better risk-to-benefit ratio compared with NSAIDS, it also has an important side effect of diarrhea. In addition, diacerein may have a mild effect on the symptoms of OA and structure-modifying effects in patients with symptomatic OA of the hip, and further research is necessary to confirm the short- and long-term effectiveness and toxicity.[33,96]

Dosage

The dose is 50 mg twice daily.

Precautions

Diacerein may cause diarrhea. It is also a long-acting drug with symptomatic effects appearing 4 weeks after beginning treatment.[96]

Surgery

Surgical treatment is usually considered only after failure of nonsurgical treatments. The two categories of surgery are nonbiologic and biologic.[89]

Nonbiologic Approaches

- *Osteotomy:* This conservative approach may provide effective pain relief and slow disease progression. Its greatest benefit is in patients with only moderately advanced disease.
- *Arthroscopy:* Removal of loose cartilage fragments can prevent locking and relieve pain. When joint space narrowing is substantial, this type of surgical procedure is of limited benefit.
- *Arthrodesis or joint fusion:* This alleviates pain and is most commonly performed in the spine and in small joints of the hand and foot. In the hip and knee, it is reserved for very young patients with unilateral disease.
- *Arthroplasty or total joint replacement:* This is the mainstay of surgical treatment of the hip, knee, and shoulder. It is the most effective of all medical interventions and can restore patients to near-normal function. It is limited in durability in persons with life expectancies exceeding 20 years and in those who wish to participate in high-demand activities.

Biologic Approaches

- Biologic restoration of articular cartilage uses resident hyaline cartilage, which is stimulated to repair its own defects.
- Biologic restoration of articular cartilage is performed using one of three types of cartilage transplantation: osteochondral autografting, osteochondral allografting, and tissue engineering.

Therapies to Consider

Omega-3 Fatty Acids

Omega-3 fatty acids, the precursors for antiinflammatory prostaglandin production in the body, can be very supportive in the treatment of patients with OA. Multiple studies have shown efficacy of increased omega-3 fatty acids in the diet or by supplementation for reducing or alleviating symptoms of rheumatoid arthritis.[97–100] In different animal (dog) studies, investigators found that dietary supplementation with omega-3 fatty acids from fish oil led to an increase in weight-bearing tolerance and a reduction in the need for the NSAID carprofen.[101,102] An in vitro study showed that omega-3 fatty acids caused a reduction in the levels of mRNA for a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4, ADAMTS-5, matrix MMP-3, MMP-13, COX-2 (but not COX-1), IL-1alpha, IL-1beta and TNF-alpha, which are key contributors to the pathologic process of OA. Investigators also found in this study that eicosapentaenoic acid was most effective, followed by docosahexaenoic acid, and finally by alpha-linoleic acid. Arachidonic acid, an omega-6 fatty acid, had no effect.[103]

Curcumin

Curcumin is the active ingredient in the spice tumeric. It has been used in various cultures around the world, particularly in India and Asia. Research on curcumin has found that it has many properties, which may explain the diversity of it's traditional uses. These properties include anticancer, antiinflammatory, antioxidant, and hypolipidemic effects.[104] Curcumin has been researched for benefits in the treatment and management of cardiovascular disease, hypercholesterolemia, diabetes mellitus, insulin resistance, weight loss, and inflammatory conditions.[104] This supplement may be most beneficial for those with OA with other concomitant conditions, such as obesity, diabetes, heart disease, or autoimmune conditions.

In 2009, an in vitro study using articular chondrocytes found that curcumin acted as a strong inhibitor of inflammatory and catabolic mediators, nitric oxide stimulated by IL-1beta, prostaglandin E_2, IL-6, IL-8, and MMP-3, produced by chondrocytes.[105]

Avocado Soybean Unsaponifiables

Avocado soybean unsaponifiables (ASU) are extracts of unsaponifiable fractions from one-third avocado oil and two-thirds soybean oil.[106] In multiple animal and human in vitro studies, investigators been found that ASU extract has an effect on various cytokines in articular chondrocytes and monocyte/

macrophages.[107] In a multicenter randomized controlled trial, persons taking ASU had slightly lower need for NSAIDs and an improvement in functional disability. Improvement was greatest in patients with hip OA.[106] Most of the in vitro and in vivo studies have used an ASU product that is patented and sold in Europe (Piascledine 1300, Laboratoires Expanscience, France). Because this formulation is unique, the data obtained from its use cannot be extrapolated to all ASU extracts, and thus further studies examining various ASU extracts from multiple manufacturers and processes of extraction are needed.[107]

Boswellia serrata

Boswellia serrata, also known as H15 or indish incense, is a botanical used in traditional Ayurvedic medicine; in vitro, it decreases leukotriene synthesis.[108] A double-blind pilot study evaluated the efficacy of H15 in 37 patients with rheumatoid arthritis. Treatment with H15 showed no measurable efficacy.[108] A double-blind randomized controlled trial found that *Boswellia* improved symptoms of knee OA. Treatment included a combination of herbs, rather than *Boswellia* alone.[109] A single-blind randomized controlled trial in which *Boswellia* was taken along with *Withania, Curcuma,* and a zinc complex found that this combination led to improvement in pain and disability in OA.[110]

Although the literature on this agent is promising, it is insufficient to support the use of *B. serrata* for OA. Taken in combination with other herbs, *Boswellia* may improve pain and function.

Ginger

Ginger root is an herb used extensively as a spice in many world cuisines. More recently, attention has focused on the possible medical benefits of ginger, including reduction of nausea and analgesic effects. One study suggested that ginger may be moderately effective in reducing pain from knee OA.[111] This 6-week multicenter randomized controlled trial evaluated the effect of a highly concentrated standardized ginger extract in 261 patients in comparison with placebo. A moderate reduction of pain was observed in the ginger-treated group. Some mild adverse gastrointestinal effects were also observed in the ginger group, but the overall safety profile was good.

Magnet Therapy

A popular therapy for the treatment of various medical conditions is the application of a magnetic field. The biologic effects of low-level magnetic fields have been studied since the 1500s. Explanations of these effects include increased circulation and decreased inflammation.[112] One double-blind randomized controlled study[113] evaluated bipolar magnets for the treatment of chronic low back pain. The researchers concluded that the application of magnets had no effect on patients' pain.[113] However, a later randomized controlled trial suggested that standard-strength magnetic bracelets may be effective in decreasing pain from OA of the knee and hip.[114] Although magnet therapy does appear to be harmless, its therapeutic use remains questionable. According to the OARSI guidelines for the management of hip and knee OA, five placebo-controlled randomized controlled trials showed that improvement in function was small and efficacy for reduction in pain was not significant with pulsed electromagnetic field therapy.[115]

Therapeutic Touch

In a 6-week single-blinded, randomized controlled trial, therapeutic touch was evaluated for effectiveness in the treatment of OA of the knee. Thirty-one participants were enrolled and randomized to therapeutic touch, mock therapeutic touch, or standard care. The main outcome measures were pain and its impact, general well-being, and health status measured by standardized validated instruments, as well as the qualitative measurement of a depth interview. Twenty-five participants completed the study. The findings were that participants receiving therapeutic touch had significant improvements in pain, function, and general health status compared with both placebo and control groups.[116] Further studies with a larger sample size and further evaluation into treatment time and time for course of treatment are needed.

Prevention Prescription

- Maintain appropriate weight.
- Exercise regularly with a combination of aerobics, resistance training, and stretching.
- Consider glucosamine and chondroitin sulfate if at high risk for osteoarthritis.
- Avoid excessive trauma to the joints.

Therapeutic Review

Nutrition

- Antiinflammatory diet: individualized — B1
- Weight loss: individualized program — A1

Exercise

- Aerobic exercise: 1-hour sessions, three times weekly — A1
- Resistance training/muscle strengthening: 1-hour sessions, three times weekly — B1
- Flexibility exercise: two to three times weekly — B1

Mind-Body Therapy

- Telephone interventions: twice weekly for 6 months — B1
- Group programs: group course with experienced teacher twice weekly for at least 12 weeks — B1
- Yoga: 1 hour weekly for 8 weeks — B1

Continued

Physical Modalities

- Knee bracing: as needed
- Heat applications: as needed
- Cold applications: 20 to 30 minutes, reapplied every 2 hours
- Transcutaneous electrical nerve stimulation: 15-minute to 4-hour session, daily to six times daily
- Swedish massage therapy: 60 minutes weekly
- Acupuncture: 15- to 30-minute sessions, weekly to three times weekly

Supplements

- Glucosamine sulfate and chondroitin sulfate: glucosamine sulfate, 500 mg three times daily; and chondroitin sulfate, 400 mg three times daily, both for a minimum of 6 weeks
- *S*-Adenosylmethionine: 400 to 1600 mg daily; common regimen, 600 mg twice daily
- Methylsulfonylmethane: 1000 to 3000 mg three times daily

Pharmaceuticals

- Acetaminophen: 325 to 1000 mg every 4 to 6 hours; maximum, 4 g/day
- Tramadol: 50 to 100 mg every 4 to 6 hours; maximum, 400 mg/day
- Nonsteroidal antiinflammatory drugs: dose variable by drug
- Opioid analgesics: doses and routes variable
- Capsaicin cream (topical): thin film of cream (0.025%, 0.075%) applied to the symptomatic joint four times daily
- Diacerein: 50 mg twice daily

Injections

- Intra-articular steroid injections

Surgery

- Knee replacement

KEY WEB RESOURCES

Johns Hopkins University Arthritis Center: http://www.hopkins-arthritis.org/patient-corner/disease-management/exercise.html	Information for clinicians on exercise in osteoarthritis
Johns Hopkins University Arthritis Center: http://www.hopkins-arthritis.org/patient-corner/disease-management/yoga.html	Information for clinicians on yoga for arthritis
Arthritis Today: http://www.arthritistoday.org/index.php	Online magazine with information on arthritis for patients
National Center for Complementary and Alternative Medicine: http://nccam.nih.gov/health/acupuncture/	Information for clinicians and patients on acupuncture
The Brace Shop: http://www.braceshop.com/	Resource for braces for arthritis

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Chapter 62

Myofascial Pain Syndrome

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Pathophysiology and Epidemiology

Myofascial pain syndrome (MPS) and similar terms (Box 62-1) refer to pain and associated sequelae developing from and aggravated by myofascial trigger points (TrPs). The actual prevalence of MPS varies, based on terminology and diagnostic criteria. Myofascial pain is considered to be the leading cause of musculoskeletal pain, however, and it affects up to 85% of the population at some point during their lives.[1] The prevalence of MPS also appears to be related to age and gender. Persons 30 to 60 years of age appear to a have a 37% (male) and 65% (female) prevalence, whereas those older than 65 years of age have a rate higher than 80%.[2,3] Although MPS is highly prevalent, because of its varied presentation and complex comorbidities, no widely accepted treatment guidelines currently exist, and physicians often characterize available individual treatment options as insufficient.[4]

The actual mechanism for initiation of a TrP is not well understood but it likely arises from leakage of acetylcholine in dysfunctional motor end plates and thereby causes shortening of sarcomeres and formation of precursor taut muscular bands. These bands, which are found commonly in the latent state in asymptomatic individuals, may become activated in response to predisposing factors (Table 62-1). These factors are believed to be the exclusive causes of active TrPs (thereby making MPS a secondary phenomenon). Once activated, TrPs are associated with multisystem, especially vascular and neurologic, dysfunction. Doppler ultrasound examination of active TrPs demonstrates constricted vascular beds and enlarged vascular volumes that create higher peak systolic velocities and negative diastolic velocities as compared with latent myofascial TrPs and normal muscle sites.[5]

Subsequent to sensitization of motor end plates, TrP activation appears to be further propagated neurologically by activation of mechanosensitive afferents, as well as their connection at the dorsal horn of the spinal cord. Once established, this process may have cortical ramifications such as thalamic asymmetry, which may create spontaneous or stimuli-generated tissue hypersensitivity in a progressive process known as central sensitization. Because of cortical sensitization, patients with MPS may exhibit phenomena including allodynia and spontaneous contralateral sensitivity initiated from a unilateral TrP.[6] The hypothesized mechanism for MPS generation is illustrated in Figure 62-1.

Once initiated, MPS has classic features, typically linked to active TrPs, that allow physical and electrophysiologic identification and differentiation from other pain conditions, including fibromyalgia (Box 62-2).[7] In addition to physical signs, differentiation is sometimes possible between MPS and fibromyalgia on the basis of comorbidities seen in patients with fibromyalgia, including greater fatigue, sleep dysfunction, mood disturbance, headaches, and irritable bowel syndrome.[8] Although differentiating between these two entities is advantageous, coexistence of MPS with fibromyalgia is quite common, thus making distinct classification often difficult and in some cases not possible.[9] MPS is believed to be a secondary phenomenon, so in addition to proper diagnosis, initiating and propagating factors must be investigated and, if possible, corrected. Of key importance is the appreciation by the treating clinician of the possible and likely psychological and lifestyle triggers of MPS. Therefore, the contributing factors in MPS are quite broad and require a biopsychosocial assessment to determine proper treatment. Some of the more common medical and psychological triggers of MPS are listed in Table 62-1.

Integrative Therapy

Lifestyle

Exercise

Low physical activity level has been linked to the development and progression of MPS. Conversely, exercise is essential in myofascial rehabilitation through its physiologic effect on tissue including improvement in tissue oxygenation,

BOX 62-1. Synonyms for Myofascial Pain Syndrome

- Myofascial pain and dysfunction
- Trigger points syndrome
- Localized fibromyalgia
- Fibromyositis
- Muscular rheumatism
- Soft tissue syndrome
- Somatic dysfunction
- Tension myalgia

TABLE 62-1. Predisposing and Coexisting Conditions Requiring Identification in Myofascial Pain Syndrome

Skeletal and Soft Tissue Abnormalities	Trauma Repetitive stress injury Muscular strain or tear Ligamentous sprains Joint instability (spondylolisthesis) Osteoarthritis Facet joint abnormality Local inflammatory conditions (e.g., tendinitis or bursitis, epicondylitis, costochondritis) Craniofacial or temporomandibular joint (TMJ) dysfunction (e.g., TMJ syndrome, headaches of various origin) Leg-length discrepancies
Functional Asymmetry	Postural and ergonomic dysfunction Pelvic girdle dysfunction? Prolonged immobility
Neurologically Mediated Reflex Sympathetic Dystrophy Syndrome	Neurologically mediated reflex sympathetic dystrophy Spinal and peripheral nerve entrapment: Cervical and lumbar radiculopathy Sciatic nerve, median nerve (carpal tunnel syndrome), others
Other Rheumatologic Disorders	Polymyalgia rheumatica Polymyositis
Metabolic Deficiencies	Calcium Magnesium Potassium Iron Vitamins C, B_1, B_6, and B_{12}
Medical Conditions	Anemia Hypothyroidism Hyperuricemia Hypoglycemia Celiac disease Chronic infections Visceral diseases
Psychological Disorders	Chronic stress Sleep deprivation and dysfunction Depression Anxiety Somatization disorders

sensitivity, and range of motion, as well as cortical effects including modulation of neurochemicals such as endorphins and serotonin. Exercises must be chosen carefully to diminish significant postexertional flaring (typically defined as more pain 2 hours after activity than at baseline). Flaring can be detrimental by potentially promoting both central sensitization and activity avoidance. To maximize the benefit of an activity regimen, a progressive and preferably guided program of active and passive movement, especially when combined with posture correction, is recommended. This type of exercise program, especially when combined with relaxation techniques, has demonstrated significant success in improving pain and functional status in patients with MPS[10] (see Chapter 88, Writing an Exercise Prescription).

Exercise should be introduced or intensified slowly to reduce the risk of a postexercise flare in pain, which is defined as having more pain 2 hours after exercise than at baseline.

Sleep

Sleep regulation is an important factor in the progression of MPS. Several comparative studies found significantly reduced sleep quality in patients with MPS than in patients with other pain disorders.[11] In addition, poorer sleep quality predicts higher comorbidity and poorer response to planned therapy. Even in patients without a pain condition who are placed in an experimental setting of frequently disrupted sleep for several nights, investigators report a significant drop in pain threshold and a rise in musculoskeletal discomfort and fatigue.[12] The clinician should discuss sleep difficulties with patients who have MPS and describe strategies to correct sleep as a paramount goal in the treatment plan, such as stress management, sleep hygiene, and biochemical interventions (see Chapter 8, Insomnia).

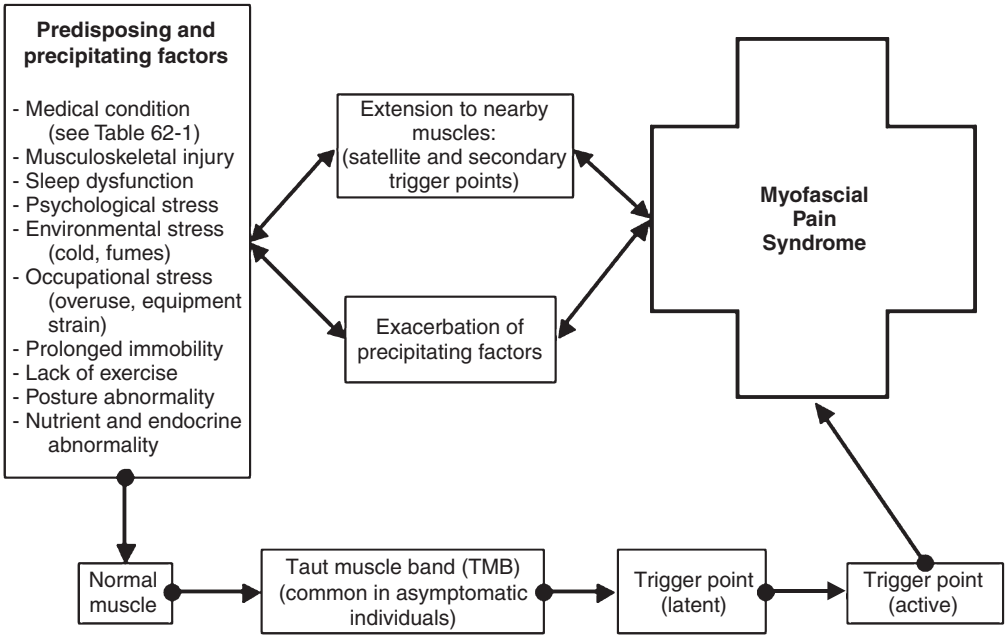
Mind-Body Therapy

The clinician should assess past or ongoing psychosocial stresses or traumas that may be related to MPS. Several questionnaires (e.g., Millon Behavioral Health Inventory) can help identify stresses or psychogenic attitudes that may be higher in MPS, including premorbid pessimism, future despair, and somatic anxiety.[13] Treatment approaches can be effectively based on the symptoms and patient's preference. Several choices of mind-body therapy are described here.

Relaxation and Awareness Techniques

Relaxation techniques—breathing techniques (see Chapter 89, Breathing Exercises), guided imagery (see Chapter 95, Guided Imagery), mindfulness-based stress reduction, and meditation (see Chapter 98, Recommending Meditation)—are believed to be helpful in pain alleviation and, specifically, the stress-mediated component of myofascial pain through a decrease in autonomic arousal. A reduction in sympathetic arousal specifically and an improvement in parasympathetic tone diminish several key physiologic influences on myofascial pain, including vasospasm, muscle spasm, and adrenal gland–mediated dysfunction in tissue inflammation and nutrient uptake. In addition, techniques such as biofeedback and mindfulness-based stress reduction have an awareness component that can be highly effective in reducing predisposing factors, including

FIGURE 62-1
Integrated mechanism for development of myofascial pain syndrome.



BOX 62-2. Classic and Confirmatory Signs of Active Trigger Points in Myofascial Pain Syndrome

- Palpable, taut muscular band containing a nodular structure
- Tenderness to palpation locally or in referred pattern replicating patient complaints
- Visual or tactile identification of local twitch response produced with needling or snapping ("guitar string") palpation
- Decreased range of movement of the involved muscle
- Increased spontaneous electrical activity on electromyography
- Low skin resistance points found over trigger points, unlike in surrounding tissue (skin resistance may normalize after treatment of trigger points)
- Imaging of local twitch response induced by needle penetration of tender nodule
- Characteristic referred pattern of pain for specific muscles involved (as described by Simmons and Travell[7])

poor posture, shallow breathing, and repetitive stress. Several studies have pointed out this benefit.

In one study, a randomized program of physical self-regulation with training in breathing, postural relaxation, and proprioceptive reeducation was taught to 44 patients with myofascial facial pain and compared with standard care. At 26-week follow-up, the two-time, 50-minute intervention demonstrated a significant reduction in pain ($P < .04$), as well as affective distress, somatization, obsessive-compulsive symptoms, tender point sensitivity, and sleep dysfunction.[14]

A useful question to ask patients with myofascial pain syndrome is where in the body they carry their stress (neck, back, stomach, head). Have patients use this sign of stress as a "red flag" that, when it appears, encourages them to step back and see what in their life may be exacerbating their pain. Once the subconscious stressor enters the consciousness, the pain often improves because the body no longer needs to sympathize.

In addition to being highly effective in decreasing the pain and sequelae of MPS, mind-body techniques can also be cost effective. In another study, a biofeedback-based program implemented in a primary care setting for functional disorders including MPS was measured against standard care ($N = 70$). Implementation of the program brought about significantly lower frequency and severity of symptoms, as well as lower medical costs, for the 6 months after the intervention ($P < .001$).[15] The clinician should reinforce the importance of mind-body techniques in overcoming MPS, a condition that the patient may understand on mainly physical terms. In addition, various techniques should be reviewed to locate those most suitable for the particular patient's needs (see Chapter 93, Relaxation Techniques, and Chapter 100, Emotional Awareness for Pain).

Biomechanical Therapy

Posture Correction

Any active treatment regimen must discuss, train for, and reinforce the need for active postural correction.[16] Dysfunctional posture both at rest and during work activities increases tissue strain and asymmetry. If not corrected, poor posture is theorized as a leading factor in the development and

maintenance of MPS. Evaluation by a well-trained clinician (physical or occupational therapist or body mechanics specialist such as a Feldenkrais or yoga practitioner) can provide invaluable information on the presence and severity of such dysfunction. Baseline and follow-up evaluations by a biofeedback therapist can also be helpful in demonstrating physiologic progress to the patient. Ongoing correction and monitoring can help patients with MPS realize the preventive capabilities of this often overlooked intervention. Several trials demonstrated that postural correction, especially when combined with behavioral therapies, can be successful in decreasing MPS.[17]

Massage Therapy, Manual Therapy, and Myofascial Release Techniques

Massage therapy and manual therapy (MT) have been shown to change several important components of MPS. In general, MT has demonstrated up-regulation of modulatory neurochemicals, including oxytocin, serotonin, and dopamine. Locally, MT has been shown to cause alteration in circulation and range of motion. The efficacy of practitioner-provided MT in MPS was demonstrated in several trials. Specifically, several schools of myofascial release techniques were developed to address the key features of MPS. Many of these techniques are based on Simmons and Travell's foundational work, *Myofascial Pain and Dysfunction: The Trigger Point Manual*[7]. Myofascial release, as well as spray and stretch techniques, should be considered as a first-line approach to MPS[18] (see Chapter 106, Strain/Counterstrain). Providing instructions on identification and home MT of TrPs has been shown to have added benefit in improving TrP sensitivity and pain intensity. Providing passive and active MT works well with other active treatments (thermotherapy and topical therapy) in improving awareness and self-management of MPS.[19]

Low-Level Laser Therapy

Low-level laser therapy (LLLT) has been used for several decades in Europe for pain management, and soft tissue conditions are among the conditions most effectively treated with this technique. The mechanism of action of LLLT is not completely elucidated, but it may be related to improvements in microcirculation, inflammatory response, and adenosine triphosphate production.[20,21] In addition, direct laser treatment of TrPs is believed to increase serotonin production, and trials demonstrated increased excretion of serotonin byproducts after treatment.[22] One 4-week trial ($N = 60$) comparing LLLT with dry needling and placebo laser demonstrated a significant improvement in pain at rest and with activity, as well as a rise in pain threshold in the laser-treated group.[23] LLLT has the advantage of being noninvasive and thus well tolerated, especially in patients with high tissue sensitivity. The treatment regimen and device specifications vary widely; clinicians should review the available research on the efficacy of the lasers they are considering incorporating into their practices.

Biostimulation

Similar to LLLT, more conventional avenues of biostimulation (e.g., electrical stimulation, ultrasound) have been applied to MPS because of their ability to increase tissue microcirculation and help correct the myofascial contraction-relaxation cycle. The mechanism of action of such techniques is related to correction of electrical disturbances found in TrP areas. Namely, TrPs typically demonstrate lower resistance and microvoltage abnormalities compared with surrounding tissue. In addition, electrostimulation has been shown to be partially inhibited by the use of naloxone, and thus, its benefit is likely related in part to endorphin up-regulation at the spinal cord and higher centers. Use of these techniques, including transcutaneous electrical nerve stimulation (TENS) and interferential and neuromuscular stimulation (NMS), has provided patient-dependent improvements in pain threshold and range of motion.[18,24] Point-specific devices such as electrotherapeutic point stimulation (ETPS) are also available to help identify and locally address TrPs. Response to these treatments is variable, so several modalities should be tried in the clinic setting to assess response. If one technique is successful, the patient should be taught to use it at home. Figure 62-2 demonstrates the application of various types of biostimulation.

Hydrotherapy and Thermotherapy

As discussed earlier, the tissue of patients with MPS tends to have abnormal microcirculation, which can have negative ramifications, including buildup of inflammatory markers and a drop in tissue temperature and effective range of motion. The application of short-term intense heat (heating pad, diathermy, warm hydrotherapy) and long-term use of low-intensity heat pads can help alter the thermal dysregulation and muscle spasm seen in MPS. Similarly, water immersion, by removing weight from the joints, facilitates reduction in muscle spasm and joint stiffness and thereby facilitates functional mobility. Because of the benign nature of these interventions, patients with MPS should undergo thermotherapy and hydrotherapy when available and, if possible, in combination with other therapies.[18]

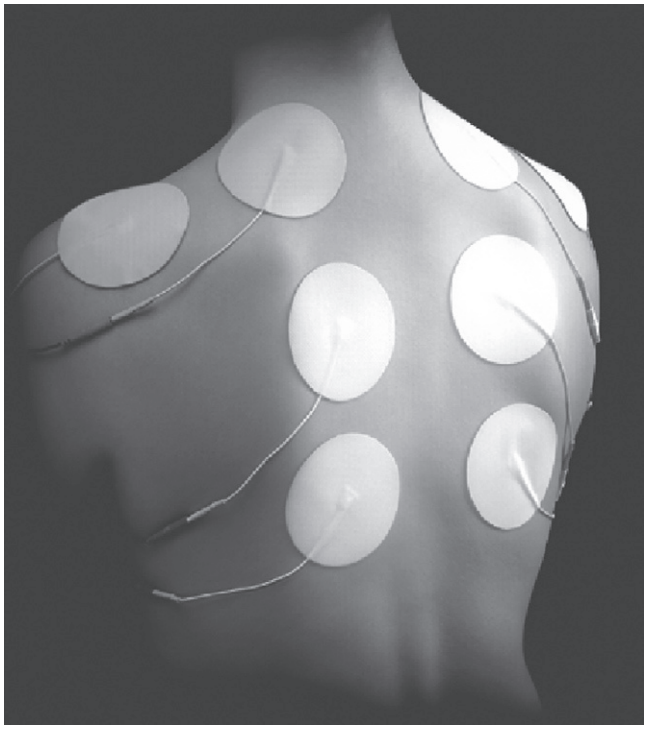
Biochemical Therapy

Topical and Transdermal Applications

Topical medications can be a useful adjunct because of their ability to disrupt hypersensitive signaling from the myofascial focus to the spinal cord and higher centers. Lidocaine in various topical formulations (cream, transdermal patch) is believed to block sodium channels that may increase pain signaling. Lidocaine 5% patches were tested in a 1-month open-label trial in 27 patients with myofascial pain.[25] By trial's end, several key parameters, including average pain intensity, mood, sleep, walking ability, and enjoyment of life, were significantly improved ($P < .05$). Antiinflammatory preparations (e.g., transdermal ketoprofen) have been shown to be helpful in related conditions, such as delayed-onset muscle soreness.[26] Moreover, in patients with temporomandibular joint dysfunction, topical applications of diclofenac have demonstrated efficacy similar to that of oral administration, with fewer adverse effects.[27]

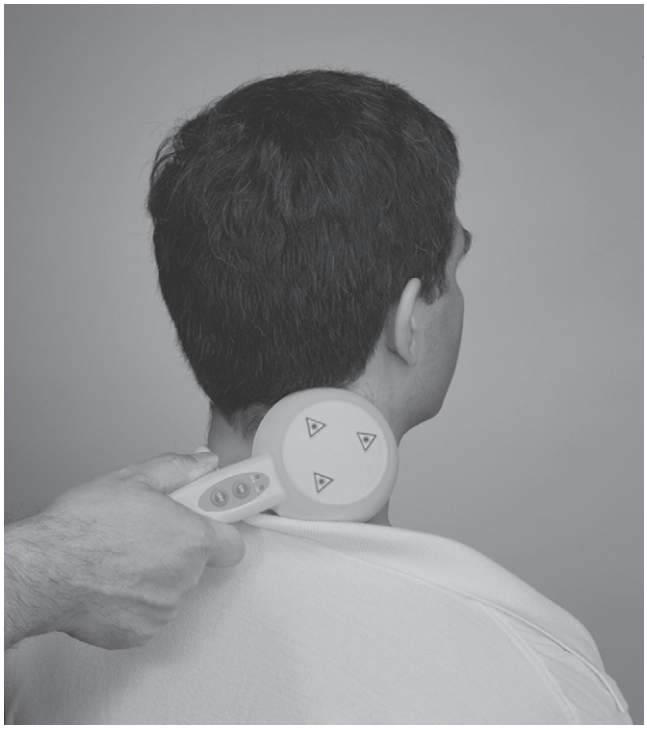
Botanical and nonprescription applications, including capsaicin and menthol, appear to have intrinsic local pain modulatory activity.[28,29] Specifically, capsaicin can deplete sensory C-fibers of substance P, the principal neurotransmitter of nociceptive impulses, and can thus potentially decrease central sensitization. Application of topical agents also provides active patient feedback on the location and sensitivity of myofascial pain. Clinicians should become familiar with local compounding pharmacies that can provide topical options for patients with myofascial pain.

FIGURE 62-2
Application of various types of biostimulation in myofascial pain syndrome. **A,** Interferential and neuromuscular stimulation. (RS 4i unit courtesy of RS Medical, Vancouver, Wash.) **B,** Individual trigger point electrostimulation. (Electrotherapeutic point stimulation unit courtesy of Acumed Medical Supplies, Toronto.) **C** and **D,** Low-level laser therapy. (**C,** Courtesy of Theralase, Markham, Ontario, Canada; **D,** Courtesy of Meditech International, Toronto.)



A

B



C

D

Dosage

Patients can apply up to three lidocaine 5% (Lidoderm) patches for up to 12 hours. Patches can be cut to size, and they come in a carton of 30 patches.

Patients can apply the capsaicin 0.025% patch (which also comes in 0.025%, 0.035%, 0.05%, 0.075%, 0.1, and 0.25% cream, gel, and lotion formulation) to the painful area three to four times daily for 3 to 4 consecutive weeks to reduce pain sensitivity. Patients should wash their hands and avoid their eyes after applying capsaicin.

Each diclofenac (Flector Patch) patch contains 180 mg of diclofenac, and one box contains five patches. One patch is applied to the painful areas twice daily.

Compounding pharmacies can prepare creams and gels with ketoprofen (the preferred compounded nonsteroidal antiinflammatory drug [NSAID]) combined with other agents (e.g., lidocaine, cyclobenzaprine, capsaicin). A dime-sized amount of gel (start with 10% to 20%) is rubbed into the painful area every 8 hours as needed.

Trigger Point Needling or Injection

Various needling and injection techniques have been endorsed for treatment of myofascial pain. The mechanistic rationale for the use of these techniques is based on several lines of evidence. The simplest technique, dry needling of primary TrPs, has demonstrated reversal of spontaneous electrical activity, one of the hallmark abnormalities noted in MPS.[30] Dry needle-evoked inactivation of a primary TrP in the shoulder region also improves pain sensitivity of satellite TrPs, as well as range of motion in the zone of pain referral.[31] Additionally, certain types of dry needling may activate muscle afferents more effectively than superficial needling to produce segmental analgesia.[32–36]

Injection techniques that involve introduction of sterile water, saline solution, or various pharmaceutical agents are conjectured to provide adjunctive benefit to needling, based on both the properties of the injected agent and the tissue pressure effects created by the volume of agent introduced. The appropriateness and superiority of various techniques, including dry needling and the injection of saline, anesthetics, corticosteroids, and botulinum toxin type A have not been clarified in clinical trials and systematic reviews because of variation in trial size and methodology.[37,38] Several trials found no distinct advantage for TrP injection over dry needling.[39, 40] Further, studies have both demonstrated and refuted the advantage of injection of active drug (e.g., lidocaine, botulinum toxin) over saline injection.[41,42]

Without a clear advantage of needling interventions, dry needling and acupuncture (see later) are initially recommended to evaluate their efficacy and patient tolerance. Injection of saline and other active agents should be reserved for more advanced or refractory cases and administered by clinicians with the proper understanding of the role of these agents in comprehensive management. Although injection therapy is potentially effective in short-term TrP management, it is often pursued without regard to the global needs of patients with MPS. To minimize a repetitive cycle of passive interventions, clinicians are admonished to address triggers and active treatment options for MPS (e.g., posture correction, home stretching, mind-body therapies) that are pursued in conjunction with injection therapy. All needle interventions with potential benefit are based on the experience of the practitioner in isolating TrPs. Adverse effects may be related to incorrect needle placement, reaction to the injected agent, or improper use of the aseptic technique.

Pharmaceuticals

Certain prescription agents, including NSAIDs, corticosteroids, muscle relaxants, antidepressants (especially tricyclic), anxiolytics, and opiates are mentioned in the treatment of MPS. Unfortunately, when looking at their efficacy in the setting of temporomandibular disorder–associated MPS, one review noted that "… evidence in support of the effectiveness of these drugs is lacking."[43]

Muscle Relaxants

Evidence for the effectiveness of muscle relaxants (e.g., tizanidine hydrochloride, cyclobenzaprine) and medication with muscle relaxation properties, including benzodiazepines and tricyclic antidepressants, is variable in MPS.[44] A Cochrane Review examining the use of cyclobenzaprine in MPS found that, based on the minimal available published research in this area and the difficulty in estimating risk versus benefit, evidence was insufficient to support the use of this drug in the treatment of MPS.[45] Although not routinely endorsed, muscle relaxants may be worth a short-term trial to assess improvement while initiating a multimodality program. In a randomized trial of temporomandibular disorder, cyclobenzaprine (10 mg/night) was compared with clonazepam (0.5 mg/night). Cyclobenzaprine was better than placebo and clonazepam when incorporated into a program of self-care and education for the management of jaw pain. Unfortunately, no significant improvement in sleep was noted.[46]

Dosage

Cyclobenzaprine, 10 mg at bedtime taken for a limited course, may provide some pain relief for temporomandibular disorder.

Precautions

This drug is structurally related to tricyclic antidepressants. Caution should be used when cyclobenzaprine is taken with this class of drugs.

Nonsteroidal Antiinflammatory Drugs

The use of NSAIDs may be justified in the short-term treatment of acute myofascial strain. In one study, ibuprofen appeared to work as well without the addition of a muscle relaxant (800 mg of ibuprofen three times/day, with or without the use of cyclobenzaprine 10 mg three times/day).[47] However, less evidence is available on the long-term use of NSAIDs in the setting of MPS.

Dosage

Ibuprofen, 800 mg three times daily with meals for short periods of time, can help reduce the pain of myofascial strain.

Antidepressants

Antidepressants are often considered in the setting MPS because of potential benefit in common mood and sleep comorbidities. The benefit of these agents for primary MPS in nondepressed individuals may not be significant, however, with the possible exception of amitriptyline, which was tested

(at 75 mg/day) in a small ($N = 31$), 32-week placebo-controlled double-blind three-way crossover study trial versus the highly selective serotonin reuptake inhibitor citalopram (at 20 mg/day). Study participants taking amitriptyline had significantly reduced myofascial tenderness and headache intensity than participants taking placebo ($P = .01$ and $P = .04$, respectively). The researchers concluded that amitriptyline may elicit its analgesic effect in myofascial pain by reducing transmission of painful stimuli from myofascial tissue, as opposed to reducing overall pain sensitivity: "We suggest that this effect is caused by a segmental reduction of central sensitization in combination with a peripheral anti-nociceptive action."[48]

Dosage

Amitriptyline, 75 mg at bedtime, can reduce myofascial pain and headaches.

Diet and Dietary Supplements

Myofascial pain has been attributed to abnormalities (typically, functional or intracellular deficiencies) of several nutrients, although no consensus exists about individual nutrients. Specifically, deficiencies of minerals (e.g., magnesium, calcium, and zinc) and vitamins or enzymes (e.g., vitamin D, vitamin B_{12}, and coenzyme Q10) have been reported in patients with MPS.[49] The level and type of deficiency, however, have not been consistent. In one trial, significant deficiencies in zinc levels in patients with MPS versus controls were noted without similar deficiencies in other nutrients such as magnesium or folic acid. These results may have reflected the type of testing done, including traditional extracellular versus intracellular testing. Although typical electrolyte analyses ("panels") may rule out gross abnormalities, levels of these electrolytes are usually normal in MPS. Clinicians should be aware of ionized or intracellular testing methods (e.g., SpectraCell, SpectraCell Laboratories, Houston) that may identify more occult deficiencies. The response to replacement of nutrients (e.g., magnesium in the setting of migraine) appears to be more highly correlated with intracellular or ionized fraction level, but not total serum levels.[50–52] On the basis of identified or suspected nutrient abnormalities, clinicians should use focused dietary and nutrient supplementation with careful patient monitoring of symptoms, to note any possible improvement.

Consider checking serum levels of vitamin B_{12}, 25-hydroxyvitamin D, coenzyme Q10, and electrolytes, as well as red blood cell magnesium levels in patients with myofascial pain syndrome.

Recommendations on the use of dietary supplements in MPS suffer from inconsistencies, as noted earlier.[53] Especially in patients with refractory cases of MPS unresponsive to lifestyle change, clinicians should proceed with supplements that may possess properties beneficial for pain and comorbid symptoms. A stepwise approach in which dietary supplements are incorporated and evaluated on a 2- to 3-month trial basis (i.e., a therapeutic trial) is suggested. These supplements may include those helpful for muscle function (e.g., magnesium, malic acid, calcium, vitamin D, coenzyme Q10), antiinflammatory action (e.g., essential fatty acids, white willow bark, *Boswellia*), or comorbidities such as sleep or mood dysfunction (e.g., St. John's wort, *S*-adenyl-L-methionine [SAMe], valerian, melatonin). As with prescription medications, the use of dietary supplements should be monitored on a regular basis to ensure benefit and to minimize adverse reactions.

Bioenergetics

Traditional Chinese Medicine

The use of traditional Chinese medicine, specifically acupuncture, was one of the earliest attempted treatments of MPS. More recently, investigators have speculated about the correlation between acupuncture and myofascial TrPs. In 1977, Melzack et al[54] postulated an approximately 70% correlation between these two entities, although this correlation has been disputed.[55] Because of the likely coexistence of these entities, a separate discussion of dry needling and localized acupuncture appears somewhat arbitrary. However, acupuncture offers treatment avenues based on meridian and energetic dysfunction, which may entail treatment at distal or reflex points (auricular therapy) and thereby provide additional therapeutic options.[56] The global assessment of the patient that is undertaken in Chinese medicine is especially helpful in MPS because of likely comorbidities that must be considered in the formulation of a treatment plan.

The specific type of acupuncture pursued for MPS is somewhat controversial. Several reports argue that deep needling may be more effective in decreasing MPS than superficial needling, although the two terms have not been well defined.[34,35] Conversely, Japanese acupuncture treatment, which typically uses superficial needling, was also shown to be effective in MPS in controlled trials.[57] The depth, frequency, and duration of treatments should be tailored to the patient; treatments typically should take place one or more times per week initially, followed by a gradual decrease with functional improvement.

Prevention Prescription

- Encourage posture awareness with frequent repositioning and adaptive stretching to reduce strain.
- Consider an ergonomic evaluation if patients remain in one position for prolonged periods at work.
- Incorporate stress management techniques to identify and reduce stress buildup. Ask patients to pay attention to where they carry stress in the body and use this to learn from the body's symptoms.
- Incorporate a regular exercise and movement program. At a minimum, patients should exercise three times/week for 30 minutes each session while stimulating movement, range of motion, and tone in all muscle groups.
- Encourage adequate quantity and quality of sleep.
- Encourage the consumption of a healthy diet rich in fruits and vegetables with adequate fluid content to ensure perfusion to muscles.
- Encourage maintenance of an ideal weight.

Therapeutic Review

Myofascial pain syndrome (MPS) is a disorder that affects up to 85% of the general population at some point and is primarily characterized by local and referred pain, as well as comorbidities affecting mood, sleep, energy, and functional status. Although numerous treatment options are available, no widely accepted treatment guidelines exist. Clinically, MPS is a condition that is often difficult to treat, and physicians often characterize available treatments as insufficient.[4] Based on its complex nature, MPS is a condition that requires a biopsychosocial evaluation and incorporation of individualized, preferably active, treatments option geared at underlying propagating factors with a focus on long-term neurobehavioral and functional rehabilitation.

Exclusion and Treatment of Conditions That Mimic or Contribute to Myofascial Pain Syndrome

- See Table 62-1.
- Symptom-focused laboratory testing should be considered, including 25-OH vitamin D_3, coenzyme Q10, carnitine, vitamin B_{12}, folate, methylmalonic acid, and, as appropriate, baseline thyroid-stimulating hormone, creatine phosphokinase, alkaline phosphatase, and complete blood count and electrolytes with intracellular magnesium to rule out modifiable causes of MPS and associated symptoms.

Removal of Exacerbating Factors

- Take measures to correct sleep dysfunction, including sleep hygiene and other interventions.
- Increase awareness of stress and environmental triggers (poor posture, repetitive stress) by using periodic daily cues. A1

Lifestyle Measures

- Incorporate stress management techniques
- Biofeedback, preferred for baseline myofascial and autonomic measures and retraining efforts A1
- Guided imagery B1
- Meditation C1
- Exercise to decrease deconditioning and improve myofascial biomechanics. Mindful exercise (e.g., yoga, tai chi) is especially helpful in improving MPS. A1

Biomechanical Interventions

- Posture evaluation and correction: Consider ongoing optimization with yoga, Feldenkrais, and physical therapy. A1
- Manual and manipulative techniques, including massage, myofascial release, and spray and stretch: These should be considered in areas of distinct trigger points. Osteopathic manipulation is desired when functional skeletal asymmetry is provoking MPS. Refer to Simmons and Travell[7] for detailed instructions. Several techniques can be taught to and successfully incorporated by the patient (e.g., compression massage with stretch). A1
- Biostimulation: Low-level laser therapy, electrostimulation, hydrotherapy, and thermotherapy are recommended on a regular basis to assess reduction in symptoms, especially pain, with transition to home therapy. A1

Bioenergetic Interventions

- Acupuncture is used to release trigger points and decrease autonomic arousal. A1
- Other energetic treatments (e.g., healing touch, Reiki) should be used to assess for and treat energy imbalance. C1

Nutrition

- Have patients increase their intake of fruits and vegetables, with a focus on appropriate levels of vitamins and minerals essential for musculoskeletal function. C1
- Consider a trial of an antiinflammatory diet or elimination diet (see Chapter 86, The Antiinflammatory [Omega-3] Diet, and Chapter 84, Food Intolerance and Elimination Diet). C1

Supplements

- Consider an 8- to 12-week trial of supplements for correction of myofascial pain and comorbid conditions (including identified deficiencies):
  - Magnesium: starting with a chelated form if available for increased gastrointestinal tolerance; magnesium glycinate, 100 to 200 mg twice daily, advance as tolerated (other formulation doses vary; typically, starting at a low dose and advanced based on gastrointestinal tolerance) B2
  - Malic acid: 600 mg, one to two capsules daily C1
  - Carnitine: 2000 mg/day C1
  - D-Ribose: 5 g twice daily C1
  - Coenzyme Q10: 100 to 300 mg/day (dose increased based on response and serum levels) C1
  - B vitamins typically used: 50 to 100 mg of thiamine (vitamin B_1) and pyridoxine (vitamin B_6), 0.5 to 2 mg of folic acid and vitamin B_{12} C1
  - Vitamin D_3: 800 to 1000 units/day (higher levels in deficiency states) B1

Pharmaceuticals

- Topical pharmaceuticals
  - Compounded creams with ingredients based on patient presentation are applied to affected areas three times/day. Patients should be warned that some topical agents cause localized burning or rare allergic reactions. Systemic absorption negligible if these agents are used as directed.
  - Ketoprofen 10% to 20% 
  - Lidocaine 5% 
  - Capsaicin 0.025% to 0.075% 
  - Cyclobenzaprine 5% 
  - Oral pharmaceutical
  - If the response to other interventions is unsatisfactory, consider a trial of amitriptyline (up to 75 mg/day) for long-term treatment, as well as a trial of short-term antiinflammatory agents for acute exacerbations. 
- Needle-based injection therapy
  - If the patient's symptoms persist or worsen despite the preceding measures, consider needle-based intervention in a stepwise approach.
  - Acupuncture or dry needling 
  - Saline injection 
  - Anesthetic injection (e.g., a combination of 2% lidocaine and 0.05% bupivacaine in a 1:3 ratio up to 8 mL total) 
  - Botox injection 

All treatments should be well integrated, with the goal of improving patient awareness of biomechanical and stress triggers. Treatments should gradually move from passive (practitioner directed and supervised) to active (patient initiated), with improving awareness of the patient's ability to address and diminish the myofascial pain cycle.

KEY WEB RESOURCES

Mayo Clinic: Myofascial Pain Syndrome: http://www.mayoclinic.com/health/myofascial-painsyndrome/DS01042/METHOD=print	Handout on myofascial pain syndrome for patients
ReliefInsite: www.reliefinsite.com American Chronic Pain Association: http://www.theacpa.org Pain log: http://www.theacpa.org/painlog/painlog.aspx	Web sites that offer pain tracking tools to enhance communication with the health care provider
Mayo Clinic: Stress Management: http://www.mayoclinic.com/health/relaxation-technique/SR00007 University of Wisconsin Health Services: Stress and Sleep: http://www.uhs.wisc.edu/services/wellness/stress.shtml	Stress management and relaxation tools Resources for stress and sleep management
UCLA Ergonomics: http://ergonomics.ucla.edu/exercises.html	Exercise and stretching guides that can be done at home
Arthritis Foundation: http://www.arthritis.org YMCA: http://www.ymca.net/	Organizations offering exercise and stretching classes, including aquatic therapy

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Chapter 63

Chronic Low Back Pain

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Low back pain (LBP), the most common type of pain in the United States, results in substantial morbidity, disability, and cost to society.[1–6] Annual direct costs associated with this condition are more than $50 billion in the United States, and indirect costs (e.g., productivity) are estimated to be even greater.[6,7]

The lifetime prevalence of LBP ranges between 60% and 85%; therefore, most adults will experience an episode of LBP at least once during their lifetime.[8] LBP is the fifth most common reason for visits to primary care physicians, and it is the single most common reason that U.S. adults use complementary and alternative medicine.[9] Of these alternative therapies, manipulation, massage, acupuncture, and mind-body approaches such as yoga are frequently used.[10] The prognosis for acute LBP (ALBP) is very good. Most episodes resolve within 6 weeks, regardless of treatment given. Recurrence rates are high (20% to 35%), however, and approximately 5% to 20% of patients will go on to develop chronic LBP (CLBP).[11–13]

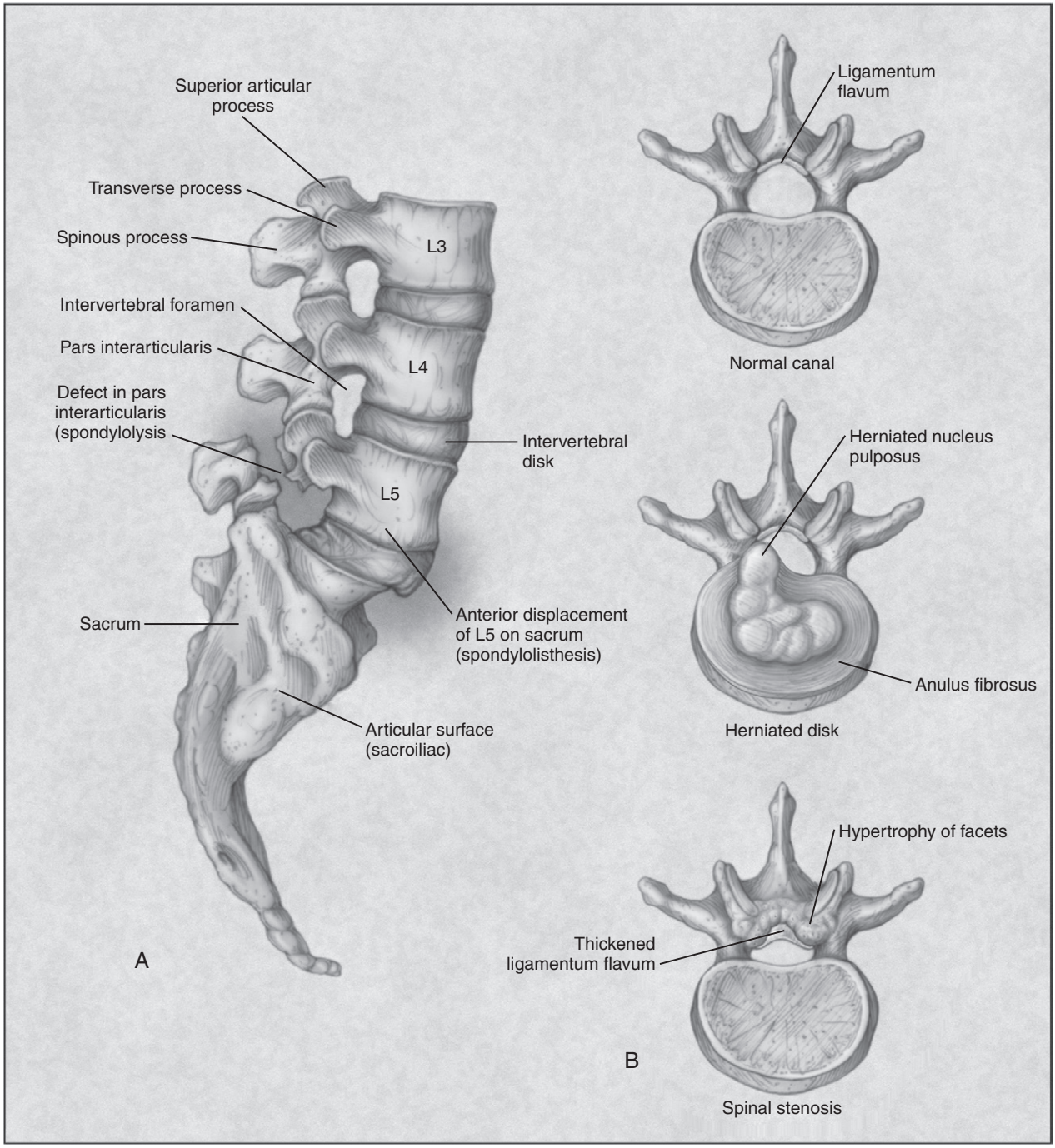
Despite its high prevalence and substantial impact on patients, the medical system, and society, back pain remains poorly understood, with relatively little consensus on optimal treatment. An integrative approach, in which the evidence for various conventional and complementary and alternative medicine therapies is considered in the context of the patient's clinical picture, preferences, and values, is therefore ideally suited to address this costly and complex condition.

Pathophysiology

LBP is a vexing clinical problem. Two conceptual frameworks have emerged for the evaluation and treatment of this condition. The first is the biomedical model, which characterizes signs and symptoms to identify the causative agent and thereby allows delivery of targeted biologically oriented interventions.[14] This model is necessary and best suited for initial evaluation and for ruling out serious disorders. The second conceptual framework is the biopsychosocial model.[15] This paradigm requires the clinician to expand on the biomedical model and accept the nonspecific nature of LBP. The purpose of the biopsychosocial evaluation shifts from the characterization of a causative agent to the identification of inappropriate attitudes and beliefs, high levels of distress, and fear avoidance behaviors that can impede recovery of function and place the patient at higher risk for developing CLBP. To manage patients with back pain effectively, providers must use both approaches.

ALBP is defined as pain in the lumbosacral region, with or without leg pain, that has been present for less than 6 weeks.[14] The condition is considered subacute when it has been present for 6 to 12 weeks. By extension, CLBP is defined as pain persisting for more than 12 weeks. Patients with ALBP and CLBP are challenging because a definitive pathoanatomic cause of the condition can be identified only in approximately 15% of cases. Definitive causes of LBP include disk herniation with suspected radiculopathy or spinal stenosis (5%), osteoporotic compression fracture (4%), and inflammatory arthropathies (3%) (Fig. 63-1). Other specific organic causes of LBP are cancer and infection (1%), cauda equina syndrome (less than 1%) and visceral disorders (less than 2%) such as aortic aneurysm and pelvic, gastrointestinal, and renal disease.[1,14,16] These definitive causes are uncommon, and most patients presenting with back pain have nonspecific LBP. Nonspecific back pain may emanate from ligaments, facet joints, muscle, fascia, nerve roots, the vertebral periosteum, or the outer portion of the disk.[1] However, precise identification of a specific diagnosis is not necessary to manage these patients effectively. In fact, far too often patients with nonspecific back pain see multiple providers and pursue a biomedical model by undergoing numerous tests and imaging procedures in a futile attempt to identify an exact cause of the pain. This exhaustive effort to identify the precise cause of the pain is time consuming and costly, and it can lead to frustration for both patient and provider. The prognosis for most patients with ALBP is good, and most patients are effectively managed with a brief assessment, patient education, judicious use of analgesics, and reassurance.

FIGURE 63-1
Specific pathoanatomic conditions causing low back pain. **A,** Lateral view of the lumbosacral spine illustrating spondylolysis of the L5 vertebra with associated spondylolisthesis at L5-S1. *Spondylolysis* refers to a defect in the pars interarticularis of the vertebra, which may be congenital or a result of stress fracture. *Spondylolisthesis* refers to the anterior displacement of a vertebra on the one beneath it. This may occur as a result of spondylolysis, as shown, or as a result of degenerative disk disease, usually in older adults. This process may contribute to narrowing of the spinal canal in spinal stenosis. **B,** The lumbar spinal canal in health and disease. *Left,* The normal spinal canal. *Center,* The spinal canal in central spinal and nerve root canal stenosis in the neutral position. *Right,* The effect of lumbar extension on the spinal canal. (From Deyo RA, Weinstein JN. Low back pain. *N Engl J Med.* 2001;344:363–370.)



Applying a biopsychosocial model to patients with LBP is particularly appropriate to identify factors that may predispose a patient with ALBP to CLBP or that may perpetuate the chronicity of a preexisting back problem. In fact, many of the most important predictors of ongoing disabling low back problems are fear avoidance and inappropriate pain coping behaviors, nonorganic signs on physical examination (Table 63-1), and psychiatric comorbidities.[17] Therefore, clinicians must recognize that the patient's experience of LBP can be positively or negatively shaped by his or her attitudes, beliefs (e.g., fear of movement and reinjury), psychosocial factors (e.g., mood, support systems, employment and occupation, financial resources), behaviors (e.g., coping skills, catastrophizing, substance abuse), and family, social, and cultural environments[18–20] (Fig. 63-2). Often, a self-reinforcing downward cycle of avoidance and disuse can lead to increasing distress and functional and occupational disability (Fig. 63-3). In contrast, motivated patients with less fear of movement and greater self-efficacy can better manage their pain and improve their function over the long term.

Evaluation

History

Patients with ALBP or CLBP should be evaluated with a comprehensive history and physical examination. During the workup, it is helpful to think in terms of three basic diagnostic categories: nonspecific LBP, back pain with suspected radiculopathy or spinal stenosis, or back pain that is a result of a specific disease.[16] The history should begin with a description of the primary complaint, to identify pain severity and functional limitations. The patient should be questioned about the pattern and nature of any lower extremity symptoms, as well as the presence of significant neurologic deficits, gait abnormalities, or bowel or bladder dysfunction. Attention to any history of trauma, immunosuppression, constitutional symptoms, substance use, comorbidities, and previous history of back troubles including spinal surgery is important. In addition, postures or spinal loading strategies (e.g., flexion, extension) that aggravate or palliate the patient's lumbar spine or extremity symptoms should be explored.

Physical Examination

Emphasis in the examination should be placed on back inspection, palpation, range-of-motion testing, orthopedic maneuvers, and a comprehensive neurologic evaluation. The clinician should observe the patient for antalgic posture, the Gower sign (using hands to "walk" up the thighs from a flexed

FIGURE 63-2
Biopsychosocial model of pain. (From Main CJ, Williams AC. ABC of psychological medicine: musculoskeletal pain. *BMJ*. 2002;325:534–537)

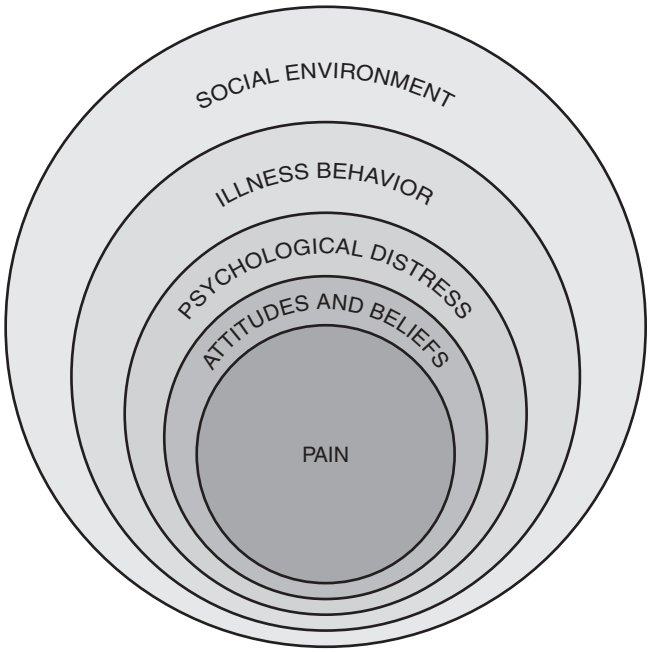


TABLE 63-1. Waddell's Nonorganic Signs*

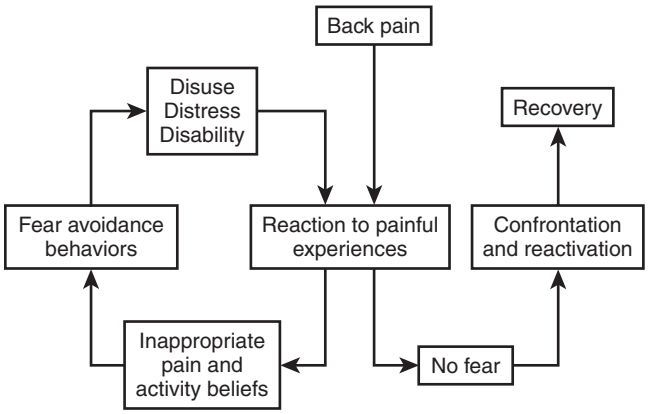
SIGN	DESCRIPTION
Superficial or Nonanatomic Tenderness	Pain with light or superficial palpation of the skin, or widespread deep tenderness that is not localized to one skeletal or neuromuscular structure, does not follow an anatomic distribution, and often extends to the thoracic spine, sacrum, or pelvis
Pain on Axial Loading or Simulated Rotation	Pain with downward pressure applied to the top of the patient's head when standing, or back pain when the shoulders and pelvis are passively rotated as a unit with the patient standing relaxed with the feet together
Nonreproducibility of Pain When Patient Is Distracted	A positive physical finding elicited during the examination that is not present later in the examination when the patient is distracted and the finding is checked again (e.g., pain with a standard straight leg raise test, but not when the examiner passively extends the leg of a seated patient)
Regional Weakness or Sensory Change	Regional, nonanatomic sensory change (stocking sensory loss, or sensory loss in an entire extremity or side of the body) or regional weakness (weakness that is jerky, with intermittent resistance such as cogwheeling or catching)
Overreaction	An exaggerated painful response to a stimulus that is not reproduced when the same stimulus is given later, or an exaggerated response to a stimulus that should not cause back pain (e.g., gently pinching the skin on the back in the area of pain)

*Elicitation of one or more of these signs on physical examination suggests a nonorganic or psychological component to the patient's back pain.
Adapted from Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA*. 2010;303:1295–1302.

position because of proximal leg weakness), or reverse lumbopelvic rhythm (bending knees to return from flexed position).[21,22] Range-of-motion testing, especially repetitive flexion and extension, is informative. Particular attention should be paid to repetitive movements that centralize the pain or cause it to move from a more peripheral location (e.g., buttocks) to a more central location (midline of the lumbar spine). Orthopedic tests such as the straight leg raise and slump test (the seated Lasègue test) may be useful in identifying nerve root tension.[23] The neurologic examination should focus on the L4, L5, and S1 myotomes (heel and toe walking), dermatomes (light touch or pin prick sensation), and deep tendon reflexes (knee and ankle)[16,24–28] (Table 63-2).

The presence or absence of *red flags* (signs or symptoms suggestive of serious definitive but less common causes of back pain including cauda equina syndrome, cancer, fracture, infection, severe disk disease or spinal stenosis with radiculopathy, and progressive neurologic deficits) must be determined first.[16,24–27] Table 63-3 lists constellations of red flags concerning for specific disorders causing LBP and recommendations for prompt further evaluation and referral.[16,24–26,28–30] For patients with suspected radiculopathy or spinal stenosis, a combination of watchful waiting and conservative treatment measures aimed at alleviating pain and improving function is appropriate. If these patients demonstrate persistent leg pain or neurologic findings after 4 to 6 weeks of conservative care, however, orthopedic or neurosurgical referral is indicated.[1]

FIGURE 63-3
Downward cycle of fear avoidance, disuse, and disability. (Adapted from Main CJ, Williams AC. ABC of psychological medicine: musculoskeletal pain. *BMJ* 2002;325:534–537.)



Imaging

The consensus across major international LBP practice guidelines is that plain radiographs, computed tomography (CT), and magnetic resonance imaging (MRI) are of limited benefit in most patients with back pain. These recommendations are based on the knowledge that abnormal imaging findings are common in asymptomatic individuals, and such findings are poorly correlated with symptom severity and clinical outcomes.[31–33] Despite these facts, the use of imaging procedures continues to rise.[31] For many patients, these findings are irrelevant and may foster detrimental beliefs about their condition. A meta-analysis concluded that "immediate, routine lumbar-spine imaging in patients with low back pain and no features suggesting serious underlying conditions did not improve clinical outcomes."[34] Lumbar imaging should be primarily reserved for the investigation of definitive causes of back pain in patients with *red flags*, such as substantial or progressive neurologic involvement.[16,24,35,36]

Subgrouping

Clinicians increasingly appreciate that the broadly defined category of nonspecific back pain does not represent a uniform population of patients. Many clinicians argue that nonspecific LBP is in fact a heterogeneous condition, and therefore, a "one size fits all" treatment approach leads to unsatisfactory results.[37] This situation has led to several attempts to subgroup patients, by linking each subgroup to a specific treatment with the goal of identifying best management strategies.[38–40] Two of the better-studied methods of subgrouping patients with back pain are the Treatment-Based Classification (TBC) system and the McKenzie Method of Mechanical Treatment and Diagnosis (MTD). The TBC uses specific clusters of signs and symptoms to classify patients into one of three main categories: specific exercises (flexion, extension, and lateral shift patterns), stabilization exercises, and manipulation. A specific set of therapeutic interventions is suggested for each of these categories. The MTD classifies patients by evaluating the cause and effect relationship

TABLE 63-2. Lumbosacral Nerve Root Syndromes

NERVE ROOT	SYMPTOMS	SIGNS
L2-4	Acute back pain radiating around the anterior leg into the knee and possibly the foot	Decreased hip flexion, knee extension, leg abduction; decreased sensation in the anterior thigh down to the medial aspect of the lower leg; diminished knee reflex in severe cases
L5	Back pain radiating down the lateral leg to the foot	Decreased foot dorsiflexion, toe extension, foot inversion and eversion; mild weakness of leg abduction in severe cases
S1	Pain radiating down the posterior leg to the foot; leg pain greater than back pain	Decreased leg extension, foot inversion, plantar flexion, and toe flexion; decreased sensation in the posterior leg and lateral foot; loss of ankle reflex
S2-4	Sacral or buttock pain radiating down the posterior leg or into the perineum	Leg weakness; saddle anesthesia; bowel and bladder dysfunction

Adapted from Rutkove SB. Overview of lower extremity peripheral nerve syndromes. In: Basow DS, ed. *UpToDate*. Waltham, MA: UpToDate; 2010.

TABLE 63-3. Specific Conditions Causing Low Back Pain

SYNDROME	RED FLAGS	FURTHER EVALUATION
Cauda Equina Syndrome	• Widespread neurologic symptoms • Fecal incontinence or urinary retention • Weakness in limbs and/or gait abnormality • Saddle numbness	• Medical Emergency: immediate magnetic resonance imaging and neurosurgical referral
Lumbar Radiculopathy	• Severe lower extremity pain • Significant neurologic deficits indicative of nerve root compression • Sensory impairment, weakness, or diminished deep tendon reflexes consistent with nerve root distribution	• If no improvement with conservative treatment after 6 weeks, magnetic resonance imaging considered
Spinal Canal Stenosis	• Pain, sensory loss, or weakness in one or both legs • Pain worse with walking or standing • Pain relieved with sitting or lumbar flexion	• Magnetic resonance imaging
Spondyloarthropathy	Presence of four or more of the following: • Age younger than 40 years • Insidious onset • Improvement with exercise • No improvement with rest • Pain at night (with improvement on arising or walking)	• HLA-B27 • Erythrocyte sedimentation rate • C-reactive protein
Cancer	• History of cancer • Age older than 50 years • Failure to improve with treatment • Worsening pain especially at night, at rest, or when lying down • Urinary retention	• Erythrocyte sedimentation rate • Plain film radiographs • Magnetic resonance imaging
Fracture	• Age older than 50 years • Osteoporosis • Significant trauma • Steroid use • Structural deformity	• Plain film radiographs (cannot distinguish new from old compression fractures) • Computed tomography • Magnetic resonance imaging
Infection	• Fever • Immunosuppression • Intravenous drug use • Multiple comorbidities • Trauma	• Complete blood count • Erythrocyte sedimentation rate • C-reactive protein • Magnetic resonance imaging

between a patient's historical pain behavior and the pain response to repeated test movements, positions, and activities. The MTD describes three syndromes: postural (end-range stress of normal structures), dysfunction (end-range stress of shortened structures possibly resulting from scarring, fibrosis, or nerve root adhesion), and derangement (anatomic disruption or displacement within the spinal segment). Each distinct syndrome is addressed with specific static physical postures and repetitive movements.[41]

Yellow Flags

Screening for *yellow flags* (factors associated with a poor prognosis for LBP) is also critical (Table 63-4).[14,18,19,36] Clinicians must uncover unhelpful beliefs that a patient may hold about his or her back pain. For example, beliefs that back pain is the result of a progressive disorder, or that passive treatment rather than active self-management is most beneficial, must be identified and corrected. Questioning patients about their beliefs regarding what can cause and help their pain, and observing for guarded movements and avoidance patterns during the examination, can help identify patients with *fear avoidance beliefs*. Identifying and correcting beliefs that physical activity and the resultant discomfort can be harmful for the back is important because these beliefs can perpetuate a vicious cycle of disuse and disability.[16,18,25] Depression, anxiety, maladaptive responses to stress, and social withdrawal should be explored and addressed as necessary.[16,25,42] Patients' economic circumstances and workplace factors such as low job satisfaction, high physical job demands, inability to modify work demands, high levels of job stress, low workplace social support, or dysfunctional workplace relationships may also perpetuate LBP.[14,18]

Integrative Therapy

The goals of LBP treatment should be to enhance coping skills, restructure inappropriate beliefs, and improve functional ability and activity tolerance. Therapeutic interventions need to be coordinated in an effort to achieve this end, and special emphasis should be placed on active patient participation, rather than passive treatments.

TABLE 63-4. Yellow Flags: Risk Factors for Disability and Chronic Low Back Pain

PSYCHOSOCIAL FACTORS	OCCUPATIONAL FACTORS	INTERVIEW QUESTIONS
• Inappropriate attitudes and beliefs • Poor or maladaptive coping strategies • High levels of emotional distress • Fear avoidance behavior • Depressed mood and social isolation • Resistance to change • Family reinforcement of illness behavior	• Work status • Low job satisfaction • High physical job demands • Inability to modify work • High levels of job stress • Working conditions • Worker's compensation claim or litigation • Health benefits and insurance	• What do you believe is causing your back pain? • What do you think will help your back pain? • Do you think your pain will ever get better? • How do you deal or cope with your back pain? • Have you been feeling worried, down, or blue? • How do your family, friends, and coworkers respond when you have pain? • Have you had time off work because of your back pain? • When do you think you will return to work?

Education and Self-Care

Education concerning the benign nature of most back pain, recovery goals, and appropriate self-care should be provided to all patients with ALBP or CLBP.[16,24,25] Brief educational interventions can be effective in reducing disability by reassuring the patient, dispelling inappropriate beliefs regarding back pain, promoting self-management, and encouraging a return to normal activities.[16,24–27] Examples of useful educational messages and self-management strategies include the following:

- Stay active and carry on as normally as possible.
- Staying active may "hurt" but will not cause "harm."
- Perform physical activities in manageable, graded stages.
- Track your own functional progress, and do more each day.

Working with the patient to correct misunderstandings, identify barriers to recovery, instill healthy coping strategies, and empower the individual to take responsibility for the long-term management of the condition is particularly important.[14,18]

Identify and correct beliefs that physical activity will worsen back pain.

Mind-Body Therapy

Behavioral Therapy

Behavioral therapy refers to various approaches that include cognitive-behavioral, operant, and respondent methods. Cognitive-behavioral therapy is based on the premise that an individual's thoughts (as opposed to external factors such as injury, people, or environmental circumstances) trigger his or her feelings and behaviors.[43] The benefit of this approach is that a positive change in thoughts and beliefs can lead to positive changes in feelings and behaviors even if the back pain remains unchanged.[43] Operant therapy uses reinforcement to change behavior. This reinforcement may be a reward for attainment of a goal or certain behavior. Alternatively, operant therapy can use a lack of reinforcement for certain maladaptive behaviors such as activity avoidance or catastrophizing. Respondent therapies, such as progressive muscle relaxation, aim to modify physiologic responses through self-training.[44,45] Evidence shows that behavioral therapy is more effective than usual care for short-term pain relief and behavioral outcomes.[46,47] Additionally, rates of return to work are better for patients receiving behavioral therapy when compared with rest, analgesics, physical therapy, or back exercises.[46] Specifically, operant conditioning has been shown to be more effective than wait list controls for short-term pain relief. Cognitive-behavioral therapy has also been shown to improve pain and disability outcomes compared with wait list controls.[46,47] When different behavioral techniques have been compared with one another, no significant differences have been found.[46] Behavioral therapies may be considered as treatment options for patients with CLBP[16,24–27] (see Chapter 100, Emotional Awareness for Pain).

Yoga

Yoga is an increasingly popular practice consisting of three major components: physical postures (asanas), breathing techniques (pranayama), and meditation. The numerous popular yoga styles vary in intensity, pace, and balance of asana, pranayama, and meditation. Several published randomized controlled trials for CLBP support the use of standardized yoga sequences for decreasing pain, improving function, and reducing analgesic use.[48–51] Given this evidence, two international guidelines recommend yoga as a treatment option for CLBP.[16,24] Patients with CLBP who pursue yoga should ideally use a program specifically tailored for back pain. Yoga styles particularly suited for restoration from CLBP include, but are not limited to, Hatha, Viniyoga, Iyengar, Kripalu, and Anusara. Instructors should have experience working with patients with chronic pain. Yoga has not been studied in ALBP, nor is recommended for this condition. Although yoga has not been studied for the prevention of ALBP or recurrent LBP, anecdotal reports and observation suggest that it may be helpful and reasonable for this purpose.

Multidisciplinary Functional Restoration

Multidisciplinary functional restoration programs are typically intensive (more than 100 hours) biopsychosocial interventions combining cognitive-behavioral therapy with physical rehabilitation. These programs are often offered by a team that may include physicians, exercise instructors, physical and occupational therapists, and mental health professionals. Moderate to strong evidence indicates that these programs reduce pain and improve function in patients with CLBP, as well as improve readiness and return to work. Less intensive programs and those without a behavioral component are less effective.[16,46,52] Multidisciplinary functional restoration programs can be considered for patients in whom less intensive treatment options have failed and who continue to exhibit high levels of physical and psychological distress and disability.[16,24,25]

First-Line Pharmaceuticals

Oral pharmacotherapy is the most commonly used intervention for CLBP. Most international guidelines recommend the use of acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) as initial pharmacologic interventions for pain control.[16,24–26]

Acetaminophen

Acetaminophen is recommended as a first-line medication for ALBP or CLBP. It has a favorable safety profile and has been found to be beneficial in multiple musculoskeletal conditions.[53]

Dosage

The recommended dose of acetaminophen is 500 mg, one to two tablets three to four times a day.

Precautions

Hepatotoxicity can occur with doses at or higher than the recommended maximum daily dose of 4 g/day, particularly in patients with preexisting liver disease or heavy alcohol use.[53]

Nonsteroidal Antiinflammatory Drugs

NSAIDs such as ibuprofen and naproxen can also be used as first-line analgesics either alone or in combination with acetaminophen. NSAIDs have moderate to strong evidence for short-term pain control in ALBP and CLBP.[16,24,25,46,53,54] Given that no single NSAID has been found to be superior to others, the choice should be based on cost, dosing schedule, and patient preference. The potential benefits associated with these medications should be weighed against possible risks. NSAIDs can cause dyspepsia, gastritis, peptic ulcer, and gastrointestinal bleeding. Prolonged high levels of NSAID use are associated with worsening renal function. Each patient should be individually assessed for the risk of these potential adverse events and counseled accordingly. As with all analgesic medications, the minimal dose that is effective should be recommended, and long-term use should be avoided if possible.

Dosage

For ibuprofen, the dose is 400 to 800 mg three times per day. The dose of naproxen is 375 to 500 mg twice daily.

Precautions

Patients taking NSAIDs on a long-term basis should undergo regular monitoring of renal function. Cyclooxygenase-2 inhibitors such as celecoxib are newer NSAIDs marketed for their gastroprotective effects. However, these drugs have been associated with an increase in cardiovascular risk, and their use should be discouraged in lieu of acetaminophen and traditional NSAIDs.[16,24,25,46,53,54]

Second-Line Pharmaceuticals

Weak Opioids

Analgesics such as codeine (15 to 30 mg up to four times daily), hydrocodone (5 to 10 mg up to four times daily), and tramadol (50 to 100 mg up to four times daily) may be considered when acetaminophen and NSAIDs are ineffective or patients have contraindications to their use.[16,24,25,53] Moderate to strong evidence indicates effectiveness of weak opioids in reducing pain and disability associated with ALBP and CLBP.[16,24,25,53] However, this benefit must be balanced by the potential for adverse effects, dependence, and abuse. The most reliable predictor of abuse is a personal or family history of substance abuse.[53]

Dosage

Doses are as follows: codeine, 15 to 30 mg up to four times daily; hydrocodone, 5 to 10 mg up to four times daily; and tramadol, 50 to 100 mg up to four times daily.

Precautions

Side effects of opioids are common and can include constipation, nausea, somnolence, pruritus, dysphoria, and sexual dysfunction.[25,53] Even though stronger opioid analgesics are often prescribed for ALBP (e.g., short-acting oxycodone) and CLBP (e.g., long-acting morphine and oxycodone), evidence supporting their use is limited, and they have a greater potential for dependence and abuse.[16,24,35,53] Stronger opioids should be considered only for short-term use in patients with severe pain who are at low risk for abuse. Rarely long-acting opioids in CLBP can be considered if all other therapeutic options have been exhausted, evidence indicates poor function related to back pain, and the patient has no personal or family history of abuse. A referral to a pain specialist may be indicated for patients requiring prolonged opioid use. All patients requiring prolonged opioids should be required to sign a narcotic pain medication agreement with the provider.

Muscle Relaxants

Muscle relaxants have antispasmodic properties and include benzodiazepines (e.g., diazepam) and nonbenzodiazepines (e.g., cyclobenzaprine, carisoprodol). Benzodiazepines are effective for short-term pain relief in ALBP or acute exacerbations of CLBP and can be used sparingly off-label for this purpose.[35,46,53] Benzodiazepine use is best restricted to bedtime only, given the strong sedating effects of these drugs. In addition, benzodiazepines have a great potential for dependence and abuse. Therefore, they should be used only on a short-term basis and should not be prescribed to patients with a history of abuse.[16,25,46,53] Nonbenzodiazepines are also effective for ALBP but are not recommended for CLBP.[16,35,46,53]

Tricyclic Antidepressants

Low-dose tricyclic antidepressants (e.g., amitriptyline, 10 to 25 mg at bedtime) can be effective adjuncts for pain relief in CLBP.[16,25,46,53] Medications in this class should not be used as first-line therapy. Selective serotonin reuptake inhibitors are not recommended for CLBP.[16,25,46,53]

Botanicals and Supplements

Devil's Claw

Devil's claw (*Harpagophytum procumbens;* see Table 64-3 in Chapter 64, Neck Pain) belongs to the Pedaliaceae family and is also known as grapple plant, wood spider, and harpago.[55,56] A Cochrane Review found two high-quality trials that examined the analgesic effects of devil's claw for back pain and showed strong evidence that this botanical was better than placebo for short-term improvements in pain.[16,56]

Dosage
Daily use of 2400 mg, divided three times per day and ingested by tablet or capsule standardized to 2% harpagosides and 3% total iridoid glycosides, is recommended.[55,56]

Precautions
Devil's claw extract may inhibit certain cytochrome P-450 enzymes, and therefore, appropriate monitoring of patients taking medications such as statins, imidazoles, and protease inhibitors is recommended. As with many botanicals and supplements, prothrombin time levels in warfarin users should be carefully monitored.

Willow Bark
Willow bark comes from a family of deciduous trees and shrubs commonly known as white willow or European willow *(Salix alba)* and purple willow *(Salix purpurea)*. Willow bark contains salicylates and is the botanical precursor to aspirin. Willow bark has been shown to be better than placebo for short-term improvements in pain.[16,56]

Dosage
The three routes of administration of willow bark are tea, capsule, and tincture.[57] Willow bark containing 240 mg of salicin taken once daily is recommended.

Precautions
Willow bark should be avoided in patients who are allergic or sensitive to salicylates. Willow bark can cause dyspepsia but usually less than seen with NSAIDs. Concomitant use of willow bark and anticoagulants and antiplatelet drugs should be avoided.[57]

Other Remedies
Several other herbal formulations and natural medicines have been investigated as treatment for ALBP and CLBP. Two of the better-known therapies are topical capsicum and glucosamine sulfate. Some evidence indicates that capsicum may be beneficial, but glucosamine sulfate is not recommended.[16,56,58,59]

Biomechanical Interventions

Spinal Manipulation
Spinal manipulation involves the application of high-velocity, low-amplitude forces to the joints of the spine through long or short levers. Spinal manipulation is primarily performed by chiropractors, but it also can be provided by osteopaths, physical therapists, and physicians. Specific manipulative techniques differ slightly within and among professions, but a unifying element is the use of a high-velocity thrust or impulse to apply the manipulative force. The exact mechanism of action of spinal manipulation has yet to be determined, but it is believed that the thrust procedure normalizes joint biomechanics, acts on the nervous system through the stimulation of afferent joint receptors, or both.

Spinal manipulation is effective in improving function and pain in both ALBP and CLBP compared with sham manipulation, analgesic medications, or exercise therapy.[60–62] Serious adverse events (e.g., disk herniation, cauda equina syndrome) associated with lumbar spine manipulation are rare, with an estimated risk of less than 1 in 1,000,000 manipulations.[63] Additionally, all major international guidelines recommend spinal manipulation as a treatment option for ALBP and CLBP.[16,24–27]

The TBC uses a clinical prediction rule to identify patients who are likely to respond to spinal manipulation. The prediction rule has been validated for use in patients with ALBP or acute exacerbation of CLBP.[64,65] The five criteria in the prediction rule are (1) duration of the current episode is less than 16 days, (2) extremity symptoms not distal to the knee, (3) low fear avoidance (less than 19) as determined by the Fear Avoidance Beliefs Questionnaire Work Subscale, (4) palpation of one or more hypomobile lumbar segments, and (5) one or both hips with internal rotation range of motion greater than 35 degrees.[64] In one report, patients who met four out of five criteria and who received manipulation had more than a 90% likelihood of a successful outcome, as defined by a 50% improvement in Oswestry Disability Questionnaire scores at 1 week.[64] In this subpopulation, the clinical benefit was also maintained at 4 weeks and at 6 months.[64]

Patients with low back pain most likely to respond to manipulation:
1. Duration of current episode less than 16 days
2. Extremity symptoms not distal to the knee
3. Low fear avoidance
4. Palpation of one or more hypomobile lumbar segments
5. One or both hips with internal rotation range of motion greater than 35 degrees

Clinical practice guidelines recommend that spinal manipulation be offered according to patients' preference or when patients have failed to improve with a short course of advice and self-care. In addition, the clinical prediction rule is a useful decision support mechanism for identifying patients who are likely to benefit from spinal manipulation.

Nonthrust Manual Therapies
Nonthrust manual therapies encompass various techniques directed at the joints and soft tissues. These techniques include mobilization, muscle energy techniques, myofascial release, strain and counterstrain (see Chapter 106, Strain/Counterstrain), and craniosacral therapy. These procedures use both active and passive movements and are distinct from spinal manipulation in that high-velocity, low-amplitude forces are not used. Nonthrust manual therapies are primarily performed by osteopaths, but they are also commonly delivered by physical therapists and chiropractors.

A meta-analysis by Licciardone et al[66] looked at six randomized controlled trials in populations with subacute LBP and CLBP. These trials used a combination of nonthrust manual therapies described under the umbrella of osteopathic manipulative therapy.[66] In some of the trials, high-velocity, low-amplitude spinal manipulation was also used. The investigators concluded that these combined therapies significantly reduced LBP as compared with active treatment (e.g., massage, chemonucleolysis), sham, and no treatment control. Furthermore, these pain reductions were observed across short-, intermediate-, and long-term end points.

Spinal mobilization provides better pain relief and greater increases in range of motion when compared with no treatment but is not significantly different from sham treatment.[67]

Moderate evidence also shows that spinal mobilization produces benefits in both acute and chronic back pain.[60] Nonthrust manual therapies may be offered according to patients' preferences or when patients have failed to improve with a short course of advice and self-care.

Exercise Therapy

Exercise therapy is the most widely used nonpharmaceutical intervention for LBP[68] (see Chapter 91, Low Back Pain Exercises). *Exercise therapy* refers to a broad range of techniques designed to improve strength, coordination, flexibility, range of motion, endurance, and aerobic capacity. These techniques can vary according to frequency, intensity, and duration. Exercise therapy is principally provided by physical therapists, but it may also be delivered by chiropractors, osteopaths, and physicians.

The benefit of exercise therapy for ALBP remains unclear. However, strong evidence indicates that exercise therapy provides a small but significant benefit in short-term and long-term pain compared with usual care in the population with CLBP.[16,24–27,69] Studies comparing different forms of exercises in the population with CLBP have not found clinically meaningful differences.[68] Individually designed, supervised, high-intensity programs are recommended because they have been found to achieve better pain reduction and functional improvements than standardized group or home programs.[69] Adverse events associated with back exercise programs are rare.[68] If home programs are used, frequent patient follow-up to encourage compliance is needed because adherence is typically poor.[68,69]

Some subgroups of patients with LBP may respond differently to various types of exercise therapy.[68] Although important differences exist between the TBC and the MTD methods of classification, one common component is the identification of patients whose symptoms "centralize" in response to specific postures or movements. The centralization phenomenon occurs when movement in a specific direction, such as lumbar flexion or extension, causes the patient's pain to decrease or move rapidly from a more peripheral location (e.g., leg) to a more central location.[70] Similarly, movement in the opposite direction "peripheralizes" the pain or reverses the effect. Indications in the patient's history that these movement patterns should be explored include constant pain that varies in intensity, pain often in seated positions, and movement restrictions that are usually asymmetric.[71]

The TBC also uses a clinical prediction rule developed by Hicks et al[21] to identify patients likely to benefit from lumbopelvic or core stabilization exercises targeting the transversus abdominis, erector spinae or multifidus, quadratus lumborum, and oblique abdominal musculature. To be placed in this category, a patient must have three or more of the following criteria: age younger than 40 years, average passive straight leg raise range of motion greater than 90 degrees, an aberrant movement pattern during trunk flexion (e.g., the Gower sign, reverse lumbopelvic rhythm), and a positive prone instability test result.[21]

As with manipulation, the major clinical practice guidelines recommend that exercise therapy be offered according to patients' preferences, especially for CLBP. In addition, insights from the TBC and MTD may be helpful in identifying patients who are likely to benefit from specific forms of exercise.

Massage

Massage refers to various techniques in which the therapist presses, rubs, and otherwise manipulates the body's soft tissues and muscles, usually with the hands and fingers. Evidence regarding the benefits of massage for both acute and chronic back pain is conflicting. In patients with CLBP, evidence suggests that massage produces similar improvement in pain and function when compared with exercise therapy, and it provides better short-term outcomes compared with mobilization, relaxation therapy, physical therapy, acupuncture, and self-care education.[25,72] In addition to short-term benefits, one clinical trial found that massage provided long-term beneficial effects when compared with acupuncture and self-care in patients with CLBP.[72] Evidence shows that acupressure massage (gently pressing specific points) produces better results than Swedish massage (effleurage, pétrissage, and tapotement), and that Swedish and Thai massage are equivalent.[72] Minor pain or discomfort is experienced in a small percentage (less than 15%) of patients during or shortly after receiving massage.[73] Working with an experienced or licensed massage therapist is important.[72] For patients with acute and subacute back pain, evidence indicates that massage provides significant short-term reductions in pain and disability when compared with no treatment or sham.[67] For acute and chronic back pain, massage may be offered in accordance with patients' preferences as a short-term measure to improve function and activity tolerance.

Physical Modalities

Physical modalities include agents such as interferential current, low-level laser, shortwave diathermy, superficial heat, cryotherapy, traction, ultrasound, lumbar supports, and transcutaneous electrical nerve stimulation. Some evidence supports the use of superficial heat for ALBP. All international guidelines uniformly recommend against the use of all other physical agents in patients with ALBP and CLBP because of insufficient or conflicting evidence of benefit.[16,24–27]

> Do not recommend physical modalities with no or little evidence of benefit, such as traction, ultrasound, lumbar supports, and transcutaneous electrical nerve stimulation.

Bioenergetic Interventions

Acupuncture

Acupuncture may achieve its effects by three proposed mechanisms: (1) release of endorphins and other neurotransmitters as a result of nervous system stimulation, (2) the gate control theory of pain, and (3) stimulation of vascular and immunomodulatory mediators of inflammation.[74,75]

Acupuncture is more effective than no treatment and conservative management for short-term pain relief

and improved function for CLBP.[76] However, the beneficial effects of acupuncture for LBP are generally short lasting.[67] Evidence indicates that pain and function are improved when acupuncture is combined with other treatments such as spinal manipulation or exercise therapy.[76] However, evidence of the benefit of acupuncture as a stand-alone modality compared with other common interventions for CLBP is insufficient.[46] One study found that acupuncture was no more effective than sham acupuncture.[75] Investigators have theorized that patients' expectations may explain this phenomenon; however, results of this line of investigation have been equivocal.[77] Serious complications of acupuncture are rare, although one systematic review did report needle pain and bleeding to be common side effects.[62] Acupuncture is a treatment option for CLBP and may be offered in accordance with patients' preferences. Acupuncture for ALBP is not recommended.[16,24,26,27,35]

Injection Therapies

The use of epidural steroid and facet joint injections for the treatment of LBP has increased significantly since the 1990s, even though evidence for their effectiveness is mixed.[78–80] During this period, numerous systematic reviews and clinical practice guidelines have been published addressing the indications for the use of these two procedures.[25,35,46,81–85] Based on these works, epidural steroid injections appear to provide potential short-term pain relief in patients with subacute or chronic leg-dominant radicular syndromes resulting from disk herniation or spinal stenosis.[25,35,46,81–87] Epidural steroid injections do not appear to confer long-term pain or functional benefits, nor do they mitigate the progression to surgery in these subpopulations with LBP.[81,83,86,87] Epidural steroid injections are not recommended for nonspecific ALBP or CLBP.[24,25,35,46,81–87]

Spinal facet joints have been shown to be pain-generating structures. However, randomized trials evaluating the use of therapeutic facet injections for CLBP have not shown a clear benefit over sham interventions.[24,25,81,85] In addition, no high-quality evidence supports the use of facet joint injections in patients with ALBP.[35,81] Therefore, facet joint injections are not recommended for use in ALBP or CLBP.[24,25,35,46,81,85]

Surgery

According to James Weinstein, spine surgeon and Director of the Dartmouth Institute for Health Policy and Clinical Practice, "the United States has the highest rates of spine surgery in the world, despite incidence and prevalence rates of spine disorders that are similar to those found in other countries. There remains little or no medical, clinical, or surgical evidence to support such variability."[88] Except for a limited number of specific conditions (e.g., cauda equina, infection, tumor) lumbar surgery should not be considered until a comprehensive trial of conservative care has been exhausted.[16,24,25,35,81,83,89]

In patients suffering from significant, nonradicular CLBP with concomitant degenerative changes in whom a 1-year trial of conservative care has failed, surgical fusion is a treatment option.[16,24,25,81,89] Evidence from higher-quality studies shows that fusion is equivalent to multidisciplinary function restoration programs and is moderately superior to nonspecific conservative treatment.[25,81,89] When clinicians consider surgical referral in this population, several factors should be taken into account. First, the benefits of fusion have been shown only in patients with moderate to severe pain or functional limitations who have not responded to at least 1 year of conservative management and who do not have significant psychiatric or medical comorbidities.[81] Second, more than 50% of patients undergoing surgery do not report "excellent" or "good" outcomes, defined as sporadic pain, slight functional limitations, and occasional analgesic use.[81]

One year of conservative therapy is often recommended before surgery is considered.

Standard diskectomy and microdiskectomy are treatment options in patients suffering from significant radiculopathy resulting from disk herniation following a trial of nonsurgical treatment.[81,83,89] Most patients in this subgroup tend to improve without surgery. However, approximately 10% will have sufficient pain and functional limitations after 6 to 8 weeks to warrant surgical referral.[81,83] Both standard diskectomy and microdiskectomy are associated with moderate short-term benefits (6 to 12 weeks) when compared with nonsurgical management, but these benefits diminish over the longer term (1 to 2 years).[81]

When significant radiculopathy resulting from spinal stenosis persists in spite of an adequate trial of conservative care, laminectomy is a treatment option.[81,89] Patients appear to have moderate benefits as a result of surgery versus nonsurgical treatment, but the average improvement in the stenotic patient is less than that seen in patients with radiculopathy resulting from disk herniation.[81] In addition, the differences in outcomes in patients with radiculopathy related to spinal stenosis who are treated surgically versus nonsurgically diminish over the longer term (1 to 2 years).[81]

Prevention Prescription

- Educate: Nonspecific low back pain is not progressive and will not disable you unless you let it.
- Maintain normal physical activity as much as possible.
- Lift properly: Bend your knees and keep your back straight.
- Take regular 5-minute breaks to stand and stretch when sitting for long periods.
- Strengthen trunk muscles and walk regularly.
- Have a regular stretching or yoga routine.
- Keep a healthy body weight.

Therapeutic Review

When deciding among the following therapeutic options for low back pain (LBP), augment the biomedical model of evaluation and management with a biopsychosocial approach.

Evaluation

- Rule out potentially serious disease (red flags) and significant neurologic involvement. If present, refer for imaging and specialty care as appropriate.
- Identify risk factors for chronicity (yellow flags).
- Do not routinely use imaging in patients with nonspecific LBP and no red flags.
- For nonspecific back pain, consider patients' preferences and clinical classifications in treatment planning.

Education and Self-Care

- Reassure patients about the benign nature and favorable prognosis of nonspecific back pain. A1
- Advise patients to stay active and carry on as normally as possible. A1
- Dispel inappropriate beliefs. A1

Pharmaceuticals

- Acetaminophen: 500 mg, one to two tablets three to four times daily B1
- Nonsteroidal antiinflammatory drugs (take with food) A2
  - Ibuprofen: 400 to 800 mg three times daily
  - Naproxen: 375 to 500 mg twice daily

Botanicals and Supplements

- Willow bark containing 240 mg of salicin: taken once daily B2
- Devil's claw: 400 mg, two capsules three times daily (standardized to 2% harpagosides and 3% total iridoid glycosides) B2

Mind-Body Therapy

- Consider cognitive-behavioral, operant, and respondent therapies, such as progressive muscle relaxation, as treatment options for patients with chronic LBP. B1
- Recommend yoga as a treatment option for patients with chronic LBP. B1
- Refer for multidisciplinary functional restoration in patients with chronic LBP in whom conservative options have failed and who exhibit high levels of physical and psychological disability. A1

Biomechanical Therapies

- Recommend 4 to 8 visits of spinal manipulation as a treatment option for patients with acute and chronic LBP. B1 A1
- Recommend 8 to 12 visits of therapeutic exercise in patients with chronic back pain. A1
- Consider a short course of 4 to 8 visits of massage as a treatment option for patients with acute and chronic LBP. B1

Bioenergetic Therapies

- Acupuncture: Consider a short course of 4 to 8 visits of acupuncture as a treatment option for patients with chronic LBP. B1

KEY WEB RESOURCES

Fear Avoidance Beliefs Questionnaire: http://www.udel.edu/PT/PT%20Clinical%20Services/journalclub/caserounds/05_06/mar06/FABQ1.pdf	Survey form and scoring methodology used to identify patients with maladaptive coping behaviors
Revised Oswestry Disability Index: http://thepainsource.com/2010/12/revised-oswestry-disability-index/	Survey form, scoring methodology, and interpretation rubric for one of the most commonly used outcomes instruments for low back conditions
Spine-Health information on the McKenzie Method: http://www.spine-health.com/wellness/exercise/mckenzie-therapy-mechanical-low-back-pain	Good overview of the McKenzie Method of Mechanical Treatment and Diagnosis
Yoga Journal yoga poses: http://www.yogajournal.com/poses/finder/therapeutic_focus/t_back_pain	Comprehensive index of yoga poses appropriate for patients with low back pain
Spine-Health information on how to select the best chiropractor: http://www.spine-health.com/treatment/chiropractic/how-select-best-chiropractor	Article offering useful tips to help physicians and patients identify competent chiropractic practitioners

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Chapter 64

Neck Pain

J. Adam Rindfleisch, MD, MPhil, and Brian Earley, DO

In many Eastern traditions, the neck is held to be our center of communication, self-expression, and creativity. The neck houses our voices, our capacity to swallow, and the major blood vessels that are the lifelines between the heart and head. Metaphors related to the neck tell us something about its association with vulnerability. Something frustrating is "a pain in the neck," and something depressing gives one a "lump in my throat." We "stick our necks out for others" when we are being brave, and we "go for the throat" when we are being aggressive.

The neck has 37 separate joints and moves an average of 600 times per hour. It has evolved to be simultaneously rigid and flexible, and it houses separate flexor and extensor muscles for the head and cervical spine. It contains our cervical spinal cord, multiple nerve roots and joint facets, and the atlantoaxial joint. The neck is indeed a vulnerable part of the body. At any given time, 10% to 15% of people are experiencing neck pain,[1] and two thirds of people have neck pain sometime during their lives.[2] Not surprisingly, neck pain is one of the most common complaints primary care providers encounter.[3] Even with a full biomedical course of treatment, neck pain often recurs.[4] An individualized, relationship-centered, and holistic integrative approach can markedly improve outcomes.

Pathophysiology

Pinpointing the exact anatomic source of neck pain is often difficult. Most neck pain is the result of cervical paraspinal muscle spasm or other musculoskeletal factors, but clinicians must rule out various other causes, as noted in Box 64-1.[1,3]

Musculoskeletal neck pain can be traumatic or nontraumatic in origin.[1] Traumatic neck pain is most commonly associated with hyperextension syndrome (whiplash). As many as 40% of whiplash injuries are estimated to result in long-term symptoms.[5] In countries where litigation for whiplash is uncommon, long-term sequelae of whiplash are almost unheard of, a situation that leads one to wonder about the role of mind-body and economic influences on pain outcomes.[6]

Nontraumatic neck pain, which is more common, can be related to a structural or degenerative disorder, but more commonly it is caused by soft tissue disorders. Twin studies revealed a link between genetics and a predisposition to development of nontraumatic neck pain.[7] Common causes of soft tissue pain include poor posture, repetitive activity, and sports injuries. A strong connection exists between soft tissue neck pain and emotional or mental states, such as anxiety and depression.[8] Myofascial trigger points—clusters of muscle fibers locked in a contractile state—are commonly present in soft tissue pain.

The pathophysiologic basis of neck pain is complex, and our knowledge of the multitude of chemical and structural processes involved is far from complete. Pain begins with tissue irritation, which may be caused by infection, joint deterioration, sustained use (or sustained immobility), psychological stress, or trauma. Irritation activates nociception. Muscle spasms often occur as the neck is voluntarily or involuntarily repositioned to avoid pain. Inflammation follows, and a vicious positive-feedback circle arises as inflammation leads to even more pain. As edema, structural changes, and harmful metabolites accumulate, they can cause ischemia of the tissues. If these alterations are not interrupted or reversed in time, long-term changes in neck structure may arise, and disability can result.

Integrative Therapy

The goals of an integrative approach to neck pain are threefold[9]:

1. Understand the pain in a broader context. Move beyond an exclusively physiologic perspective to explore how emotions, work, social issues, relationships and other factors contribute. What burdens is a person "carrying" on his or her shoulders? Asking people their views on why they have pain can offer interesting insights. Ideally, preventive measures would be instituted before pain ever manifests.

BOX 64-1. Key Points to Remember in the Evaluation of Neck Pain

- Consider a tumor in a patient who has pain at night or whose pain does not improve when the body is supine.
- Neck pain with associated neurologic symptoms (e.g., dizziness, paresthesias, and weakness) merits diagnostic imaging studies, most commonly computed tomography or magnetic resonance imaging of the neck.
- Severe neck pain associated with fever is meningitis until proven otherwise.
- If neck pain is associated with joint pain in other areas, rule out a systemic rheumatic disorder, such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or gout.
- Neck pain can be referred from a source in the head or arms. Consider dental disorders, temporomandibular joint disorders, and rotator cuff injuries. Cervical spine disorders may lead to patient descriptions of the eyes being "pulled" or "pushed" if the sympathetic nerve plexuses that surround the arteries of the neck and innervate the eyes are irritated.
- Referred neck pain can arise from nearly any organ system. Myocardial ischemia, gallbladder disease, gastrointestinal ulcers, hiatal hernias, and pancreatic inflammation are all in the differential diagnosis. Referred diaphragmatic pain and tumors of the apical lung must also be considered.
- Keep in mind that uncommon local sources of neck pain can include the carotid arteries, vertebral arteries, lymph nodes, and the thyroid.

Data from references 1 to 3.

2. Explore where the cycle of pathophysiology described earlier may be interrupted and how that could best be done. Identify the initial insult or insults causing the pain. Supplements or diet may help to lessen inflammation. A mind-body approach may alter the tendency to fear or avoid the pain. Manual therapy, acupuncture, or exercise may help patients diminish the pain by learning to carry themselves differently. The key is to collaborate on a plan of action, with care taken not to overwhelm people with too many options. Trust your intuition as a provider.
3. Remain mindful of therapeutic complications and what is likely to cause pain recurrences. Pain can often be a powerful teacher. Why is this signal arising, and what changes are needed so that the signal will no longer be necessary? It is easy for a pattern to arise where the pain is masked, rather than truly treated. Some therapies (e.g., long-term narcotics) can lead to long-term problems and should be used cautiously.

Lifestyle

Box 64-2 lists some of the risk factors for neck pain.[2,9,10] Smoking, obesity, work activities, and substance abuse should all be given attention in an integrative visit.

BOX 64-2. Risk Factors for Neck Pain

- Depression
- Drug abuse
- Increasing age
- Heavy physical work, manual labor
- High job demands
- History of headaches
- Lack of control over work situation
- Low job satisfaction
- Work with exposure to repetitive vibration or unusual postures
- Obesity
- Smoking (and frequent coughing)

Data from Devereaux MW. Neck pain. *Med Clin North Am.* 2009;93: 273–284; and Teats RY, Dahmer S, Scott E. Integrative medicine approach to chronic pain. *Prim Care.* 2010;37:407–421.

Exercise and Movement

Patients with chronic neck pain demonstrate altered muscle activation patterns during the performance of tasks that may influence how rapidly their muscles become fatigued.[11] Medical research is limited regarding the potential benefits of the Alexander technique, Feldenkrais, and Pilates for neck pain, but these therapies are increasingly popular with patients with chronic pain, are effective for other musculoskeletal complaints, and tend to be safe.[12,13] Qi gong (which also may be classified as a bioenergetic therapy) also holds promise, although more studies are needed[14] (see Chapter 90, Prescribing Movement Therapies).

To assume that exercise for musculoskeletal neck pain would be beneficial seems logical. A Cochrane Review concluded that limited evidence of benefit exists for strengthening, stretching, or eye fixation exercises for neck pain with headache and for active range-of-motion exercises or a home exercise program for acute problems such as whiplash. The benefit of stretching and strengthening for chronic mechanical neck disorder was deemed "unclear."[15] Another review found that exercise, at least when combined with cognitive-behavioral therapy, reduced the number of days of work lost because of neck pain.[16]

Cervical Support

Early mobilization was found to be superior to cervical collar use in the treatment of neck pain.[17] One small randomized, controlled trial from Sweden did find that cervical pillows could be useful for both neck pain and poor sleep.[18] Proper neck positioning during sleep is important. Prolonged flexion of the neck should be avoided; maintenance of the neck's natural lordotic curve is preferable. Cervical spine pillows may be useful. Evidence on whether traction is beneficial is insufficient.[19]

Repetitive Strain

Certain movements and activities can put the musculoskeletal structures of the neck under chronic stress and tension. Examples are holding a phone between the shoulder and the ear (administrative work), carrying a heavy purse or backpack on one shoulder, staring at a computer monitor for

long periods of time, and looking over the shoulder (farming). Bifocals may lead to awkward flexion of the neck as well. The effects of such postures should be brought to patients' attention. Many people "carry their stress" in their neck and shoulder muscles. Chronic stress can result in a constant readiness to duck or to dodge danger, and many people chronically tense the muscles used for these actions without realizing it.

Nutrition

Essential Fatty Acids

Increasing intake of omega-3 fatty acids and reducing consumption of omega-6 fatty acids lower the levels of prostaglandins and leukotrienes that cause inflammation[20,21] (see Chapter 86, The Antiinflammatory Diet). Several months may pass before patients derive a benefit from using the antiinflammatory diet, and the diet is most likely to be beneficial when neck pain has been chronic.

Saturated Fats

Eating saturated fats, which come primarily from animal products such as red meat and dairy foods, can also contribute to inflammation and pain.[22] A transition to a vegetarian diet, or at least toward a significant reduction in saturated fat consumption, is worth recommending. Some patients may benefit from a trial of an elimination diet, particularly for dairy and meat products (see Chapter 84, Food Intolerance and Elimination Diet).

Antioxidants

Elevations of free radicals can result from poor nutrition, excessive stress, and toxic environmental exposure. Foods rich in antioxidants, such as fruits and vegetables, seem to play a role in reducing pain by removing free radicals.[23] High doses of supplemental antioxidants, such as vitamin E, have been the subject of some controversy and may be inadvisable in patients with heart disease or other chronic conditions.[24] Eating a combination of green, yellow, red, purple, and orange produce will guarantee that numerous beneficial antioxidants are consumed.

Take care not to underestimate the impact of mental health on the course of neck pain. Encourage the use of at least one of the many mind-body therapies that may offer benefit.

Mind-Body Therapy

Pain perception does not necessarily correlate with the severity of an injury. Some people with structural neck abnormalities develop chronic pain, whereas others do not. In a landmark study in the *New England Journal of Medicine*, magnetic resonance imaging (MRI) examinations of 98 *asymptomatic* individuals indicated that 52% had one or more bulging disks.[25] Similarly, nearly everyone who is older than 70 years has some degree of cervical spondylosis, but not everyone that age has neck pain.[2] Pain is often centrally mediated, with abnormal intensification of sensation noted in the portions of the brain that govern a chronically painful part of the body.[9] Fortunately, the brain's plasticity allows for the possibility for "rewiring" the brain; sensory processing may be changed to someone's advantage. The key is to discern how to help someone with pain make that happen, and this is where mind-body approaches can come into play.[26]

Emotions and Neck Pain

Emotional well-being plays an important role in whether pain arises.[27] A Stanford University study that evaluated both symptomatic and asymptomatic patients with abnormal MRI findings concluded that the severity of the MRI lesions did not predict the presence of pain; rather, pain severity correlated with whether patients had underlying psychological issues.[28] Pain is more likely to become chronic in people who tend to catastrophize[29] or somaticize.[30] Stress also plays a role. A British study of 12,907 people concluded that the association between perceived neck pain and mental stress was much stronger than the association between neck pain and repetitive occupational activities.[31]

In his book, *The Mindbody Prescription: Healing the Body, Healing the Pain*, John E. Sarno, MD, suggested that unexpressed emotions are responsible for neck, back, and limb pain in most patients.[32] Sarno held that unexpressed anger, accumulated as a result of internal and external pressures, is of particular significance. He proposed that, after physical concerns have been appropriately ruled out, the following elements can be used to help people markedly decrease pain:

- *Learn about pain.* Patients attend a series of lectures describing the relationship between pain and emotions.
- *Focus on emotions when pain strikes.* When patients become aware of the pain, they must consciously shift their focus toward the psychological, as opposed to physical, causes of their discomfort.
- *Maintain physical activity.* Patients must overcome fears that physical activity will worsen the underlying condition. This step is implemented after the pain has been decreased through exploration of emotional issues.
- *Discontinue physical or physiologic treatments.* Sarno contended that focusing on physical causes of pain distracts the mind from the unexpressed emotions that are the pain's true cause. Medications are used sparingly for episodes of severe pain only.
- *Consider counseling.* If needed, patients are encouraged to seek help from a counselor in moving through the various emotional issues they encounter during the program.

Although outcomes research on the efficacy of Sarno's program is limited, the program has proved helpful for many people with chronic neck pain. Once potentially dangerous causes of pain have been ruled out, the risk of harm from participating in such a program is minimal. Many health care institutions offer pain management and coping groups, which may be similarly helpful (see Chapter 100, Emotional Awareness for Pain).

Journaling

By writing about stressful events, patients may be able to reduce pain and inflammation. One study found that symptoms of asthma and rheumatoid arthritis improved

significantly in people who wrote about stressful life events in a journal for just 20 minutes for 3 consecutive days.[33] To assume that other disorders may also respond to this approach is reasonable (see Chapter 96, Journaling for Health).

Hypnosis

Hypnosis has been found to be useful in helping patients manage chronic pain.[34,35] In one study, 25 patients with head and neck pain were treated with acupuncture. After a washout period, they were treated with hypnosis. Both interventions were found to be helpful, but hypnosis scored slightly better, with an average reduction of 4.8 points on a 10-point symptom scale, compared with 4.2 points for acupuncture. Acupuncture was more appropriate for acute pain, whereas hypnosis appeared to work better for psychogenic pain. Subjects who also received healing suggestions by audiotape had less pain than those who did not[36] (see Chapter 92, Self-Hypnosis Techniques).

Interactive Guided Imagery

Interactive guided imagery is based on the philosophy that insight and knowledge gained from the creation of internal images can be used to improve symptoms. One interactive guided imagery technique is to have a patient visualize an image representing a particular symptom. The patient is asked to have a dialogue with the image that arises and to explore why it is present and what it would "need" for healing to occur. The image can serve as a means by which the conscious mind can access the subcounscious[37] (see Chapter 95, Guided Imagery).

Relaxation Exercises

Relaxation exercises, such as breathing techniques and progressive muscle relaxation, can reduce sympathetic stimulation, a potential contributor to muscle tension and pain. One study comparing relaxation, exercise, and ordinary activity for neck pain treatment did not find a benefit from either intervention in comparison with placebo.[38] Nevertheless, perhaps these techniques can serve as a safe and potentially useful way to empower patients to decrease their neck pain (see Chapter 93, Relaxation Techniques).

Biofeedback

Biofeedback uses technology or instrumentation to help people gain awareness of and control over various body processes.[39] Functional MRI studies indicated that biofeedback training can allow people with pain to alter pain perception by controlling activation of the rostral anterior cingulate cortex and other brain locations.[40,41] Severe chronic pain can be decreased. Sensors placed over the trapezius muscle can be used to train a patient to relax more efficiently. A small study of older patients with trapezius pain showed a 70% reduction in pain with biofeedback-assisted relaxation.[34] Biofeedback is worth considering in patients with neck pain.[42]

Bioenergetic Therapies

Acupuncture

The principle that energy flows through or over the surface of the body is common to several healing systems worldwide. Acupuncture, a 3000-year-old therapy based on the idea that the body contains multiple energy channels, or meridians, maps out more than 350 major points. Needles are inserted at those points to improve the flow of energy (known in China as qi). Many of these points are located within or in close proximity to the neck.[43,44]

Evaluations of acupuncture as a treatment for chronic neck pain show promise. A 2006 Cochrane Review concluded that "moderate evidence" indicated that acupuncture is effective for chronic neck pain.[45]

- Acupuncture led to pain relief immediately after treatment and in the short term compared with sham treatment or being on a waiting list.
- Acupuncture led to at least short-term benefit for patients with radicular symptoms when compared with patients who were placed on a waiting list.
- Acupuncture was more effective than massage at short-term follow-up.

A 2008 review by the Task Force on Neck Pain and Associated Disorders also noted that acupuncture was superior to sham treatment, no treatment, and many other modalities for chronic neck pain.[46] Less evidence is available at this time to indicate whether acupuncture is useful for acute neck problems.[47]

Box 64-1e, which lists contraindications to acupuncture, can be found online at expertconsult.com.

Acupuncture has been found to be extremely safe when it is offered by a well-trained provider.[48]

Good evidence supports the use of acupuncture for chronic neck pain.

Other Energy Medicine Modalities

Many Eastern traditions hold that the neck houses the throat chakra, a wheel of energy that extends anterior and posterior to the body at the level of the thyroid. Although therapies that purport to balance the human energy field, such as therapeutic touch and Reiki, require further study, some interesting findings are beginning to emerge,[49,50] especially with regard to emotional responses to illness. Harm is minimal, provided that patients do not defer potentially lifesaving biomedical therapies to focus on receiving energy medicine treatments.

Manual Therapies

Manual medicine is another common approach to neck pain. Manual techniques are done by various health professionals, including medical doctors (especially doctors of osteopathy, or DOs), physical therapists, massage therapists, manual therapists, and chiropractors.[51] Spinal manipulation performed by chiropractors, in fact, is the most common complementary and alternative therapy provided in the United States.[52] In the early 2000s, approximately 70,000 chiropractors were licensed in the United States, 10,000 in Japan, 6000 in Canada, 2500 in Australia and 16,000 in the United Kingdom.[53]

BOX 64-1e. Safety Considerations in Recommending Acupuncture

Suggested contraindications to acupuncture include the following:
- Pregnancy (a relative contraindication)
- Bloodborne viral illness
- Bleeding disorders
- Skin infections
- Pacemakers
- Cardiac arrhythmias
- Epilepsy (only electroacupuncture contraindicated)

Only 50 cases of severe complications were noted in the United States in a 20-year period. Most of these complications, such as pneumothorax and the migration of broken needle fragments under the skin, are unlikely when practitioners are well trained. For acupuncture in the neck, the carotid arteries in particular must be carefully avoided.

Refer patients only to board-certified or licensed acupuncturists; useful resources for locating such professionals are www.medicalacupuncture.org/findadoc/ and www.acupuncturetoday.com/locator.

Data from Lyte CD. *An Overview of Acupuncture.* Washington, DC: U.S. Dept. of Health and Human Services, Health Sciences Branch, Division of Life Sciences, Office of Science and Technology, Center for Devices and Radiological Health, Food and Drug Administration; 1993; and Vas J, Perea-Milla E, Mendez C, et al. Efficacy and safety of acupuncture for chronic uncomplicated neck pain: a randomised controlled study. *Pain.* 2005;126:245–255.

Nomenclature

The nomenclature of biomechanical therapies can be confusing. Chiropractic and physical therapy manual techniques are typically broken into two groups. Manipulation refers to a technique that uses a high-velocity, low-amplitude (HVLA) thrust.[54–56] Mobilization refers to techniques that incorporate lower-velocity, passive movements to the joints.[54] Osteopaths use the term manipulation to describe more than 100 different techniques including but not limited to HVLA.[56] Osteopathic manipulation is categorized into various groups of techniques, listed in Table 64-1.[57,58] In this chapter, manipulation refers to the term as defined by chiropractors and physical therapists, and osteopathic manipulative treatment (OMT) refers to manipulation as defined by the osteopathic profession.

Safety

The safety of manipulation of the cervical spine has been questioned. Most of these potential risks occur because of the rapid thrust. Therefore, the safety of high-velocity manipulation techniques has been studied much more than mobilization or non-HVLA OMT techniques. As noted in Box 64-3,[59–62] however, few contraindications exist, and manipulation seems to be significantly safer than other modalities (including antiinflammatory medications) commonly used for musculoskeletal conditions.[63,64] A study by Rubinstein et al[65] showed that the "benefits of chiropractic care for neck pain seem to outweigh the potential risks."

Common transient effects of cervical manipulation include local pain, headache, tiredness (fatigue), and radiating pain.[66,67] Transient effects occur in 30% to 61% of patients, begin within 4 hours after spinal manipulation, and usually resolve within 24 hours.[66,67]

Substantive reversible risks of manipulation are much less common. Worsening disk disease can occur with manipulation, but it occurs in fewer than 1 in 3.7 million patients.[66] This adverse effect is more common with manipulation of the low back than in cervical manipulation. Because of this risk, manipulation is relatively contraindicated in patients

BOX 64-3. Contraindications to Manipulation (High-Velocity Osteopathic Manipulative Treatment) of the Neck

- Aneurysm
- Bone tumor
- Carotid or vertebrobasilar disease
- History of pathologic fractures
- Vertebral infection
- Acute vertebral fracture
- Ligament rupture and instability
- Metastatic carcinoma
- Osteopenia or osteoporosis
- Anticoagulation therapy
- Previous surgery involving neck joints
- Rheumatoid arthritis of the cervical spine
- Unstable odontoid peg

Data from references 59 to 62.

TABLE 64-1. Examples of Various Osteopathic Manipulative Techniques

High-Velocity Low-Amplitude (HVLA) Techniques	The physician uses an HVLA thrust to push through a joint restructure to restore the range of motion of that joint.
Springing Techniques	The physician repetitively, gently rocks or pulses against the restriction of a joint to restore the range of motion of that joint.
Muscle Energy Techniques	The physician asks the patient to pull against the physician's resistance to rebalance the muscles around a dysfunctional joint.
Soft Tissue Techniques	The physician kneads, stretches, or applies inhibitory pressure to relax the soft tissues.[57]
Functional Techniques	The physician monitors the soft tissues while small motions are applied to the joint to decrease resistance. These techniques often use the patient's breathing to cause the restriction in the joint to "release."
Strain-Counterstrain Techniques	These techniques involve palpating tender points and putting the joint in a position to take away the palpatory pain of these points. This position is held until the restriction releases (approximately 90 seconds).[58]
Facilitated Positional Release	In these techniques, the joint or tissue is taken to the position of most comfort. Traction or compression is applied to facilitate an immediate release of the tissue tension.
Still Technique	This technique, thought to be developed by Dr. Still, is set up like facilitated positional release, but after traction or compression is applied, the joint is taken into the joint's restriction and is then returned to neutral.
Cranial Osteopathy	This gentle, manual technique emphasizes balancing the tensions of the dura.
Lymphatic Techniques	Various techniques that generally involve gentle techniques aimed at promoting the movement of the lymphatic fluid are used to promote healing of several conditions.

Data from Ward RC, Hruby RJ. *Foundations for Osteopathic Medicine*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003, except where otherwise referenced.

with signs or symptoms of disk herniation until this disorder has been ruled out radiographically.[68]

The most concerning risks of cervical manipulation are those that are nonreversible. The most common of these is iatrogenic stroke, although vertebral dissection can also occur. These complications are quite rare, and in a review of injuries caused by manipulative therapy between 1925 and 1993, only 185 cases of serious injury were reported.[69]

Research in Manual Therapies for Neck Pain

Chiropractors and physical therapists have performed more manual therapy studies than other health professionals, and this is true when it comes to studies of neck pain as well.[70] Whether study findings are generalizable from one type of therapy to another is difficult to know because of the differences in categorization of the various types of manual therapies (see earlier), the difficulties in creating sham manipulation, and the use of osteopathic manual manipulation (in the United States) as adjuvant therapy.[71] Therefore, in this chapter, research done on manual medicine for the neck is divided into studies done by chiropractors or physical therapists and studies done by osteopaths.

Chiropractic and Physical Therapy Studies

Approximately 40% of episodes of care for back pain are managed by chiropractors.[72] For these visits, neck pain is the second most common reason (behind low back problems) for a patient to visit a chiropractor. Approximately 24% of visits to a chiropractor are for neck pain.[73] Chronic neck pain has been studied by chiropractors more than acute neck pain, and Gross et al summarized the findings in multiple Cochrane Review meta-analyses. In these reviews, Gross et al assessed whether manipulation or mobilization improved pain, function or disability, patient satisfaction, quality of life, and perceived effect in patients with neck pain (with or without headache or radicular symptoms). The 2004 meta-analysis of 33 trials showed that combined mobilization, manipulation, and exercise achieved clinically important improvements in pain, global perceived effect, and patient satisfaction in subacute and chronic neck disorders with or without headache.[74] A more recent review of 27 trials found immediate- or short-term pain relief with a course of cervical manipulation or mobilization alone, but the effects were not maintained over the long term.[75]

Less literature is available on the use of manipulation and mobilization for acute neck pain.[56,76] A small pilot study of 36 patients showed less pain intensity ($P < .05$) and a greater range of motion ($P < .05$) immediately following a single manipulation to patients with acute neck pain.[77]

Manual/Physical Therapy

Newer research showed that manipulation of the thoracic spine results in immediate improvement in neck pain.[54] A follow-up study showed that using thrust manipulation techniques in the thoracic spine resulted in greater short-term reductions in pain and disability than nonthrust mobilization in patients with neck pain. No additional side effects were noted in the thrust-treated group.[78] Previous studies had also shown significant improvements in patients with whiplash-associated disorders after thoracic mobilization was used.[79] Investigators proposed that techniques performed in the thoracic back may be an even safer option in patients with neck pain. However, further research must be done to assess long-term effects and to determine whether thoracic manipulation is most beneficial in isolation or in combination with some form of neck manipulation for the treatment of neck pain.[54]

Osteopathy

Only 2 small studies are available in the osteopathic literature to assess the effects of OMT on patients with chronic neck pain. In the first study, 17 patients with chronic neck pain lasting a mean of 168.8 weeks (4 to 1040 weeks) were recruited. These patients were treated with OMT for a total of 4 weeks (twice weekly for 2 weeks and once weekly for the final 2 weeks). They were analyzed before treatment, at 2 weeks, and at 4 weeks for changes in pain and disability. Significant improvements were found in pain ($P = .001$) and disability ($P = .001$) over the treatment course in the group receiving OMT. Improvements in pain and disability were found to be significant in patients with chronic pain and in those with subchronic pain. Further follow-up was not done in the study.[80]

In a second, slightly larger, study, 41 patients with nonspecific neck pain were divided into 2 groups. One group of 17 patients received ultrasound therapy only (every week for an average of 10 weeks), whereas a second group received ultrasound (every week for an average of 10 weeks) and OMT (every other week for an average of 10 weeks). Pain was measured at each of the treatments, 1 week after the treatments, and 3 months after the last treatment. The OMT used a combination of various techniques. Pain intensity decreased in both groups, with more improvement noted in the group receiving OMT ($P = .02$). No long-term follow-up was done.[81]

One study looked at OMT in patients with acute neck pain. In this study, 58 patients were randomized to receive either OMT or 30 mg intramuscular ketorolac (a known effective NSAID for musculoskeletal pain). The OMT provided included a combination of HVLA thrust, muscle energy, and soft tissue techniques. Both groups showed a significant reduction in pain intensity ($P < .01$ for both groups), but patients receiving OMT reported a significantly greater decrease in pain intensity ($P = .02$).[56]

Manipulation, mobilization, and osteopathic manipulative treatment, especially in combination with exercise, have been shown to be safe and effective in the treatment of chronic neck pain. These options also appear to be appropriate in acute neck pain, although substantially less research is available to support this approach.

In summary, the available literature indicates that manual therapies hold promise and are worth considering in the management of neck pain.

Strain-Counterstrain and the Cranial Base Release

Two techniques that the primary care provider can incorporate into his or her practice for the manual therapy of neck pain are strain-counterstrain and the cranial base release (Fig. 64-1 and Box 64-4). Strain-counterstrain is helpful for relieving trigger points and muscle spasms (see Chapter 106, Strain/Counterstrain). The cranial base release is beneficial for patients with suboccipital neuralgia and tension headaches. For challenging cases, appropriate referral is indicated.

Surgery

Considering surgery, such as disk fusion, is reasonable when patients have symptoms of radiculopathy, progressive myelopathy, neurologic deficits not improved with other forms of treatment, or imaging-confirmed operable conditions.[82] Evidence supporting the use of surgery for chronic neck pain resulting from degeneration radiculopathy is not conclusive, however, according to a 2010 Cochrane Review.[83] The review found no benefit at 1 year postoperatively for patients with mild symptoms preoperatively, and the reviewers noted that additional research is needed to confirm when surgery is most appropriate.

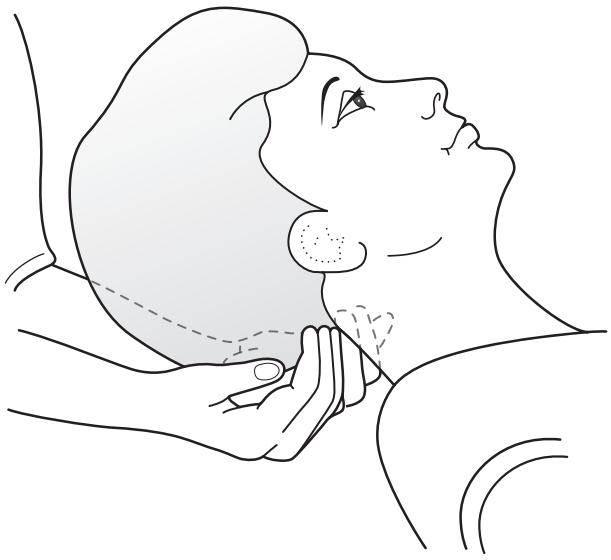
Pharmaceuticals

Western medical therapy goes to great lengths to suppress inflammation and nociception. Steroids, cyclooxygenase-2 inhibitors, NSAIDs, and other medications are effective largely because they interfere with the inflammatory cascade. Muscle relaxants, opioids, and antidepressants are used to alter nervous system signaling at various levels.

Table 64-2 lists medications commonly used in the treatment of neck pain, along with recommended doses and precautions regarding their use.[84–86] A 2007 Cochrane Review concluded that, for mechanical neck disorders, "Muscle relaxants, analgesics, and NSAIDs had limited evidence and unclear benefits."[87] The review also noted that although studies are limited, corticosteroid injections within 8 hours of injury for whiplash, steroids plus lidocaine injections for chronic pain, and lidocaine injections for trigger points seem to have some benefit. Injection of botulinum toxin was not found to be helpful.

Between 1997 and 2004, the use of opioids for treating spinal disorders increased by 108%, but pain, poor quality of life, and percentages of disability claims have not shown improvement.[86] Long-term narcotic administration down-regulates endorphin receptors, which are partially responsible for the pain relief conferred by mind-body therapies such as hypnosis and guided imagery. In other words, long-term narcotic use can impede the symptomatic relief that comes from these therapies.

FIGURE 64-1
Hand positions for cranial base release. See Box 64-4 for explanation of technique. (From Chaitow L. *Cranial Manipulation Theory and Practice: Osseous and Soft Tissue Approaches.* New York: Churchill Livingstone; 1999:119.)



BOX 64-4. Cranial Base Release

The cranial base release (also known as the suboccipital release) is a manual cranial technique that can be incorporated into your daily practice. It is most useful for patients with cervical myofascial tension that has led to suboccipital neuralgia and headache. If you find it helpful, consider referring the patient to a cranial osteopathic practitioner.

The cranial base release loosens soft tissues that attach to the base of the cranium. If hypertrophic and inflamed, these tissues can restrict occipital motion and cause pain.

- See Figure 64-1. The patient is supine on the table. Seat yourself at the head of the table with your arms resting on and supported by it.
- Rest the backs of your hands on the table. The fingertips, which are bent toward the patient's posterior neck, are positioned at the base of the occiput in the suboccipital sulcus.
- Your fingertips serve as a fulcrum for the patient's occiput. The back of the skull should rest comfortably in your palms. The patient should allow the full weight of the head to rest in your hands. The resultant pressure will induce tissue release at your fingertips.
- As relaxation proceeds and your fingers sink deeper into the soft tissues, apply gentle cephalic traction with your fingertips for a few minutes. This movement allows the arch of the atlas to disengage from the occiput. Cephalic traction should be started only after you are a few minutes into the technique, to allow for initial relaxation.

  This "release" of deep structures of the upper neck reduces tension, improves drainage and circulation to the head, and helps reduce intracranial congestion.

Data from Chaitow L. *Cranial Manipulation Therapy and Practice: Osseous and Soft Tissue Approaches.* New York: Churchill Livingstone; 1999:113–114.

TABLE 64-2. Pharmaceuticals Commonly Used to Treat Neck Pain

MEDICATION	EXAMPLE(S) AND DOSAGE	COMMENTS/PRECAUTIONS
Tricyclic Antidepressants (TCAs)	Amitriptyline: 10, 25, 75, 100, or 150 mg at bedtime, up to 300 mg/day Nortriptyline: 10–25 mg, titrated up by 25 mg every 3–4 days to maximum of 75–150 mg/day Taper dose when stopping therapy	Modulation of ascending and descending pathways Can give for 2–4 wk for pain reduction Decrease dose if excess sedation or anticholinergic effects Sedating Consider checking serum levels if high doses used for long periods
Muscle Relaxants	Cyclobenzaprine: 10 mg at bedtime or three times/day	Anticholinergic side effects May cause anxiety and restlessness Do not give with TCAs More effective than placebo in back and neck pain[84]
Nonsteroidal Antiinflammatory Drugs (NSAIDs)	Ibuprofen: 200–800 mg with food up to every 6 hr to a maximum dose of 3200 mg Naproxen: 250–500 mg/day with food	Can cause gastrointestinal bleeding, anticoagulation No one NSAID known to be better than others[85]
Acetaminophen	325–650 mg every 4–6 hr as needed to a maximum of 3000 mg/day	Use caution in liver disease Comparable to NSAIDs for arthritis pain
Opioids	Hydrocodone/acetaminophen: 5/500 or 5/325 mg (other doses also available); one to two tablets every 4–6 hr as needed Tylenol with codeine: 30/300 mg; one to two tablets every 4–6 hr as needed	Best to use short-term only Significant addictive potential Constipation common Use caution with alcohol or sedatives No clear benefits long term for quality of life, pain level, or disability[86]

Pharmaceuticals should be used only as a stopgap measure, if at all possible, to allow for symptom management while safer and more "in-depth" therapeutic options are being instituted for the long term.

Pharmaceuticals should be considered only as stopgap approaches, to be used on a short-term basis as the root causes of pain are being sought. Research on long-term opioid use is becoming less supportive of chronic pain medication use.

Supplements

Omega-3 Fatty Acids

Ideally, as with any nutrients, essential fatty acids should be obtained through a healthy and varied diet, but this often proves difficult. Not many foods contain omega-3 fats in large amounts. Fish oil supplements decrease inflammation for many conditions, and although studies of its use specifically for neck pain are few, a reasonable approach is to give these supplements a try (see Chapter 86, The Antiinflammatory Diet).

Dosage

The dose is 3 to 8 g fish oil daily.

Precautions

Doses of more than 3 g of fish oil a day may have an anticoagulant effect and should be used with caution in patients who are prone to bleeding disorders or who are taking anticoagulant or antiplatelet medications.[88]

Phytoantiinflammatory Agents

Few studies have focused specifically on the role of herbal remedies in treating musculoskeletal neck pain. However, several trials have evaluated the overall antiinflammatory properties of herbal remedies and the use of these remedies for pain in general,[9,47,89] as well as for conditions such as osteoarthritis,[90,91] rheumatoid arthritis,[90] and low back pain.[91] Overall, these supplements are quite safe and well tolerated. Most of them work by altering levels of one or more compounds involved in the inflammatory cascade, including cyclooxygenase-2, lipoxygenase, nitric oxide, tumor necrosis factor-alpha, interleukin-1 and interleukin-6, and prostaglandin E_2.[88] For mild to moderate chronic pain, phytoantiinflammatory agents are worth considering, with the intent of decreasing pharmaceutical use and reducing the risk of adverse effects. As with conventional medications, these agents would ideally be used only in the short term while other approaches are used to reveal the root of the neck pain. Table 64-3 lists some of the most commonly used phytoantiinflammatory agents, their dosage, evidence of their efficacy, and precautions related to their use.[47,88–108]

TABLE 64-3. Herbal Antiinflammatory Agents*

BOTANICAL AND DOSE	EFFICACY EVIDENCE	PRECAUTIONS
Avocado (*Persea americana*)/Soy Unsaponifiables[47,89] 300–600 mg/day	Decreased NSAID intake in people with knee and hip OA Stimulated collagen growth	Seems to take 2 mo to reach full effect, and effects linger for 2 mo after patients stop taking them Do not use in people with banana or chestnut allergies
Boswellia[88,90,93,94] **(*Boswellia serrata*, Indian Frankincense)** Extract: 300 or 333 mg three times/day	Preliminary evidence of benefit for knee OA; effect persisted 1 mo after stopping treatment Conflicting research regarding efficacy for RA	No evidence of harm from any preparation Rare GI effects
Cat's Claw[88,95–98] **(*Uncaria guianensis* or *Uncaria tomentosa*)** ***U. tomentosa* most common in United States (dosing varies with species)** Capsules: 350–500 mg once or twice/day Tincture: 1–2 mL, two or three times/day Freeze-dried aqueous extract: 100 mg/day Oxindole alkaloid-free extract: 20 mg three times/day	Freeze-dried extract decreased knee pain with activity in OA Modest improvement with some forms in RA Decreased need for drugs in OA May also have antioxidant and immune-stimulating properties	Studies have not shown harmful effects May lower blood pressure May inhibit CYP 3A4 May interfere with immunosuppressants May work better if oxindole alkaloids removed May increase bleeding risk Avoid in pregnancy Not for children younger than 3 yr old
Devil's Claw[88,89,95,97,99–101] **(*Harpagophytum procumbens*)** Dried root: 1800–2400 mg in aqueous solution three times/day Tincture: 0.2–1.0 ml (1:5) in 25% alcohol three times/day	Rated by Natural Standard, a producer of good-quality, evidence-based monographs, as having "good" (level B) scientific evidence for therapeutic use Effective for back pain	Rated as safer than analgesic medications; side effects rare May alter GI tract acid levels; avoid in duodenal ulcer disease May lower blood glucose and increase bleeding risk
Ginger[88,93,97,102,103] **(*Zingiber officinale*)** Powdered root: 500 mg to 1 g twice or three times/day Tincture (1 g:5 mL): 1.25–5 mL, three times/day	Evidence limited; moderate effect on OA of the knee in 247 patients, but mixed results in another, smaller study	Occasional mild GI effects Whole root consumption may increase stomach acid Theoretical increase in anticoagulation (no evidence in humans)
Phytodolor[89,97,104] **Mixture of aspen *(Populus tremula)*, common ash *(Fraxinus excelsior)*, and goldenrod *(Solidago virgarea)*** Tincture: 20–40 drops tincture three times/day in a beverage, taken for 2–4 wk to reach full therapeutic benefit	Rich in salicylates Studies of more than 300 subjects showed reduced drug dosing in rheumatologic disease Improved grip in OA Comparable to diclofenac in one OA study	No adverse effects noted in trials Theoretical side effects similar to aspirin; avoid in patients with salicylate allergy No drug interactions known Should be avoided in pregnancy
Rose Hips (from *Rosa canina* subspecies)[88,89] Rosehip powder or seeds: 5 g/day	Improved pain scores and decreased pain medication consumption in OA	No contraindications
Turmeric[88,95,96,105–107] **(*Curcuma longa*)** Root: 1.5–3 g/day, divided into several doses (can be made into tea; 1 heaping teaspoon is 4 g)	Many mechanisms of action, including alteration of arachidonic acid metabolism Improved swelling, stiffness and walking time in RA Improved OA pain and disability but not other clinical parameters May lower LDL and raise HDL	Generally recognized as safe in doses of 8 g/day or more Can be taken in place of an NSAID Seems to protect stomach against NSAIDs
Willow Bark[88,95,108] **(*Salicis* cortex)** Powdered bark: 1–3 g three to five times/day	Studies indicated benefit for mild pain Best evidence was for dose-dependent effect in 191 patients with back pain Antiinflammatory effect was largely related to salicylate content	Theoretically, may have similar side effects to aspirin, but this has not been found Occasional nausea, rash, and wheezing Caution with use in asthmatic patients

CYP, cytochrome; GI, gastrointestinal; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NSAIDs, nonsteroidal antiinflammatory drugs; OA, osteoarthritis; RA, rheumatoid arthritis.
*Efficacy data are based primarily on studies of symptom control in RA, OA, or back pain. No studies focusing specifically on the treatment of neck pain were found.
Evidence regarding the use supplements containing gamma-linolenic acid (GLA), such as evening primrose oil, black currant seed oil, and borage seed oil, for pain has been less convincing. Of the three, borage oil has the highest GLA content and should be tried first at a dose of 500 to 1000 mg twice/day.[88]
Other promising supplements include stinging nettle, green-lipped mussel extract, *Geranium robertianum*, *Tripterygium wilfordii* (Hook F), and green tea.[88,89]

Prevention Prescription

- Avoid tobacco and other substance use.
- Maintain a healthy body weight.
- Exercise regularly, and include exercises that strengthen the neck muscles.
- Ensure that the normal curve of the neck is maintained when sleeping.
- Take measures at work to minimize the risk of pain:
  - Avoid heavy lifting, or be sure to do it safely.
  - Try to cultivate a sense of control in the work environment.
  - Neck pain is less likely when someone has higher job satisfaction.
- Pay close attention to posture:
  - Frequent backpack use can increase neck pain.
  - Make sure that posture is good when reading or using a computer.
  - Use a headset rather than holding a phone between the ear and shoulder.
- Eat a diet that will prevent or reduce inflammation:
  - Increase dietary intake of omega-3 fatty acids or supplement with fish oil or flaxseed oil.
  - Increase fruit and vegetable intake to 8 to 10 servings a day.
  - Avoid foods high in saturated fats.
- Maintain a healthy social support network.
- Decrease stress levels. Use stress-reduction techniques regularly, such as meditation, progressive muscle relaxation, journaling, and any others that prove helpful.
- Treat anxiety or depression, if they are present.

Therapeutic Review

Lifestyle Modifications Including Exercise

- Exercise should be encouraged to prevent and treat soft tissue neck pain. B1
- Postural therapies, such as Alexander technique, Feldenkrais, and Pilates therapy, can provide cervical muscle support. C1
- Preserve the normal lordotic curve of the neck during sleep; cervical spine pillows may help. B1
- Avoid repetitive strain (holding telephone on the shoulder, leaning over a desk, carrying heavy over-the-shoulder bags, looking over the shoulder). B1

Nutrition

- Increase intake of foods high in omega-3 fatty acids (cold-water fish, flaxseed products, nuts, green leafy vegetables). B1
- Decrease intake of foods rich in omega-6 and trans-fatty acids (hydrogenated vegetable oils, margarine, processed foods). A1
- Decrease saturated fat intake. B1
- Eat foods rich in antioxidants, including a variety of colors of fruits and vegetables. B1

Mind-Body Therapy

- Address underlying emotional issues that may be causing or exacerbating pain and spasm. A1
- Journaling, self-hypnosis, biofeedback, and guided imagery are worth exploring. B1
- Reduce chronic stress and watch for indications of psychological causes of neck pain, such as depression and anxiety. A1

Bioenergetic Therapies

- Acupuncture is a well-studied, potentially beneficial, and safe adjunctive treatment if performed by a trained professional. A1
- Therapeutic touch and other "hands-on" healing techniques are of potential benefit and quite safe. C1

Biomechanical Therapies

- Consider manipulative therapies:
  - Be cautious with high-velocity, low-amplitude manipulation because it may have some sequelae. B2
  - Soft tissue manipulation and massage are other possibilities. B1
- Cranial base release and strain-counterstrain are useful techniques that can be easily performed in the office environment. C1
- Surgery should be used with caution and only in patients with a known nerve root or spinal cord disorder. B3

Supplements

- Taking 1 to 4 g/day of omega-3–rich oil capsules can help reduce inflammation. A1

Pharmaceuticals

- For chronic pain, if other approaches not effective, consider a tricyclic antidepressant (TCA), such as amitriptyline, 10 to 25 mg at night, or a serotonin-specific reuptake inhibitor, such as fluoxetine, 10 to 20 mg in the morning. Doses of these agents may be gradually increased as needed. 
- Consider prescribing a muscle relaxant for 2 to 3 weeks. Cyclobenzaprine, 10 mg at bedtime, is a reasonable choice if the patient is not already taking a TCA. 
- Provide a nonsteroidal antiinflammatory drug, such as ibuprofen, 400 to 600 mg every 6 hours with food. 
- Consider the use of narcotics for severe pain on a short-term basis only: hydrocodone/acetaminophen, 5/500-mg tablets, one to two every 4 to 6 hours as needed. 

Botanicals

- Consider a phytoantiinflammatory agent to complement or replace pharmaceutical therapy (see Table 64-3). 

KEY WEB RESOURCES

University of Wisconsin School of Medicine suboccipital release technique: http://www.fammed.wisc.edu/our-department/media/618/sub-occipital-release	Video showing how to perform a suboccipital release or cranial base release for neck pain and suboccipital neuralgia and tension headaches
American Osteopathic Association: http://www.osteopathic.org/osteopathic-health/Pages/default.aspx	Information on osteopathy and how to find a DO in your area
Back and Body Care neck pain information: http://www.backandbodycare.com/home/neck/neck.htm	Patient-created site with information for patients on neck pain
Everyday Health alternative treatments for neck pain: http://www.everydayhealth.com/pain-management/neck-pain/alternative-and-complementary-therapies.aspx	Patient-oriented site with numerous neck pain–specific articles on an array of approaches to neck pain
Continuum Center for Health and Healing: New approaches to chronic pain: http://www.healingchronicdisease.org/en/chronic_pain/index.html	Patient-oriented site designed to teach various approaches for dealing with chronic pain
Mayo Clinic neck pain information: http://www.mayoclinic.com/health/neck-pain/DS00542/DSECTION=alternative-medicine; http://www.painexercises.net/	Patient information on complementary medicine and neck pain; searchable site for exercises for various types of pain
Dr. Howard Schubiner's Mind Body Program: www.unlearnyourpain.com/	Site focusing on the mind-body factor as it relates to chronic pain

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Chapter 65

Gout

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Pathophysiology

Gout is a painful deposition of uric acid crystals in the synovial tissues of the body. Acute attacks usually manifest as a painful monarticular inflammatory arthritis, classically of the first metatarsophalangeal joint, although other joints as well as the kidneys may be affected. A polyarticular presentation is more common with increasing age and length of disease (Fig. 65-1).

Purines are ubiquitous in the body and in nature. As adenine and guanine, they form part of the building blocks of DNA and RNA. Uric acid is the product of purine metabolism by the enzyme xanthine oxidase. Uric acid is excreted primarily by the kidneys, but also by the small bowel. The buildup of uric acid crystals can result from overproduction (10% of cases) or underexcretion (90%) or a combination of the two. A 24-hour urine assay with a finding of more than 800 mg of uric acid supports the diagnosis of overproduction, whereas a finding of less than 600 mg suggests underexcretion.[1]

Because of the numerous diseases with a similar presentation, the diagnosis should be confirmed by aspiration of synovial fluid, examination of which reveals needle-shaped monosodium urate crystals with negative birefringence. Care should be taken not to miss potentially devastating mimics, most notably septic arthritis.

Gout has been recognized since ancient times, with mentions by the Egyptians as early as 2640 BC. In the fifth century BC, Hippocrates referred to gout as "the unwalkable disease." Gout has also been called "the disease of kings" because of the association with the intake of heavy foods and alcohol, apparently common in members of the ruling class. The name "gout" is derived from the Latin *gutta* ["drop"], a reference to a drop of one of the four medieval humors once believed to rule our health or lack thereof.[2]

New Clinical Significance

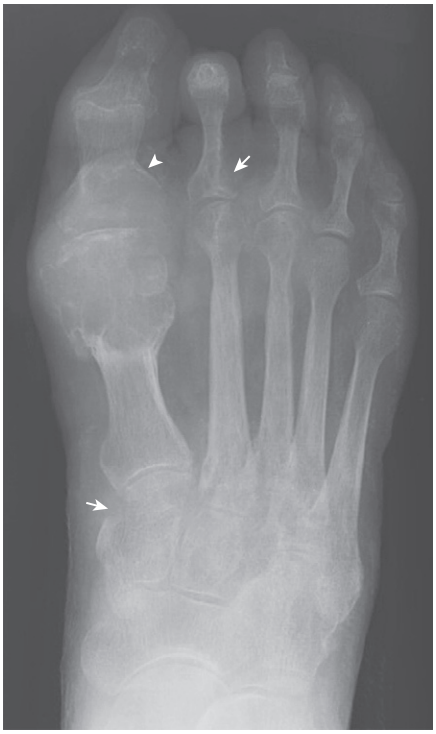
Although gout is often considered solely in terms of its presentation as an acute inflammatory arthritis, it is truly a systemic disease with significant associated metabolic comorbidities. Gout is linked to obesity, hypertension, dyslipidemia, insulin resistance, hyperglycemia, and coronary artery disease.[3] Data from the third National Health and Nutrition Examination Survey (NHANES III) demonstrated that metabolic syndrome was present in 62.8% of persons with gout but in only 25.4% of those without gout.[4] The Framingham Study demonstrated an *independent* 60% increased risk of coronary artery disease in men with gout after controlling for other factors.[5] The 12-year prospective Health Professionals Follow-up Study of 51,529 men showed that those with gout had a 55% increased risk of fatal myocardial infarction, a 28% increased risk of *all-cause mortality*, and a 38% increased risk of death from cardiovascular disease.[6] These strong associations were independent of age, body mass index, smoking, family history, diabetes, hyperlipidemia, and hypertension. The implications of these data cannot be overstated. Gout is an independent risk factor for death from *all* causes.

Hyperuricemia can *cause* hypertension.

One proposed mechanism of this relationship may involve a renally mediated increase in blood pressure caused by hyperuricemia. In a rat model of gout, elevated uric acid caused increased blood pressure through activation of the renin-angiotensin system and inhibition of neuronal nitric oxide synthase. Blood pressure normalized with appropriate pharmacologic management and reductions of uric acid. This causal relationship may warrant early administration of urate-lowering therapies in patients with gout and hypertension.[7]

The association of gout with numerous metabolic diseases warrants aggressive lifestyle counseling and screening to prevent long-term morbidity (Fig. 65-2). All persons with gout should thus receive extensive education regarding the health implications of this disease. Comorbidities, once identified, should be promptly managed, and patients should

FIGURE 65-1
Radiographic forefoot abnormalities in tophaceous gout. Extensive bone destruction is seen at the great toe metatarsophalangeal joint with overhanging edges *(arrowhead)* and soft tissue swelling. Smaller erosions are present involving the first tarsometatarsal and second metatarsophalangeal joints *(arrows)*. (From Firestein G: *Kelley's Textbook of Rheumatology.* 8th ed. Philadelphia: Saunders; 2008.)



be made aware of the interconnectedness of their various diseases. These preventable diseases of lifestyle may result in significant health consequences even with prompt identification and treatment. Therefore, patients must be encouraged, through appropriate use of behavioral change models such as appreciative inquiry or motivational interviewing, and empowered to make positive changes in their lives (see Chapter 99, Motivational Interviewing Techniques).

Gout is a metabolic disease that independently increases the risk of all-cause and cardiovascular mortality. Like other metabolic diseases (e.g., diabetes), gout warrants aggressive lifestyle counseling and modification.

Integrative Therapy

Weight Loss

Encourage weight loss and maintenance of a healthy body mass index. Adiposity is associated with hyperuricemia, whereas weight loss leads to reductions in gout incidence.[8] Weight loss also has the greatest benefit on mediating the numerous comorbidities associated with gout. All patients with gout should be encouraged to control weight through exercise and diet modification. Emphasis should be placed on the associated increased risk of cardiovascular and all-cause mortality in persons with gout.[6]

Nutrition

Decrease consumption of red meat and most seafood. Persons consuming higher amounts of beef, pork, and lamb have a 41% increased risk of gout. Persons consuming higher amounts of seafood have a 51% increased risk of gout.[9] Given the potential cardiovascular benefits of omega-3 fatty acids found in oily fish, patients can be counseled and may consider moderate intake of small, sustainably caught, cold-water fish (i.e., sardines).

Increase intake of omega-3 fatty acids. Patients wishing to avoid absolutely the purines associated with fish should be encouraged to increase dietary intake of plant sources of omega-3 fatty acids such as flaxseed, purslane, walnuts, and leafy greens. Supplementation (see the later section on omega-3 fatty acids) may also be encouraged.

Increase intake of vegetables, legumes, nuts, and vegetable proteins. Purine-rich vegetables, which were once thought to contribute to gout, are now understood to have no impact on the incidence of the disease.[9] Furthermore, increased intake of vegetable protein was actually associated with up to 27% lower incidence of gout in one report.[9] Additionally, numerous cardiovascular and metabolic benefits are associated with the aforementioned foods, and this association is particularly relevant given the negative impact of gout on cardiovascular and metabolic conditions.

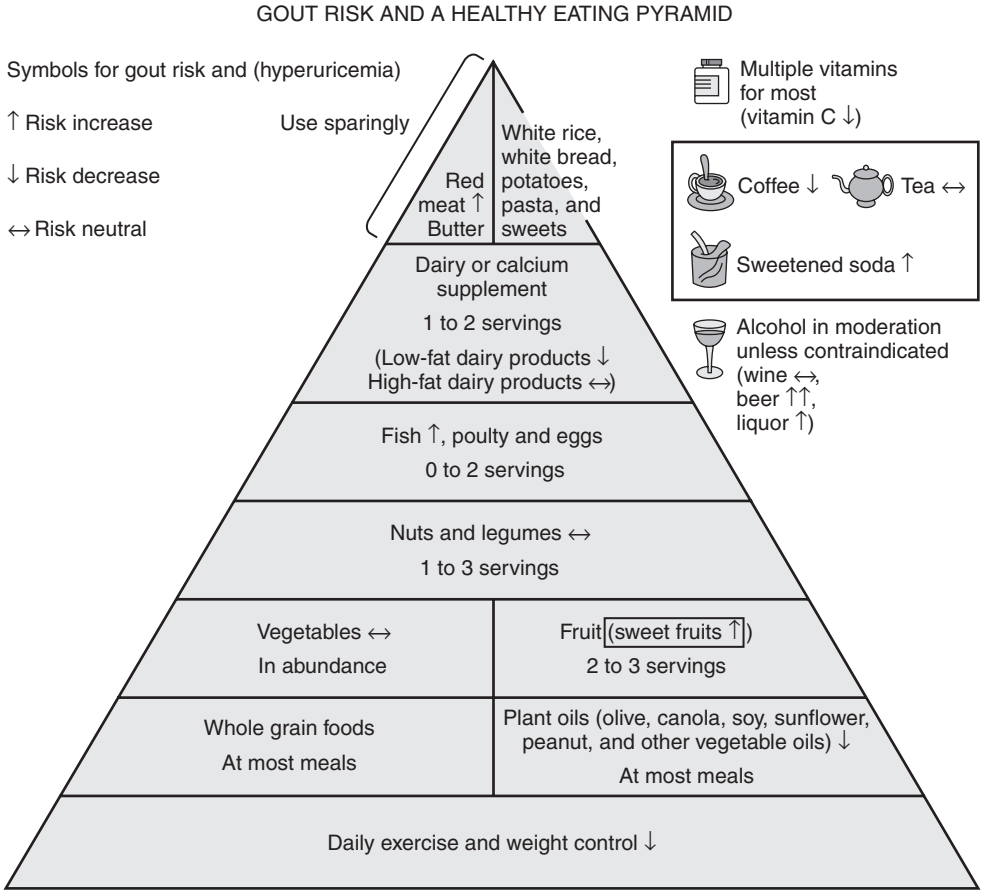
In response to newer evidence, experts are no longer advocating the avoidance of purine-rich vegetables or an overall purine-restricted diet. Avoidance of animal meat seems to have a larger impact than does reduced purine intake.

Decrease intake of sugar-containing beverages and fructose. Sugar intake was independently associated with elevated uric acid levels in men.[10] Additionally, a direct relationship exists between intake of fructose-containing soft drinks and hyperuricemia, as well as gout.[11,12] Diet soft drinks do not appear to affect uric acid levels, but their use should be discouraged because of an association with metabolic syndrome.[13] Sweet fruits may increase uric acid levels, but the health benefits of these foods far outweigh the associated risks, which can easily be countered through numerous other dietary modifications (e.g., lower consumption of meat, alcohol, and refined sugars).

Limit alcohol to no more than one to two drinks per day, and drink wine rather than beer or liquor. Alcohol intake has been positively correlated with gout. Beer has the strongest association. Each 12-oz beer consumed increases the risk of gout by 50% compared with nonbeer drinkers. Distilled spirits have a smaller but still significant association, whereas wine does not appear to be strongly associated with an increased risk of gout.[14] Numerous studies have demonstrated the health benefits of moderate alcohol consumption.[15] Nonetheless, recommending intake of alcohol to those currently abstinent is probably not advisable. Persons wishing to imbibe should consider wine the healthiest option.

Increase intake of low-fat dairy, up to two servings per day. Low-fat dairy intake, specifically milk and yogurt, appears

FIGURE 65-2
Gout pyramid. (From Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol.* 2010;22:165–172.)



to have a protective effect on the incidence of gout.[9] A randomized control trial of milk confirmed its urate-lowering effect.[16] The mechanism is likely related to the milk proteins casein and lactalbumin.[17] Low-fat dairy also has the advantage of protecting against metabolic syndrome.[13] Full-fat dairy, which is high in proinflammatory fats, should be avoided.

Drink water. Although no studies have quantified or confirmed the effect, adequate hydration is often considered a mainstay of treatment and prevention. The rationale is that a dehydrated state concentrates uric acid and leads to precipitation. Patients should be advised to drink a minimum of 48 oz of water per day.[18]

Consider coffee. Coffee appears to reduce uric acid levels by a mechanism *not linked to caffeine content*.[19] Modest intake of coffee may be considered part of a therapeutic prevention program. Abrupt increases in coffee consumption may trigger an acute gouty attack and should therefore be discouraged.

Alkalinize urine. A study of an acidic versus alkaline diet found a direct correlation between urine pH and uric acid excretion. This occurred despite the lower purine content of the acidic diet.[20] Patients may therefore be encouraged to follow an alkalinizing diet, low in animal protein and rich in vegetables.

Supplements

Vitamin C and Bioflavonoids

Vitamin C supplementation was once thought to exacerbate gout. More recent data, however, reversed that belief. Vitamin C most likely decreases serum uric acid levels through competitive binding of proximal tubule uric acid reuptake channels and may also increase uric acid clearance through a modest improvement in global glomerular filtration.[21] Studies showed an inverse relationship between vitamin C intake and uric acid levels.[22] A double-blind randomized controlled trial showed that supplementation with 500 mg per day of vitamin C significantly lowered uric acid levels compared with placebo.[23] A 20-year, large prospective study published in the *Annals of Internal Medicine* confirmed an inverse relationship between vitamin C intake and the incidence of gout, with as much as a 45% lower incidence in study participants ingesting more than 1500 mg of vitamin C per day.[24]

Although we now know that vitamin C can prevent and aid in the treatment of gout by reducing uric acid levels, an additional benefit may be conferred by increasing intake of citrus foods and by taking supplements with the citrus bioflavonoid hesperidin. Hesperidin is found in citrus foods, as well as in plants of the family Lamiaceae (mint family), such

as the common herb rosemary. An extract of rosemary demonstrated antinociceptive effects in an animal model of gout, and hesperidin was identified as a *chief contributor to this effect*.[25]

Dosage

All patients should increase their intake of citrus foods. Patients may also consider increasing their intake of herbs from the family Lamiaceae, especially rosemary. Interested patients should also take 500 to 1500 mg of high-quality vitamin C with citrus bioflavonoids including hesperidin.

> Newer research shows that vitamin C is protective against gout.

Eicosapentaenoic Acid and Gamma-Linolenic Acid

Although purine-rich seafood has been shown to increase uric acid levels and gout,[9] eicosapentaenoic acid (EPA), found in certain fatty fish, and gamma-linolenic acid (GLA) have been shown to suppress inflammation in monosodium urate–induced arthropathy (i.e., gout).[26] EPA and GLA appear to work through complementary mechanisms. Besides decreasing the inflammation of acute gouty arthropathy, omega-3 fatty acids also have demonstrated cardiovascular benefits.[27] This finding is significant, given the association of gout with cardiovascular mortality. In patients wishing to avoid the purine intake associated with fish, supplementation with EPA or GLA may be encouraged. GLA is an omega-6 fatty acid found in evening primrose oil, borage oil, and black currant seed oil.

Dosage

Although ideal dosing has not been determined, consider supplementing with 500 mg of EPA or 3000 mg of evening primrose oil.

Cherry

Consumption of cherries and cherry juice should be encouraged. Studies indicated that intake of 280 g (two servings) of Bing sweet cherries lowered plasma urate levels and increased urine urate levels in healthy volunteers.[28] There is also a trend toward decreased C-reactive protein and nitric oxide with cherry intake, a finding suggesting that cherries may help inhibit inflammation. Indeed, a double-blind placebo-controlled trial of cherry juice in long-distance runners showed that runners who ingested cherry juice 7 days before running reported less postrun pain than those who ingested placebo juice.[29]

Dosage

The recommended dose is approximately half a pound of cherries (approximately 2 cups) or an equivalent amount of cherry juice consumed daily.

Quercetin

In addition to displaying antiinflammatory properties, the flavonoid quercetin inhibits xanthine oxidase.[30] Quercetin can also play a role in the treatment and prevention of cardiovascular diseases by reducing blood pressure and oxidized low-density lipoprotein.[31] Quercetin may thus be of some clinical use in patients with gout, but no clinical trials have been performed to date.

Dosage

Food sources of quercetin include onions, apples, berries, grapes, green and black tea, citrus fruits, capers, tomatoes, broccoli, and leafy greens. Encourage adequate intake of these foods. Consider supplementation with up to 500 mg twice daily.

Bromelain

Use of a proprietary bromelain-containing product was clinically equivalent to diclofenac in a double-blind randomized controlled trial of patients with acute pain from osteoarthritis of the hip.[32] Similar benefits may be conferred to persons with gout, although no studies have yet been performed.

Dosage

Encourage daily consumption of pineapple, which is the source of bromelain. Alternatively, supplementation with 500 mg once or twice daily may be considered.

Botanicals

Hibiscus (Hibiscus sabdariffa)

Mounting evidence demonstrates that hibiscus calyx has blood pressure–lowering qualities, which are believed to result from an effect similar to that of angiotensin-converting enzyme (ACE) inhibitors.[33] Hibiscus tea increased uric acid excretion and clearance in healthy volunteers, but it did not affect serum uric acid levels.[34]

Dosage

Patients with gout and borderline hypertension may wish to try hibiscus, 1.5 g calyx as tea taken twice to three times daily. This can be purchased in the bulk herb section of most progressive grocery stores. Hibiscus tea is also readily available in Mexican grocery stores, where it is known as Jamaica.

Physical Medicine

Acupuncture

Acupuncture alone appears to be an effective treatment for acute gouty attacks. A trial of acupuncture compared with Western treatment with allopurinol and indomethacin found acupuncture to be superior (93% effective versus 80%; $P < .01$). The acupuncture-treated group also had greater reductions in serum uric acid and fewer adverse effects.[35] This trial was limited by its small size ($N = 60$) and the use of allopurinol during acute attacks, a practice that is generally not employed by Western physicians, but is not necessarily contraindicated. Nonetheless, the outcomes were impressive, and given the lack of significant side effects, acupuncture can be recommended as a viable option for the management of acute gouty attacks.[36] Referral to a licensed practitioner of traditional Chinese medicine may also be considered.

Ice

In contrast to most arthritides, application of ice to inflamed gouty joints causes significant pain relief. Although most arthritic conditions benefit from heat application, patients with gout prefer ice.[37] Frequent use of topical ice during

painful attacks should be encouraged. This difference may also help distinguish gout from other inflammatory mimics (e.g., rheumatoid arthritis) and thus help aid in diagnosis.

An observed response to the therapeutic application of ice may help distinguish gout from other inflammatory arthritides.

Rest

Patients inevitably resist movement of a painful joint, and this rest should be allowed within reason until symptoms are resolving.

Traditional Chinese Medicine

Numerous trials of traditional Chinese medicine have demonstrated its clinical effectiveness. A small trial ($N = 67$) of blood-letting cupping in addition to Chinese herbs compared with a control group receiving diclofenac found both treatments to be effective in improving acute gouty arthropathy.[38]

The traditional Chinese herbal formulation Simiao pill or Si Miao, which is a combination of herbs commonly used in the treatment of gout, was clinically superior to a Western medicine control in a randomized trial of three distinct formulations.[39] Simiao pill traditionally consists of a specific blend of the following individual herbs: *Phellodendron chinense*, *Atractylodes lancea*, *Achyranthes bidentata,* and *Coix lacryma-jobi*. This formulation of Simiao pill was also found to have in vivo uricosuric and nephroprotective effects in hyperuricemic rats.[40]

Dosage

Based on the specific formulation, generally between three and seven tablets are taken three times daily.

Pharmaceuticals: Acute Treatment of Gouty Arthritis

Nonsteroidal Antiinflammatory Drugs

Despite the relative lack of high-quality large randomized controlled trials, nonsteroidal antiinflammatory drugs (NSAIDs) are considered first-line agents for an acute gouty episode. Indomethacin has historically been favored, but given the lack of data or rationale for its use, any high-dose regimen should suffice.[41]

Dosage

Indomethacin, 50 mg three times daily, or naproxen, 500 mg twice daily, or ibuprofen, 600 mg three times daily, is taken as needed for 5 to 10 days.

Precautions

Standard NSAID precautions should be reviewed, and therapy should be tapered as soon as clinical improvement is noted. Aspirin should be avoided because of the potential uric acid–raising effect of salicylates.

Colchicine

Alexander of Tralles, a sixth-century Byzantine physician, was the first to use *Colchicum autumnale* for the treatment of gout. Although this plant, autumn crocus, is no longer recommended because of significant toxicity, its active derivative colchicine is still widely used for acute gout attacks, despite the absence of head-to-head studies to show that it offers benefit over any other acute method of treatment. The older methods of hourly high-dose treatments and intravenous colchicine are no longer recommended because of the risk of toxicity and unnecessary side effects, as well as a lack of significant benefit over oral dosing.

Dosage

Oral colchicine, 1.2 mg followed by 0.6 mg 1 hour later (total dose, 1.8 mg), is initiated as soon as possible in gouty flare.[42] Some patients may wish to use daily colchicine, 0.6 mg, for suppression, although use of the other preventive methods should be preferentially encouraged because colchicine has no effect on uric acid.

Precautions

Do not use in cases of end-stage renal disease. Potentially severe drug-drug interactions do exist. Check specific interactions before prescribing.

Glucocorticoids

Oral, intravenous, or intra-articular steroids may be useful when NSAIDs or colchicine are contraindicated.

Dosage

Oral prednisolone, 35 mg, was equivalent to twice-daily naproxen, 500 mg, in a double-blind randomized controlled trial.[43] This dose can be tapered over 7 to 10 days as clinical improvement ensues. In monarticular cases, intra-articular injection of 10 to 40 mg triamcinolone can be effective, although data are limited.[44] Intravenous glucocorticoids can be used in patients unable to take oral prednisone or in polyarticular crisis.

Precautions

Standard steroid precautions should be observed. Take oral steroids with food as early in the day as possible. If split doses are used, advise taking a second dose with lunch rather than dinner to avoid insomnia.

Pharmaceuticals: Prevention

Angiotensin-Converting Enzyme Inhibitors Versus Diuretics

Although diuretics have been blamed for precipitating many a gouty crisis, their negative effect is actually less than that of hypertension itself.[45] At low doses, thiazide diuretics have a relatively small effect on serum uric acid levels, and the addition of an ACE inhibitor or angiotensin receptor blocker can offset this increase. That said, the uric acid–lowering effects of an ACE inhibitor should be considered for first-line treatment of hypertension in patients with gout.

Probenecid

Probenecid is a uricosuric drug and therefore helpful in cases of underexcretion. It is the gold standard in older patients who are taking thiazide diuretics.[1] Uricosuric agents should be avoided in persons susceptible to nephrolithiasis such as those with tophaceous disease or urate overproduction.

Dosage
The starting dose is 250 mg twice daily, titrated up to the effective dose, usually 500 to 1000 mg twice daily.

Precautions
Probenecid is less effective at glomerular filtration rates lower than 60 mL/minute. Avoid use of this drug in persons prone to nephrolithiasis and in those with cystinuria.

Allopurinol
Allopurinol inhibits xanthine oxidase activity. Unlike probenecid, allopurinol is useful in all causes of hyperuricemia. Because of theoretical risk, allopurinol is generally not started during an acute attack. Patients taking allopurinol should not, however, stop the medication if an acute attack does occur.

Dosage
Allopurinol can be started at 100 to 300 mg daily and titrated up until normal uric acid levels are achieved. Most patients can be adequately treated with 300 mg daily, although the maximum daily dose is 900 mg. To reduce the risk of precipitating a gouty attack, low-dose colchicine may be started simultaneously.[46]

Precautions
Up to 5% of patients will experience side effects, including rash, leukopenia, thrombocytopenia, diarrhea, or drug fever. The allopurinol hypersensitivity syndrome is a rare (less than 0.1% of patients) but potentially fatal adverse reaction consisting of erythematous rash, fever, hepatitis, eosinophilia, and acute renal failure.

Therapies to Consider

Botanicals
Numerous ethnobotanical studies are being conducted on traditional antigout agents, many of which are yielding promising results and confirming the wisdom of indigenous healing systems.

In mice, in vivo trials of the Ayurvedic gout treatments *Coccinia grandis* (ivy gourd) and *Vitex negundo* (five-leaved chaste tree) demonstrated significant decreases in serum uric acid levels. Impressively, *Coccinia grandis* in particular showed urate reductions nearly equivalent to those of allopurinol (3.90 ± 0.07 mg/dL versus 3.89 ± 0.07 mg/dL).[47]

Polynesians have used noni *(Morinda citrifolia)* juice for treatment of various ailments, including gout. Noni was found to have in vitro inhibition of xanthine oxidase,[48] but no clinical trials have been performed to date.

Populus nigra (black poplar) and *Betula pendula* (silver birch) were found to have the highest level of xanthine oxidase inhibition in a study of traditional Czech herbal folk remedies for gout.[49]

In a similar study of 120 traditional Chinese antigout treatments, the following herbs demonstrated the most pronounced xanthine oxidase inhibition: *Cinnamomum cassia* (Chinese cinnamon), *Chrysanthemum indicum,* leaves of *Lycopus europaeus* (bugleweed, gypsy wort), and the rhizome of *Polygonum cuspidatum* (Japanese knotweed).[50]

Supplements
In vitro studies showed that folic acid is a weak inhibitor of xanthine oxidase.[51] More potent effects on inhibition were traced to the activity of a common folate contaminant, pterin aldehyde.[52] Nonetheless, few in vivo trials have been conducted. Daily doses of folate of 1000 mcg failed to lower serum uric acid concentrations in five hyperuricemic subjects.[53] I therefore do not recommend that folate be prescribed for gout unless stronger evidence emerges to support its usefulness.

Niacin has a small uric acid–raising effect, which is doubtful to be of negative clinical significance.[54]

Prevention Prescription

- Encourage weight loss and maintenance of a healthy body mass index.
- Decrease consumption of red meat and most seafood.
- Increase intake of vegetables, legumes, nuts, and vegetable proteins.
- Decrease intake of sugar-containing beverages and fructose.
- Limit alcohol to no more than one to two drinks per day, and drink wine rather than beer or liquor.
- Increase intake of low-fat dairy, up to two servings per day.
- Maintain adequate hydration.
- Consider moderate coffee consumption.
- Increase food intake of vitamin C and consider supplementing with 500 mg.
- Increase intake of cherries; half a pound per day should be adequate.
- Increase intake of omega-3 fatty acids or take a supplement.

Therapeutic Review

Lifestyle Modification

- Encourage weight loss if overweight. A1
- Maintain hydration. C1
- Limit intake of beer and liquor. A1

Nutrition

- Decrease consumption of red meat and most seafood. A1
- Increase intake of vegetables, legumes, nuts, and vegetable proteins. A1
- Decrease intake of sugar-containing beverages and fructose. B1
- Increase intake of low-fat dairy, up to two servings per day. B2
- Consider moderate intake of coffee. B2

Supplements

- Increase intake of vitamin C through foods; consider supplementing with 500 mg daily. A1
- Eat more cherries: up to half a pound (2 cups) per day. B1
- Supplement with eicosapentaenoic acid (EPA) and/or gamma-linolenic acid (GLA): EPA, 500 mg daily or evening primrose oil, 3000 mg daily. B2
- Eat more pineapple or take bromelain supplements, at 500 mg daily. C1
- Consume more apples, grapes, onions, and tea or take quercetin supplements, at 500 mg twice daily. C1

Botanicals

- Hibiscus tea can be used for borderline high blood pressure and may lower uric acid levels. C2

Physical Medicine

- Acupuncture can help relieve a gouty attack. B1
- Ice and rest painful joints. B1

Pharmaceuticals

- Acute treatment
  - Use nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., indomethacin, 50 mg three times daily) for first-line treatment unless contraindications exist. B2
  - Consider colchicine, but use only a low-dose regimen of 1.8 mg divided over 1 hour (1.2 mg and repeat 0.6 mg in 1 hour). B2
  - Use glucocorticoids in patients unable to take NSAIDs or colchicine. C2

Prevention

- Use probenecid for inadequate uric acid excretion. Start at 250 mg twice daily, and increase to 500 mg twice daily as needed. B2
- Use allopurinol for all causes of uric acid excess. Start at 100 to 300 mg daily. Increase as needed to reduce serum uric acid to less than 6 mg/dL. B2

A 24-hour urine assay with the finding of more than 800 mg of uric acid supports the diagnosis of overproduction (10%), whereas a finding of less than 600 mg suggests underexcretion (90%).

KEY WEB RESOURCES

Gout and Uric Acid Education Society: http://gouteducation.org/	Good information for both patients and clinicians on the new approach to gout
GoutPal: http://www.goutpal.com/	Web site supported by an individual with gout that offers community support and nutritional and therapeutic resources

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References are available online at expertconsult.com.

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Chapter 66

Carpal Tunnel Syndrome

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Pathophysiology

Carpal tunnel syndrome (CTS) is a compressive neuropathy of the median nerve that affects women three times as often as men and usually develops after the age 30 of years.[1] Symptoms typically include pain, numbness, tingling, weakness of the thumb and first finger, and involvement of the palm and other fingers except the fifth. Wasting of the thenar eminence may be visible. Activities that may precipitate CTS include repetitive stress activities involving the wrist such as mechanical work, gardening, house painting, meat wrapping, and typing.[2] Trauma, both recent and remote, should be explored, and one of the "keystone" bones of the carpal floor, the lunate, has been implicated in ventral compression of the median nerve against the flexor retinaculum when it is subluxed or displaced.[3] CTS is also commonly seen in persons involved in the occupations listed in Table 66-1.[4]

The carpal tunnel contains nine flexor tendons and the median nerve. The tunnel is created by the three sides of the carpal bones and the flexor retinaculum.[5] Any development that leads to tunnel narrowing or increased pressure within the limited space may cause CTS. These conditions may include edema, bony overgrowth, or inflammation of the tendons. The pressure compresses the median nerve and the small blood vessels that feed the nerve, with resulting ischemia and decreased nerve conduction. Initially, the compression and ischemia result in pain, numbness, and tingling. Chronic compression may result in more prolonged symptoms and signs such as weakness and wasting of the thenar eminence.[6] Some conditions that may be associated with CTS are listed in Table 66-2.[7,8] At times, the origin may be multifactorial, both functional (overuse) and structural (osteoarthritis).

Clinical Manifestations and Diagnosis

Patients typically present with sensory or motor changes along the distribution of the median nerve, which includes the thumb, index finger, middle finger, and radial half of the ring finger.[6] Patients may experience greater pain at night or after sleeping. Some patients find relief of symptoms by shaking their hands, which may temporarily relieve ischemia.[9] Pathognomonic physical findings may be absent early in the course of CTS; as pressure increases within the carpal tunnel, however, patients may demonstrate weakness of the thumb, which causes difficulty with writing or holding objects. Thenar eminence atrophy may be present on physical examination in advanced CTS.[10] Other nerve and vascular compressive syndromes that can cause the same or similar symptoms and signs should also be explored. These disorders can occur separately or concomitantly with CTS in what are known as double-crush and triple-crush syndromes. These syndromes can include cervical root impingement, thoracic outlet syndrome, cubital tunnel syndrome, ulnar neuropathy, pronator syndrome, median nerve neuropathy of the forearm, brachial plexopathy, anterior interosseous nerve syndrome, and Raynaud phenomenom.[11]

The National Institute of Occupational Safety and Health defines CTS as having two or more of the following criteria:

- One or more of the following symptoms affecting at least part of the nerve distribution of the hand: paresthesia, hyperesthesia, pain, and numbness
- One or more of the following symptoms: physical findings of median nerve compression including a positive Hoffman-Tinel sign or a positive Phalen test result, diminished sensation to pinprick in the median nerve distribution, and electrodiagnostic findings indicating median nerve dysfunction across the carpal tunnel[12]

The exact location of nerve entrapment can be diagnosed with electrodiagnostic studies; however, results of nerve conduction studies may be normal in clinically symptomatic patients.[13]

TABLE 66-1. Occupations Associated With Carpal Tunnel Syndrome

- Food processing
- Manufacturing
- Logging
- Construction work
- Poultry work
- Use of vibratory tools

Data from Bernard B, ed. Musculoskeletal Disorders and Workplace Factors: A Critical Review of Epidemiologic Evidence for Work-related Musculoskeletal Disorders of the Neck, Upper Extremity, and Low Back. DHHS (NIOSH) publication no. 97–141. Cincinnati: National Institute for Occupational Safety and Health; 1997; and Scott K, Kothari M. Etiology of Carpal Tunnel Syndrome. <www.UpToDate.com>; 2010 Accessed November 2, 2011.

TABLE 66-2. Causes of Carpal Tunnel Syndrome

Endocrine	Use of corticosteroids or estrogen Myxedema from hypothyroidism Amyloidosis Gout Diabetes mellitus Acromegaly Obesity
Musculoskeletal	Acute trauma Fractures Overuse injury Inflammatory/rheumatoid arthritis
Pulmonary	Tuberculosis
Reproductive	Pregnancy

Data from Solomon D, Katz J, Bahn R, et al. Nonoccupational risk factors for carpal tunnel syndrome. *J Gen Intern Med.* 1999;14:310–314; and Stevens J, Beard C, O'Fallon W, et al. Conditions associated with carpal tunnel syndrome. *Mayo Clin Proc.* 1992;67:541–548.

Integrative Therapy

Lifestyle

Behavior Modification

Elimination of aggravating factors and repetitive motions may help reduce symptoms of CTS, but many patients do not have the opportunity to change occupations. Patients may obtain some relief by using their hands less forcefully, taking frequent breaks, and performing stretching and strengthening exercises. The practitioner should query the patient about hobbies that require repetitive motion as well, because patients may not associate those hobbies with their symptoms. A wrist splint worn during waking hours may provide additional symptom relief, but most patients cannot tolerate daytime splinting. Occasional use of the same splints while sleeping may also bring about some relief during the waking hours.[14] Splints should be individually adjusted (most have a metal stay within a sleeve on the volar surface) to maintain the angle of the wrist to 1 to 5 degrees from neutral into extension. Many braces available off the shelf place the wrist into too high a degree of extension.

Exercise

A 10-month aerobic exercise program demonstrated a reduction in symptoms of CTS, but whether these results were related to the natural course of the disease or to the therapy is unclear.[15] Although performing aerobic activity for cardiovascular health is certainly in the patient's best interests, such exercise has not been proven to be of benefit for CTS treatment, so no evidence supports its use. Stretching of the flexor tendons, the major occupants of the tunnel, may have some benefit in reducing compression of the median nerve (see Fig. 66-2).

Ergonomic Keyboards

Results of studies comparing the use of ergonomic keyboards for amelioration of symptoms of CTS have been mixed.[16] If a patient believes that using such a keyboard will help, it may be worth the higher price to try the device because it has no adverse effects. No evidence exists for its use. The position in which patients place their hands may have more to do with effectiveness than the keyboards themselves. Patients should avoid resting their wrists on the surface while extending their wrists to reach their fingers to the keyboard. Pianists and touch typists classically hover their hands above their respective keyboards.

Pharmaceuticals

Acetaminophen

Acetaminophen has a limited role in CTS owing to a lack of antiinflammatory properties. Acetaminophen appears to display analgesic and antipyretic effects by inhibiting the isoenzymes cyclooxygenase-1 (COX-1) and COX-2 in the central nervous system. This inhibition does not seem to extend into the periphery, thereby eliminating any anti-inflammatory properties.[17] Because it has a relatively safe profile, however, acetaminophen remains a good choice for relief of mild to moderate pain in CTS, especially in patients who have concomitant osteoarthritis.

Dosage (Adult)

The recommended dose of acetaminophen (Tylenol) is 500 mg every 4 to 6 hours; the maximum dose is 3000 mg/day.[18]

Precautions

Use acetaminophen with caution in patients with a history of liver disease and in patients who consume more than three alcoholic beverages daily.[19] In addition, consideration should be given to the appropriate dosage of acetaminophen when patients are taking other concomitant medications that are similarly metabolized by the liver. At recommended dosages, acetaminophen is considered safe in pregnancy.

Nonsteroidal Antiinflammatory Drugs

Median nerve compression caused by inflammation of the flexor tenosynovium can cause patients a great deal of pain.[20] Nonsteroidal antiinflammatory drugs (NSAIDs) exert pain-relieving and antiinflammatory properties through prostaglandin inhibition by inhibition of COX-1 and COX-2 isoenzymes.[19] In general, all NSAIDs have similar efficacy in analgesia and antiinflammatory effects. These effects have yet to be proved adequate in control of symptoms of CTS,

however, despite their common use in treatment of this condition. In a study comparing the efficacy of NSAIDs, oral steroids, diuretics, and placebo, only steroids achieved a significant improvement in signs and symptoms of CTS.[21]

Dosage

Common NSAIDs and dosages are listed in Table 66-3.

Precautions

Use NSAIDs with caution in patients with a history of gastrointestinal bleeding, ulcers or perforation, hypertension or other cardiac disorders aggravated by fluid retention, asthma, renal insufficiency, or coagulation defects, as well as in pregnant patients.[17,19,22]

Diuretics

A rise in tissue pressure in the carpal tunnel is theorized to lead to perineural edema.[23] Diuretic therapy has been employed in efforts to rid the body of excess fluid accumulation and ameliorate CTS. Although case reports exist of the successful use of furosemide to alleviate symptoms of CTS associated with iatrogenic fluid administration, larger comparative studies refute the benefit of diuretic use in CTS.[24] In a study comparing bendrofluazide (a thiazide diuretic not available in the United States) with placebo, no improvements in CTS symptoms were seen.[16] Diuretics should not be used in treatment of CTS.

Corticosteroids

The human body endogenously produces glucocorticoids. At supraphysiologic doses of exogenous corticosteroids, an antiinflammatory response is seen. Modified cellular transcription and protein synthesis lead to local inhibition of leukotriene penetration, suppression of the humoral response, and a reduction in lipocortins, thus diminishing the inflammatory response.[19] In CTS, corticosteroids may be given orally or directly injected into the carpal canal. Short-term oral steroid therapy with conventional treatment, such as splinting, has reduced symptoms in patients with CTS. In a study comparing the use of NSAIDs, diuretics, oral steroids, and placebo, only the group receiving oral prednisolone demonstrated significant relief of CTS symptoms.[21]

Corticosteroid injection, on the radial side of the palmaris longus tendon, has shown short-term efficacy in providing CTS symptom relief.[25,26] In a study comparing surgical decompression with local steroid injection, patients receiving steroid injections had better symptom relief 3 months after treatment than did patients who had undergone surgery.

TABLE 66-3. Common Nonsteroidal Antiinflammatory Drugs Used for Pain Relief

GENERIC NAME	BRAND NAME*	RECOMMENDED ADULT DOSE	ROUTE	MAXIMUM DAILY DOSE
Aspirin	Bayer Aspirin	325–650 mg every 4–6 hr	Oral or rectal	3600 mg
Salsalate	Salflex	500–1000 mg every 8–12 hr	Oral	3000 mg
Ibuprofen	Motrin and Advil	200–400 mg every 4–6 hr	Oral	2400 mg
Diflunisal	Dolobid	500–1000 mg every 12 hr	Oral	1500 mg
Choline magnesium	Tricosal	500–1000 mg every 8–12 hr	Oral	3000 mg salicylate
Naproxen sodium	Aleve and Anaprox	220–550 mg every 8–12 hr	Oral	1500 mg
Naproxen	Naprosyn	250–500 mg every 12 hr	Oral	1500 mg
Ketoprofen	Orudis KT	12.5 mg every 6–8 hr; second dose may be taken after 1 hr if needed	Oral	75 mg
Fenoprofen	Nalfon	300–600 mg every 6–8 hr	Oral	3200 mg
Flurbiprofen	Ansaid	200–300 mg in 2–4 divided doses	Oral	300 mg
Oxaprozin	Daypro	600–1200 mg/day	Oral	1800 mg
Indomethacin	Indocin and Indocin SR	25–50 mg 2–3 times/day	Oral	200 mg
Diclofenac	Voltaren	50 mg every 8 hours; 75 mg every 12 hr	Oral	150 mg
Etodolac	Lodine	200–400 mg every 6–8 hr	Oral	1200 mg
Nabumetone	Relafen	500–1000 mg 1–2 times/day	Oral	2000 mg
Meloxicam	Mobic	7.5 mg/day	Oral	15 mg
Piroxicam	Feldene	10–20 mg/day	Oral	20 mg

Data from references 18, 19, and 22.
*More than one brand may exist for an agent.

At 6 months and 12 months, however, the percentage of patients in whom relief of symptoms was maintained after injection began to decline, whereas the level of relief in the surgically treated group remained constant.[26] Steroid injections are most beneficial to patients with mild to moderate CTS, thus delaying the need for surgery. Injection may be repeated 3 weeks after the initial dose, but the need for a third dose in less than 1 year indicates a need for surgical treatment.[25]

Dosage

A standard dosage for oral steroids in CTS has not been determined. A study comparing two prednisolone regimens—2 weeks of 20 mg/day followed by 2 weeks of 10 mg/day versus 2 weeks of 20 mg/day followed by 2 weeks of placebo—for long-term improvement found no difference in treatment response with respect to duration of steroid therapy.[27] Hence the lower dosage should be used to minimize adverse effects.

Injection therapy consists of methylprednisolone acetate, 20 to 40 mg mixed with 1 mL of 1% lidocaine, or 6 mg of betamethasone combined with 1% lidocaine.[26]

Precautions

Long-term oral steroid use has been associated with immunosuppression, hyperglycemia, hypertension, Cushing syndrome, osteoporosis, and electrolyte disturbances. Injection of steroids must be performed by a skilled practitioner trained in CTS injection to avoid nerve atrophy and necrosis, which may be created by entry of corticosteroid into the median nerve sheath.[19,22,25] The use of corticosteroids in pregnancy is controversial. Although drug monographs indicate corticosteroids to be relatively safe in pregnancy (safety category B), animal studies indicated possible long-term developmental abnormalities. More research using corticosteroids in pregnancy is needed.[28]

Cyclooxygenase-2–Selective Inhibitors

In an effort to protect gastrointestinal mucosa while maintaining pain relief and antiinflammatory properties, medications specific for COX-2 inhibition were developed in the 1990s.[29] COX-2 inhibitors do not inhibit platelet aggregation, but they are not without risk. Although COX-2 inhibition does prevent the production of prostacyclin (prostaglandin I_2 [PGI_2]), it does not inhibit thromboxane A_2, which is responsible for platelet aggregation and vasoconstriction. PGI_2 inhibits platelet aggregation and facilitates vascular smooth muscle contraction. Investigators have theorized that selective inhibition of COX-2 causes a shift toward a prothrombotic state,[22] thus raising the risk of stroke and myocardial infarction. In September 2004, the COX-2 inhibitor rofecoxib (Vioxx) was withdrawn from the market because postmarketing surveillance demonstrated a higher relative risk of stroke and myocardial infarction in patients receiving the drug. In April 2005, valdecoxib (Bextra) was also withdrawn from the market. Celecoxib (Celebrex) is the only COX-2 inhibitor remaining available for prescription.[30] The U.S. Food and Drug Administration (FDA) requires labeling of containers to warn patients and prescribers that celecoxib as well as other NSAIDs may increase the risk for heart attack and stroke. COX-2 inhibitors may be effective in mild to moderate pain relief, but the benefits and risks of therapy must be weighed before prescribing, especially because these drugs have not been proved to be of benefit in the treatment of CTS.

Dosage

The dose of celecoxib is 100 to 200 mg twice daily; the maximum dose is 800 mg/day.[18,19]

Precautions

COX-2 inhibitors should be used with caution in patients with a history of congestive heart failure, hypertension, asthma, or renal insufficiency. Patients who are pregnant or are allergic to sulfonamides should not take celecoxib.[17,19,22]

Botanicals

Patients using dietary supplements should be advised to choose brands that have been certified for content and purity. Testing for content and purity is not a mandatory requirement for dietary supplements. Trusted organizations that voluntarily test product purity are the United States Pharmacopeia (USP), the Association of Analytical Communities (AOAC), and Consumer Labs (consumerlabs.com). Table 66-4 is a list of sample USP-verified brands.[31]

Ginger (Zingiber officinale)

Ginger, also known as African ginger, black ginger, cochin ginger, and imber, is a mixture of several compounds. Compounds include gingeroles, beta-carotene, capsaicin, caffeine, curcumin, and salicylate.[32] However, these chemical entities seem to vary according to the form of the herb. Ginger is most often used for relief of nausea, vomiting, motion sickness, dyspepsia, flatulence, migraine headache, rheumatoid arthritis, osteoarthritis, and pain. Although the exact mechanism remains unknown, investigators have speculated that some of the constituents in ginger may inhibit COX-1, COX-2, lipoxygenase pathways, tumor necrosis factor-alpha, PGE_2, and thromboxane B_2.[33] Each of these inhibited mechanisms plays a role in inflammation. A randomized placebo-controlled crossover study was conducted comparing the efficacy of ginger, ibuprofen, and placebo in patients with osteoarthritis. Although ibuprofen was found to be the most effective at treating pain, both ibuprofen and ginger both had a significant pain-rating reduction in comparison with placebo.[34] Ginger may be of benefit in

TABLE 66-4. United States Pharmacopeia–Verified Brands

- Berkley & Jensen
- Equaline
- Kirkland Signature
- Nature Made
- Nature's Resource
- Nutri Plus
- Safeway
- Sunmark
- Tru Nature
- Your Life

Data from United States Pharmacopeia. USP-Verified Dietary Supplements. <http://www.usp.org/USPVerified/dietarySupplements/supplements.html/>; Accessed 14.10.11.

patients who have both CTS and osteoarthritis. Patients with nausea and vomiting of pregnancy and CTS may benefit from the antinausea properties of ginger as well.

Dosage
In osteoarthritis management, Eurovita Extract 33, a specific ginger extract, is often used. The dosage of this formulation is 170 mg orally three times/day or 255 mg twice daily.[33]

Precautions
Because of possible inhibition of platelet aggregation, ginger should be used with caution in patients who are concurrently undergoing anticoagulant therapy or have coagulation disorders. Common adverse reactions with ginger are gastrointestinal discomfort, heartburn, and diarrhea. The use of ginger during pregnancy is relatively safe when it is orally ingested for medicinal purposes. Although some concerns have been expressed about ginger and its involvement in altering fetal sex hormones, and one case report of spontaneous abortion exists, the overall risk of fetal malformation does not appear to be higher than the baseline (1% to 3%).[33]

Willow Bark (Salix alba)
Willow bark, also known as white willow bark, brittle willow, and simply willow, is a dietary supplement from the Salicaceae family. It is most often used by patients to treat headache or pain caused by osteoarthritis, myalgia, gout, and dysmenorrhea. Although components of willow bark include flavonoids and tannins, the pain-relieving properties are attributed to the salicin glycosides present in the compound. After ingestion of willow bark, the salicin glycosides are converted in the intestine to saligenin, which is then metabolized to produce salicylic acid. At this point, elimination becomes the same as for aspirin (acetylsalicylic acid).[33] Like aspirin, willow bark demonstrates analgesic, antipyretic, and antiinflammatory properties. Platelet aggregation may be inhibited by willow bark, but to a lesser extent than by aspirin. Studies comparing willow bark, diclofenac, and placebo in patients with osteoarthritis and rheumatoid arthritis found willow bark to be no better than placebo for pain relief.[35] Although no studies have evaluated willow bark use for CTS, this substance can be regarded as having efficacy similar to that of aspirin and other NSAIDs in pain management.

Dosage
Willow bark should be dosed according to the salicin content in the supplement: salicin, 120 to 240 mg orally in two to three divided doses daily.[33]

Precautions
Safety concerns about using willow bark are similar to those for salicylate therapy. Willow bark may cause gastric irritation, nausea, vomiting, and bloody stools. It should be used with caution in patients who are also taking antiplatelet medications or other salicylate-containing products. Insufficient evidence exists for using willow bark in pregnancy. Pregnant women are advised to avoid it.

Arnica (Arnica montana)
Also known as arnica flower, leopard's bane, and mountain tobacco, arnica is used to treat inflammation and as an immune system stimulant. The boost in immune response is thought to decrease healing time in bruises, aches, and sprains. The primary active constituents in arnica are sesquiterpene lactones.[33] Although the exact mechanisms are not completely understood, the antiinflammatory effects seen with arnica seem to differ mechanistically from those of NSAIDs. A specific sesquiterpene lactone, helenalin (which is implicated in inflammation), inhibits nuclear transcription factor NF-kappaB.[36] Helenalin has also been shown to inhibit platelet function. In a randomized placebo-controlled study using arnica to control pain and swelling in patients who had undergone surgical repair of CTS, no difference in swelling was seen in patients receiving arnica and in those receiving placebo. However, a significant reduction in pain was seen 2 weeks after surgery in patients receiving arnica.[37] Arnica may be useful in patients who have undergone surgical treatment for CTS, but the potential side effects and toxicity, as well as the difficulty in obtaining standardized doses, may be obstacles to its use.

Dosage
Unless diluted, arnica is toxic when taken by mouth. Although no standard or well-studied doses or arnica preparations are available, the usual homeopathic preparations are diluted to 1:10 and 1:100 strengths. Serial dilutions continue until the desired strength is reached. For example, a 1:100 solution that is diluted 30 times is said to be 30 C potency.[37] Caution should be exercised because of the difficulty in obtaining a standardized dose and the possible side effects.

Precautions
Arnica in homeopathic doses is generally safe.

> Arnica belongs to the Asteraceae/Compositae family. Patients allergic to other members of this family will also be allergic to arnica. Additional members of the Asteraceae/Compositae family include ragweed, chrysanthemums, marigolds, daisies, and many other herbs.[33]

Supplements

Vitamin B_6 (Pyridoxine)
Vitamin B_6 is required by the body for many functions, including metabolism of amino acids, carbohydrates, and lipids. Vitamin B_6 is also a coenzyme in various metabolic reactions, such as transamination of amino acids, conversion of tryptophan to niacin, synthesis of gamma-aminobutyric acid, metabolism of serotonin, norepinephrine, and dopamine, and the production of heme for hemoglobin. It is also required in myelin sheath formation.[33] Clinically, vitamin B_6 is used to offset neuropathy caused by certain medications, such as isoniazid. Vitamin B_6 was first thought to be an effective treatment in CTS on the basis of low tissue levels seen in deceased patients with CTS. Investigators now know, however, that pyridoxine levels decline in deceased or infarcted tissue.[33] Two studies involving a total of 50 subjects with CTS demonstrated no benefit for vitamin B_6 in comparison with placebo.[38]

Mild deficiencies in vitamin B_6 are relatively common. Sources of this vitamin include potatoes, milk, cheese, eggs, fish, carrots, spinach, and peas. Vitamin B_6 is useful in

treating general deficiency and neuritis. Patients with CTS receiving benefit from pyridoxine therapy are thought to have an underlying deficiency or neuropathy. More studies are needed to assess the effectiveness of vitamin B_6 in CTS, but the supplement may be useful in patients with an underlying deficiency.

Dosage

For vitamin B_6 deficiency, 2.5 to 25 mg/day orally is taken for 3 weeks, with a maintenance dose of 1.5 to 2.5 mg/day thereafter. For neuritis, the dose is 10 to 50 mg/day orally.[33]

Precautions

Adverse reactions associated with vitamin B_6 therapy include abdominal pain, nausea, vomiting, increased serum aspartate aminotransferase values, and decreased serum folic acid concentrations. At doses exceeding 1000 mg, this vitamin has been shown to cause sensory neuropathy. It should be used with caution in patients concurrently taking phenytoin, phenobarbital, or levodopa. Pyridoxine may increase the metabolism of these drugs and thereby reduce the plasma levels of phenytoin, phenobarbital, or levodopa.

The U.S. Recommended Dietary Allowance (RDA) values for vitamin B_6 are as follows:

- *Men:* 19 to 50 years old, 1.3 mg; 51 years old and older, 1.7 mg
- *Women:* 19 to 50 years old, 1.3 mg; 51 years old and older, 1.5 mg. Some researchers think that the RDA for women 19 to 50 years old should be increased to 1.5 to 1.7 mg.
- *Pregnant women:* 1.9 mg; lactating women: 2 mg[33]

Biomechanical Therapy

Massage Therapy

A small study (N = 16) showed a short-term benefit of pain reduction and functionality improvement in patients treated with four weekly massages by a therapist (not further defined) as well as daily self-massage.[39] The type of massage described resembled pétrissage and effleurage-type stroking and was focused on the hand and forearm. No group received sham massage, so whether the benefits resulted from direct action of the massage on the carpal tunnel and surrounding tissues to mobilize fluid or from neurotransmitter release in the central nervous system is unclear. Because teaching a patient to massage his or her own hand and forearm has minimal cost, a trial of this modality may be of benefit.

Yoga

In another small study, a group of patients taking part in a highly individualized and methodical yoga program (Iyengar approach) demonstrated significant reduction in pain and significant improvement in grip strength compared with a control group offered a wrist splint in addition to continuation of the current treatment.[40] No significant difference was reported in median nerve motor and sensory conduction time between the two groups. The yoga regimen, for which the group met twice weekly for 8 weeks, was designed to focus on improving strength and balance in each joint in the upper body and also covered a relaxation technique. Although a larger study with long-term follow-up is needed, yoga may be an option for patients who are able to afford such a program, as well as for those who may be unable or unwilling to use other approaches or treatment options for CTS.

Physical Therapy and Occupational Therapy Modalities

Wrist Splinting

Nighttime splints that prevent flexion of the wrist are inexpensive options useful in the treatment of CTS and should be a first-line choice for most patients with mild to moderate CTS. Although full-time splint use may produce better results, most patients generally do not tolerate daytime use of the appliance. Splints that keep the wrist in a neutral position may be more beneficial than those placing the wrist in extension. Patients should try a noncustom orthotic first, which is less expensive than the custom-fitted counterpart. Generally, negative effects are not associated with splint use, other than the initial discomfort of wearing a new appliance. Splinting may be used in combination with other therapies. One study demonstrated splinting to be superior to steroid injection of the carpal tunnel in patients with mild and moderate CTS, in terms of both symptomatic relief and improvements in sensory and motor nerve conduction velocities.[41] These results were obtained with near-nightly use of the splint for 1 year, a regularity and duration that may be more difficult to obtain in a nonstudy patient population. Patients whose CTS is unresponsive to this therapy after 3 weeks of use must be reexamined; in addition, patients with thenar wasting on initial presentation may benefit from another treatment modality. Pregnant patients may be especially good candidates for splinting.

Ultrasound Therapy

Ultrasound therapy may be of benefit in patients with mild to moderate CTS, although the cost and frequency of treatments may be a barrier. One study demonstrated an improvement in symptoms and motor distal latency in wrists receiving ultrasound treatment that was not seen in wrists receiving sham ultrasound.[42] The investigators postulated that the antiinflammatory and tissue-stimulating effects of ultrasound could be responsible for the results, although more research is needed. Other modalities are less expensive and less time consuming, so ultrasound should be considered after those have been tried and are unsuccessful. Long-term benefits of ultrasound therapy are unknown.

Chiropractic Manipulation

Chiropractic manipulation has not been proved to be of benefit in the treatment of CTS. One randomized clinical trial demonstrated an improvement in symptoms in the group receiving chiropractic manipulation, but this group also underwent ultrasound and received wrist splints, thus making it impossible to determine whether symptom improvement resulted from chiropractic manipulation or from the other modalities.[43] No significant difference was noted between the group treated with chiropractic manipulation and the group treated with medication, who also received splints. Manipulation was defined as high-velocity,

low-amplitude thrust, myofascial massage, and loading procedures to the wrist, elbow, and shoulder, as well as treatment to the cervical and upper thoracic regions. A few published case reports of the efficacy of chiropractic manipulation for treatment of CTS exist, but more studies are needed before this approach can be recommended for this condition.

Osteopathic Manipulative Treatment

Randomized controlled studies of osteopathic manipulative treatment (OMT) for the treatment of CTS are scarce. Palpatory examination was noted to be 92% sensitive but only 75% specific when compared with electrodiagnostic studies for determining CTS.[44] However, cadaver studies demonstrated an elongation of the transverse carpal ligament after treatment with OMT (nonthrust techniques designed to stretch the transverse carpal ligament) directed at the wrist, in conjunction with static loading (weights).[45,46] Whether these results may be applied to living patients remains to be seen, although animal studies showed minimal change in postmortem biomechanical properties of ligaments after freezing,[47,48] so these findings may possibly be relevant. The female cadaver wrists tended to be smaller and had greater elongation of the transverse carpal ligament, especially when OMT was done first, followed by static loading.

Osteopathic physicians practice many specialties, and many serve as primary care physicians and can easily perform OMT in the office, as shown in Figure 66-1, during the first presentation of the complaint. The patient can be instructed in self-stretching exercises (shown in Fig. 66-2), which can be done at home at no cost and often with increasing relief of symptoms. One small study ($N = 16$ wrists) demonstrated a reduction in symptoms with OMT,[49] and another reported magnetic resonance imaging evidence that OMT and self-stretching enlarged transverse and anteroposterior dimensions of the carpal canal.[50] However, three of the four patients undergoing this treatment had symptoms of CTS after trauma, which may respond differently than CTS of other causes, such as repetitive motion. Large randomized trials including sham OMT are needed before OMT can be clearly stated as being beneficial for CTS. Given the low risk of adverse events with OMT as well as the low cost, however, a patient can be treated by a combination of approaches, including self-stretching and wrist splints. Before more invasive approaches (i.e., injection, surgery) are considered, a trial of OMT may be of benefit. Additionally, the holistic philosophy of osteopathic medicine mandates taking into account the person as a whole, considers other potential aggravating factors, and seeks ways to reduce or remove these factors.

Surgery

The three basic types of surgical procedures for carpal tunnel release, all of which attempt to visualize and cut the transverse carpal ligament, are as follows:

- Traditional open (approximately a 5-cm incision)
- Mini-open (approximately a 2.5-cm incision)
- Endoscopic (one or two portals)

Relief of symptoms is similar with all three types, but patients undergoing endoscopic surgery performed by an experienced surgeon will likely return to work sooner than will patients having traditional open surgery.[6] A 2005 randomized controlled trial demonstrated open surgery to be superior in terms of symptom relief but not grip strength, compared with a single steroid injection for CTS, over a

FIGURE 66-1
A, The physician's thumbs apply pressure away from the center of the wrist, while the fingers below simultaneously apply an upward force to create a spreading effect. **B**, Once an initial stretch has been achieved and held, the physician can then gently extend the patient's wrist farther (by pushing patient's fingers with his or her knee) and create more of a spread by moving his or her thumbs farther away from the center of the wrist. The goal is to increase the length of the transverse carpal ligament and widen the carpal canal, thereby reducing the amount of pressure on the median nerve. (Adapted from Sucher BM. Myofascial release of carpal tunnel syndrome. *J Am Osteopath Assoc.* 1993;93:92–101.)

A B

FIGURE 66-2
A, The patient is instructed to stand near a wall, place the affected hand's palm flat against the wall (fingertips down), and, with the other hand, add a downward force to the thumb of the affected hand. With this maneuver, the elbow is compressed by pressure from the iliac crest, and the pressure can be gently increased as stretching occurs. **B,** The patient can also perform a similar technique while seated, by placing the palm (fingertips down) on the inside of one thigh and the olecranon process on the other side and then bringing the legs together as the free hand exerts downward pressure on the thumb. The patient should be taught this stretching maneuver in the office and should perform it 5 to 10 times a day. (Adapted from Sucher B. Myofascial manipulative release of carpal tunnel syndrome: documentation with magnetic resonance imaging. *J Am Osteopath Assoc.* 1993;93:1273–1278.)

A

B

20-week period.[51] Although most patients report satisfaction with surgical outcomes, some caveats apply:

- Hand strength may take months to recover.
- The surgical scar site may be tender for up to a year after the operation.
- Attorney involvement (in cases of Workers' Compensation) may predict a worse surgical outcome.[52]

Before considering surgical intervention, one must carefully rule out reversible causes of CTS, and referral to a specialist to be certain of the diagnosis may be warranted. Patients with mild CTS symptoms should especially be made aware of the risks and benefits of surgery. Pregnant patients should not be considered candidates for CTS surgery, because their symptoms will probably improve after delivery.

If surgical intervention is being considered, the patient should be referred to a surgeon experienced in carpal tunnel syndrome and should undergo electromyography before the surgical procedure to be certain of the diagnosis.

Bioenergetics

Therapeutic Touch

Therapeutic touch has not been shown to be better than sham therapeutic touch in the treatment of CTS.[53]

Traditional Acupuncture

Although the National Institutes of Health issued a consensus statement supporting the use of acupuncture in the treatment of CTS,[54] randomized controlled trials are needed.[55] In 2004, the modality was approved as a treatment for CTS in Massachusetts for Workers' Compensation cases. Acupuncture may be regarded as an adjunct to other therapies or as an alternative to surgery for mild cases of CTS. One barrier is the cost of acupuncture.

Laser Acupuncture

Laser acupuncture is probably not of benefit in the treatment of CTS.[16]

Traditional Chinese Medicine

A retrospective single-case series of 11 patients with CTS who were treated with Jackyakamcho-tang (Shaoyaogancao-tang), an herbal formulation that has been used for

spasmodic muscles and pain in Eastern countries, demonstrated an analgesic effectiveness of approximately 72%.[55] This study had many limitations, however, and approximately 11% of the patients treated also had adverse effects.

Therapies to Consider

Many models of health care outside the traditional Western model likely offer beneficial treatments for many ailments of the Western world, such as CTS. Some involve a detailed and highly individualized assessment of the patient, and treatment is often multifaceted, with a combination of products (traditional Chinese medicine) that are not easily found or identified in the United States without some advanced knowledge. Ayurvedic medicine, for example, takes into account a balance of the life energies as well as the constitution of the individual, and the treatment offered varies from patient to patient, thus making it difficult to perform randomized controlled trials to study its effects. As we continue a push toward evidence-based medicine, potential therapies for CTS treatment and other disorders will emerge.

Prevention Prescription

- Avoid repetitive hand motions, especially those with forceful thrusting.
- Avoid prolonged gripping.
- Avoid prolonged positioning of the wrist in extremes of flexion or extension.
- Avoid gripping vibrating workplace tools for a prolonged time.
- Avoid isolated finger motions, such as typing, for a prolonged time.
- Schedule rest and stretching breaks every 1 to 2 hours.

Therapeutic Review

If a patient presents with mild to moderate symptoms of carpal tunnel syndrome (CTS), has no thenar flattening, and has had symptoms for less than 1 year, a stepwise approach is appropriate. Most therapies can be combined with nighttime splinting. If a patient has unrelenting numbness or pain or a history of symptoms lasting longer than 1 year, a thorough examination should be conducted to ensure a correct diagnosis, and then referral to a surgeon specializing in CTS release may be the most appropriate therapy.

If a patient presents with thenar atrophy, this indicates long-standing neurologic compromise, so more aggressive diagnostic and therapeutic options should be given priority.

Lifestyle Changes

B1

- Have the patient
  - Reduce activities that bring on symptoms.
  - Take frequent breaks to rest hands.
  - Perform stretching or strengthening exercises for the hands (see Fig. 66-2).

Splint Therapy

A1

- The patient should wear a splint as often as possible, even during the day if tolerated.
- Start with a rigid over-the-counter appliance first, ensuring proper fit and prevention of wrist flexion.
- Better results may be achieved with the wrist held in neutral position rather than extended.
- Reconsider therapy if no benefit is seen after 3 weeks.

Yoga

B1

- A patient who is willing to try yoga, despite the cost of an individualized program, may see some benefit from it.

Ginger

B2

- The dose of Eurovita Extract 33 is 170 mg three times/day or 255 mg twice/day
- Ginger may be of benefit in patients with both osteoarthritis and CTS, as well as in pregnant patients with CTS and nausea or vomiting.
- Ginger should be used with caution in patients taking anticoagulants.

Osteopathic Manipulative Treatment

B2

- Osteopathic manipulative treatment (OMT) can be done in combination with other therapies.
- In addition to OMT in the office (see Fig. 66-1), patients can do self-stretching exercises at home (see Fig. 66-2) 5 to 10 times/day until symptom resolution or for 2 to 3 weeks, at which point reassessment is warranted if no improvement has occurred.

Oral Steroids

B2

- Prednisolone is taken at 20 mg/day for 2 weeks.
- The use of steroids in pregnancy is controversial.

Continued

Steroid Injection

- Injection of methylprednisolone acetate, 20 mg mixed with 1 mL of 1% lidocaine, into the carpal canal by a physician trained in this procedure may offer some relief of symptoms. It may also delay the need for surgery.
- Use of more than three doses in 1 year suggests a need for surgical intervention.

Ultrasound

- Although costly and time consuming, ultrasound may be beneficial in patients with mild to moderate CTS. It can be combined with splint therapy, OMT, or medications.

Traditional Acupuncture

- Acupuncture can be used as a possible alternative to surgery for mild CTS.
- It may be costly and is usually not covered by medical insurance.

Surgery

- Surgery is likely most useful for patients with unrelenting pain or numbness, thenar atrophy, or treatment failure with other modalities.
- The clinician must be certain of the diagnosis and must choose a surgeon who has performed many CTS procedures.
- Referral to a CTS specialist for evaluation is recommended before surgery is suggested to the patient.
- Surgery is not advised for pregnant patients with CTS, which will probably resolve with delivery.
- Indications for surgery are unrelenting pain, thenar eminence atrophy, loss of motor function with diminished finger strength, and failure of other treatments.

KEY WEB RESOURCES

National Institute of Neurological Disorders and Stroke, National Institutes of Health carpal tunnel syndrome (CTS) fact sheet: http://www.ninds.nih.gov/disorders/carpal_tunnel/detail_carpal_tunnel.htm	Fact sheet and information page touching on diagnoses, etiology, and treatments
MedicineNet article on CTS: http://www.medicinenet.com/carpal_tunnel_syndrome/article.htm	A comprehensive and patient-friendly site referencing and explaining CTS
American Society of Surgery for the Hand information on CTS: http://www.assh.org/Public/HandConditions/Pages/CarpalTunnelSyndrome.aspx	Information on surgical treatment of CTS

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Chapter 67

Epicondylitis

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Pathophysiology

Lateral epicondylosis (LE) and medial epicondylosis (ME) are common, painful, debilitating soft tissue disorders. LE (tennis elbow) affects up to 7 patients per 1000 per year in general medical practices.[1] ME (golfer's elbow) is much less common and is associated with less functional impairment.[2] Both conditions are well known as sport-related injuries, but they have their greatest effect on workers with repetitive stressful hand tasks.[3] The most common causes of LE and ME may be low-load, high-repetition activities such as keyboarding, although formal data are lacking.[4] The cost of time away from work because of these disorders is significant.

Our understanding of the pathophysiology underlying LE and ME has changed. Both LE and ME were traditionally seen as inflammatory conditions. The terms *lateral epicondylitis* and *medial epicondylitis* are often used indiscriminately to refer to chronic overuse elbow injury. However, most overuse tendon injuries, including LE and ME, show no histopathologic evidence of inflammatory cells.[5–7] Rather, they are chronic degenerative conditions. Therefore, *epicondylosis* is the preferred term.[8,9] The current understanding identifies overuse of or trauma to elbow extensor or flexor tendons, microtearing, and failed tendon healing as the key mechanisms of injury. The result is weakened, fibrosed, and, finally, calcified and necrotic tendon insertions at the lateral or medial epicondyle.[10,11] Although inflammation may be present early in the disease process, biopsy studies show an absence of inflammatory mediators and cells, as well as dramatically disorganized collagen (Figs. 67-1 and 67-2). Tendinopathy has been used as a general term for this class of injury.[11,12]

Lateral epicondylosis and medial epicondylosis are examples of overuse tendinopathies, complete healing of which often requires 3 to 12 months.

Integrative Therapy

The treatment of epicondylosis was assessed in more than 100 randomized controlled trials (RCTs) and critical reviews, most addressing LE. The results of these reviews can be disheartening, given that no therapy was definitively better in the long term than conservative treatment. Existing studies often suffer from small sample size, poor evaluation over longer periods (12 to 24 months), and inconsistency of diagnostic criteria, treatment protocols, and outcome measures. Key issues, such as quality of life, the cost and benefit of various therapies, and return to work parameters are relatively unstudied. Very few studies compare a given intervention with either watchful waiting or physical therapy designed specifically for epicondylosis. However, although better research is sorely needed, recommendations can be made based on both clinical trial data and clinical experience.

Lifestyle

Healing Context

An integrative approach for the treatment of LE and ME focuses on pain relief, preservation of movement, muscle conditioning, and prevention. Most patients respond well to conservative treatment. The clinician should explain the pathophysiology of epicondylosis to the patient and should establish realistic expectations about treatment and expected time to full recovery. Many patients are surprised by both the nature of the condition (noninflammatory) and the extended period often required for complete healing. Most patients recover completely in 3 to 6 months regardless of treatment.[10] Some patients with LE and ME suffer from symptoms that are refractory to initial therapy, however. In a general practice trial of watchful waiting, 20% of patients who had elbow pain for longer than 4 weeks did not experience resolution of the pain and disability within 1 year.[13]

FIGURE 67-1
Histology of a normal tendon. (From Wilson JJ, Best TM. Common overuse tendon problems: a review and recommendations for treatment. *Am Fam Physician*. 2005;72:811–818. Copyright 2005 American Academy of Family Physicians.)

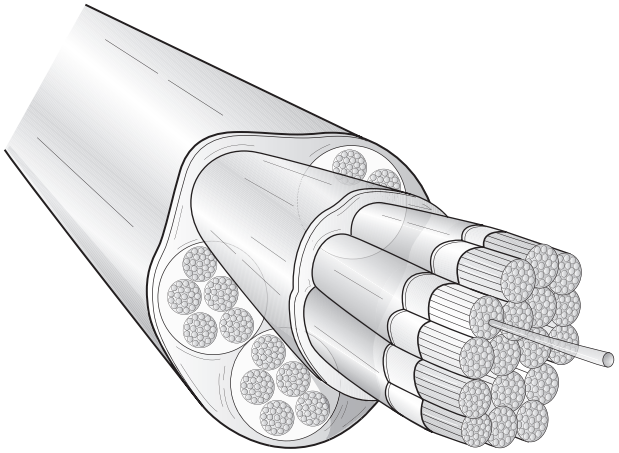
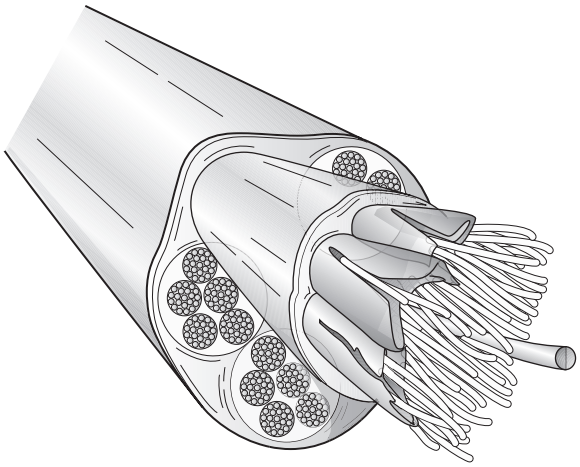


FIGURE 67-2
Histology of a damaged tendon. Note the collagen disorientation and separation. (From Wilson JJ, Best TM. Common overuse tendon problems: a review and recommendations for treatment. *Am Fam Physician*. 2005;72:811–818. Copyright 2005 American Academy of Family Physicians.)

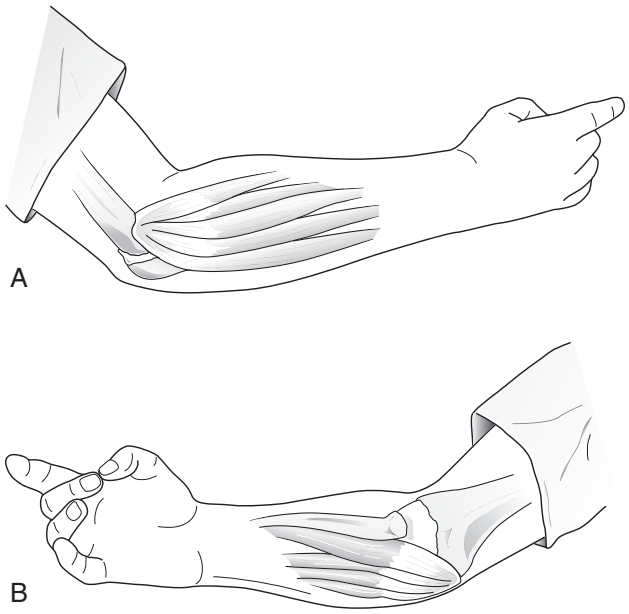


Relative Rest

The pain of LE and ME is likely caused, and is certainly exacerbated, by activities that overuse the extensor and flexor tendons (Fig. 67-3). Pain from LE can be decreased by limiting wrist extension; ME-related pain can be decreased by limiting wrist flexion and pronation.

Patients whose work activity necessarily exacerbates pain should be transferred to more benign tasks or lighter or shorter duty or should be given medical leave. Because relative rest makes good clinical sense but is unstudied, the duration and extent of rest or leave, as well as the effect of short breaks, should be monitored clinically.

FIGURE 67-3
A, Lateral epicondylosis. **B,** Medial epicondylosis.



Ice

Because the role of inflammation in tendinopathies is unclear, the importance of icing, a traditional antiinflammatory technique, is also uncertain. However, cryotherapy is probably effective in the acute phase (first 7 days), especially in the setting of trauma. A 2004 systematic review of icing treatment for soft tissue injury found that application of ice through a wet towel for 10 minutes every 4 to 6 hours was effective.[14]

Mind-Body Therapy

Psychosocial Stress

The severity of epicondylosis has been found to be related to the intensity of work environment stress.[3] Patient education about stress relief techniques, and workplace assessment to reduce psychosocial stressors, may affect the level of pain of LE and ME. It may also help prevent further tendinopathy when these measures are combined with other therapy.

Evidence suggests that acupuncture alleviates lateral epicondylosis pain in the short term.

Bioenergetic Therapy

Acupuncture

Acupuncture is based on the idea that patterns of energy flow (qi) through the body are essential for health. Disruptions of this flow are believed to be responsible for disease.

Acupuncture may work on epicondylar pain through activation of endogenous opioids.[15] Reviews and RCTs reported that needle acupuncture was significantly more effective than sham acupuncture in treating LE,[16] that acupuncture could increase the duration of pain relief and the proportion of people with at least 50% pain reduction after only one treatment,[17] and that acupuncture increased the proportion of

subjects who reported a good or excellent result of treatment (22 out of 44 with acupuncture, compared with 8 out of 38 without acupuncture).[18] Acupuncture is a reasonable therapeutic option if pain and disability are refractory to more conservative treatment.

Precautions

Acupuncture must be performed by a trained specialist. Only one study reported any harm from needle acupuncture.[19] The investigators noted that one patient withdrew from the study because of needle pain. Given that needle acupuncture has provided pain relief in the short term and has very low risk, it is a reasonable treatment option for patients in whom more conservative management has failed.

Pharmaceuticals

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) target the inflammatory process thought to play a role in the early stage of LE and ME. A systematic review of the use of topical NSAIDs (diclofenac and benzydamine) for lateral elbow pain in adults found that pain was significantly improved after 4 weeks of NSAID use in comparison with placebo.[20] However, no differences in grip strength or range of motion were reported. Another study noted significant improvements in pain and function after iontophoresis and diclofenac.[21]A systematic review of oral NSAIDs found that diclofenac significantly reduced short-term pain compared with placebo, but the studies reviewed did not assess function or long-term pain.[22]

> Nonsteroidal antiinflammatory drugs and corticosteroid injections have been shown to relieve acute epicondylar pain but not to improve outcomes in the long term.

Although beneficial in the short term, use of NSAIDs is controversial because the role of inflammation is not fully understood; inflammation may have an efficacious role in soft tissue healing. In addition, the studies assessed the use of NSAIDs in the acute phase, when spontaneous healing is most likely. Acetaminophen has not been studied, but it may provide relief of mild to moderate pain without gastrointestinal risk.

Dosage

Topical diclofenac 3% gel is applied twice daily for 1 to 2 weeks. The regimen for topical diclofenac with iontophoresis is as follows: 3% gel, 150 mg using a 4- to 8-mA intensity for 20 sessions of 25 to 30 minutes each.

The dose of oral diclofenac is 75 mg twice daily for 1 to 2 weeks. The dose of oral ibuprofen is 600 mg each 6 hours for 1 to 2 weeks.

Precautions

Topical NSAIDs may cause skin irritation. Oral NSAIDs may cause abdominal pain and diarrhea, and patients have an increased risk of gastrointestinal complaints (relative risk, 3.0 to 5.0).[23]

Corticosteroid Injections

Corticosteroid injections also target inflammation and have been a mainstay of conventional therapy for LE and ME. Clinical trial data support their use on a limited basis for pain and disability from LE and ME, although the effects may be relatively short lived; clinical trial and systematic review data suggested that the effectiveness of these injections is limited to 6 months or less. One review concluded that steroid injections were effective over the short term (2 to 6 weeks) compared with placebo, elbow strapping, physical therapy, and NSAIDs, but not in the long term.[22] The best study compared steroid injections with physical therapy and watchful waiting; at 6 weeks, the injection-treated group was most improved, but at 1 year, the other two groups experienced a higher rate of complete symptom relief.[24] A systematic review and clinical trial both reported that corticosteroid injection use was associated with limited effectiveness at 1 year.[25,26] Corticosteroid injections may have a role in patients whose work or sport activity requires rapid, short-acting relief of pain. Patients can be reinjected at 4 to 6 weeks, to a maximum of three injections.[20]

Dosage

The dose is 1 mL of 40 mg/mL methylprednisolone in 2 to 3 mL of 1% lidocaine.

Precautions

One systematic review found that 17% to 27% of patients in two RCTs suffered some skin atrophy. A more common adverse event is postinjection pain, experienced by approximately half of patients.[27] The theoretical outcome of tendon rupture was not found in two separate reviews, and this complication seems to be rare.[22]

Other Injection Therapies

Two other injection-based therapies, prolotherapy and platelet-rich plasma (PRP), received attention in small but well-done RCTs. In both cases, patients had approximately 3 mL of solution injected at the insertion of the common extensor tendon with optional injection of surrounding ligamentous tissue. A peppering injection technique is often employed for these injections. Although the precise mechanism of action for both techniques is not well known, both purport to heal damaged, degenerative tendons at the tissue level. As such, both therapies address the contemporary understanding of LE and ME as degenerative conditions.

PRP is a concentrated solution of autologous platelets that can deliver growth factors directly to areas of degeneration and is hypothesized to enhance tissue healing.[28,29] Autologous blood is drawn at the point of care and is centrifuged to separate the portion with the greatest abundance of platelets. Studies reported that PRP for LE could result in improved quality of life, pain, and function, and PRP could modify the disease course at the level of the damaged tendons.[26,30] Promising early clinical trial and anecdotal evidence resulted in increasingly common use of PRP in clinical practice.[28,29] One RCT reported that at 52 weeks, subjects with LE who received PRP injection reported a 66% effect size compared with baseline, whereas study participants who received steroid injections reported only a 17% improvement ($P < .05$) in disease-specific quality of life.[26]

Prolotherapy, an injection-based therapy reported to enlarge and strengthen ligaments, was assessed in systematic and descriptive reviews.[31,32] Prolotherapy is used for various soft tissue conditions including LE and ME. Inflammation is thought to initiate a local physiologic reaction favoring anabolic processes that strengthen tendon and ligament tissue at the bony insertion. Injectants include hypertonic dextrose and morrhuate sodium. In one RCT, subjects with severe refractory LE responded well to three prolotherapy treatments.[33] Compared with participants receiving blinded saline injections, subjects treated with prolotherapy experienced pain reduction (absolute effect size between groups of 68%; $P < .01$) and improved isometric strength ($P < .05$) compared with control saline injections by 16 weeks, and these effects were maintained at 52 weeks.

Both prolotherapy and PRP injection appear safe when performed by an experienced injector and are reasonable treatment options for patients in whom more conservative management has failed. Neither is typically covered by third-party payers. Costs for each vary considerably.

Dosage

Formal dosing for both PRP and prolotherapy is not standard. Both therapies use specific injection techniques. Obtaining these services is best done in consultation with physicians who are experienced with these procedures. Both procedures are performed in outpatient settings without significant analgesia, similar to corticosteroid injections. Both solutions are injected at tender points at the insertion of the common extensor tendon and radial collateral ligament.[2,5,7] PRP injection therapy has been performed in a single treatment session, whereas prolotherapy is more typically performed in a minimum of in three treatment sessions separated by approximately 4 weeks.

Biomechanical Medicine

Physical Therapy

Exercise and physical therapy make sense clinically and are well accepted. Eccentric exercises preferentially load tendons and promote the formation of new collagen. These exercises were reported to be beneficial in one small RCT comparing exercise for epicondylar pain at 8 weeks with ultrasound and friction massage,[22] as well as in other tendinopathies.[34,35]

> Exercise and physical therapy are reasonable conservative modalities, although their overall long-term efficacy is unclear.

One review and one well-done RCT reported that exercise, stretch, and mobilization were effective therapies and yielded significant improvement compared with wait-and-see, placebo, and ultrasound approaches.[36,37] Unfortunately, physical therapy protocols vary, and studies do not describe them in detail. Examples of exercises and recommendations for their use are given in Figure 67-4.

Orthoses (Braces)

Orthotic devices (brace, splint, cast, or strap) are thought to decrease the pain of LE or ME by removing damaging load from lateral and medical epicondylar tendon attachments. A systematic review of five RCTs assessing various orthotic devices was unable to make a general recommendation for their use.[38] However, the notion of reducing stress and strain at the tendon insertion makes sense and is generally accepted; clinically, many patients respond well to a simple and inexpensive elbow strap or wrist splint combined with relative rest. Complete immobilization with any orthotic should be avoided because of the risks of deconditioning and muscular atrophy.

Precautions

Local deconditioning should be avoided.

Surgery

A 2005 review found no RCTs assessing surgical intervention for LE or ME.[22] However, case series data suggest efficacy of surgery in patients with symptoms refractory to more conservative therapy. The goal of surgery is to excise abnormal tissue or release the affected portions of the extensor or flexor tendon. One case series reported that of 1300 patients undergoing surgery for refractory epicondylar pain (1000 for LE and 300 for ME), 85% experienced complete pain relief and strength return, 12% had partial improvement, and 3% had no improvement.[11] Surgery is a reasonable option for patients with significant pain for whom more conservative therapy has failed.

Precautions

Precautions include postoperative concerns such as infection and nerve damage. In the study cited previously, however, reported complications were rare.[11]

Prevention Prescription

Lifestyle
- Stop smoking.
- Reduce stress.

Avoid Exacerbating Activities
- Reduce or avoid the lifting of objects with the arm extended.
- Reduce repetitive gripping.
- Decrease overall tension of gripping.
- Avoid extremes of wrist bending and full extension.
- Work or train with the elbow in a partially flexed position.
- Use wrist supports when weight training.
- Enlarge the gripping surface of tools or rackets with gloves or padding, use a hammer with extra padding to reduce tensions and impact, and hold heavy tools with two hands.

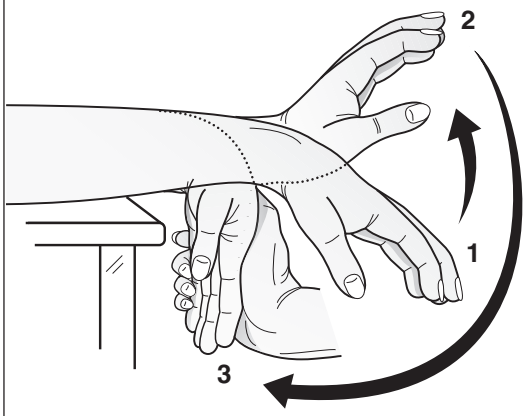
Ergonomic Evaluation
- Evaluate repetitive motion activity, duties, equipment, and techniques, especially in work situations.
- More complete information on ergonomic evaluation of computer, laboratory, and industrial settings is available through the Centers for Disease Control and Prevention (see Key Web Resources).

Exercise
- Use stretching and strengthening exercises once daily, along with frequent periods of short rest.

FIGURE 67-4
Physical therapy for lateral epicondylosis.

Lateral Epicondylosis Physical Therapy

Start exercises with set **A** and proceed slowly through the set. Advance to exercises with weights when pain begins to decrease, usually after 7-10 days.



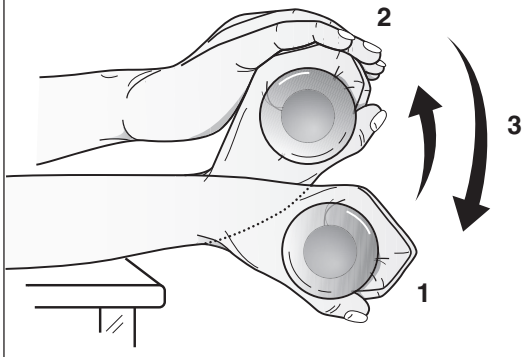
A. Active range of motion and strengthening

1. Place forearm on table with hand off edge of table, palm down.
2. Move hand upward.

Hold position for 15 seconds.
Return to starting position.
Perform 1 repetition every 4 seconds.
Perform 1 set of 12 repetitions twice per day.

After 7-10 days, or as range of motion improves and pain diminishes, advance to step **3**:

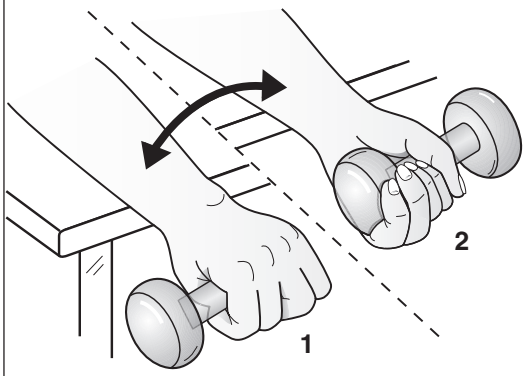
3. With other hand, grasp at thumb side of hand and bend wrist downward gently.
Perform 1 set of 4 repetitions twice per day.



B. Exercise with weight

1. Place forearm on table, palm down, weight in hand.
2. Use other hand to raise wrist fully upward.
3. Release wrist and slowly lower weight.

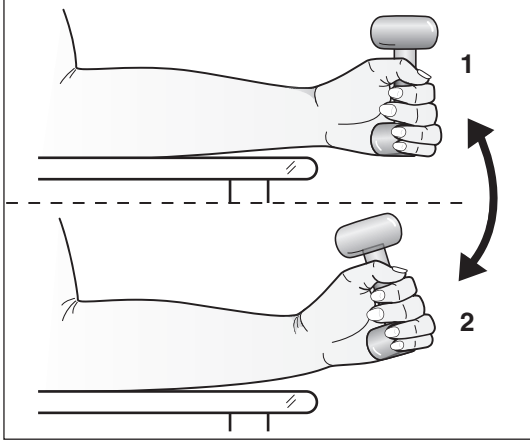
Start with 1/2-lb weight, advance to 1-lb weight.
Perform 1 repetition every 4 seconds.
Perform 3 sets of 10 repetitions once every other day.
Rest 1 minute between sets.



C. Exercise with weight

1. Support forearm on table or armchair, hand palm down holding weight.
2. Rotate hand to thumb up.
Return to starting position.

Start with 1/2-lb weight, advance to 1-lb weight.
Perform 1 repetition every 4 seconds.
Perform 3 sets of 10 repetitions once every other day.
Rest 1 minute between sets.



D. Exercise with weight

1. Support forearm on table or knee.
Hold weight in hand, thumb up.
2. Lift weight upward.
Return to starting position and repeat.

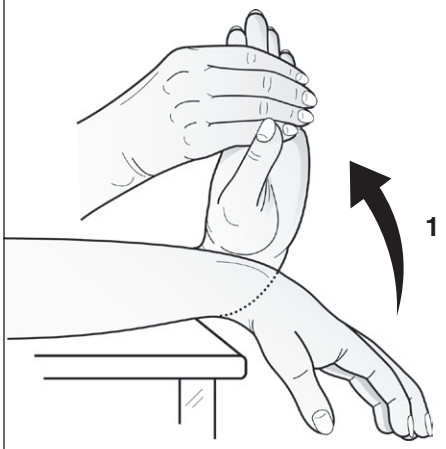
Start with 1/2-lb weight, advance to 1-lb weight.
Perform 1 repetition every 4 seconds.
Perform 3 sets of 10 repetitions once every other day.
Rest 1 minute between sets.

Continued

FIGURE 67-4, cont'd

Medial Epicondylosis Physical Therapy

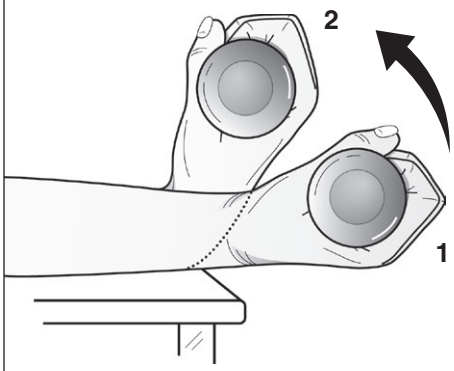
Start exercises with set **A** and proceed slowly through the set. Advance to exercises with weights when pain begins to decrease, usually after 7-10 days.



A. Stretch exercise

1. Grasping fingers of one hand with other hand, pull hand back gently. Keep injured elbow straight.

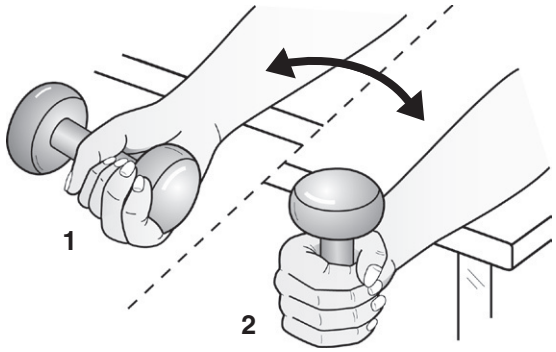
Hold position for 15 seconds.
Perform 1 set of 4 repetitions twice each day.
Rest 30 seconds between repetitions.



B. Exercise with weight

1. Grasp weight with hand.
Place forearm on table with hand off edge of table, palm up as shown.
2. Move wrist upward.
Return to starting position.

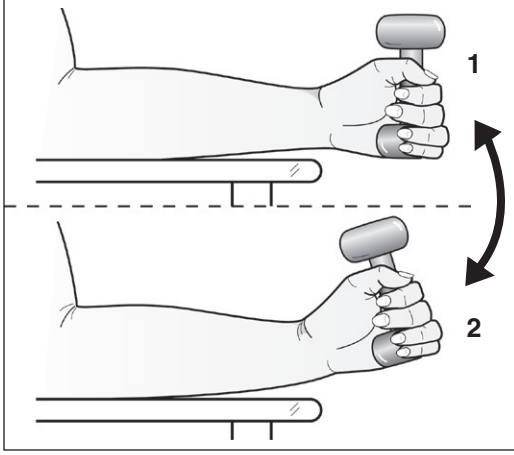
Start with 1/2-lb weight, advance to 1-lb weight.
Perform 1 repetition every 4 seconds.
Perform 3 sets of 10 repetitions once every other day.
Rest 1 minute between sets.



C. Exercise with weight

1. Support forearm on table or armchair.
Position hand palm up with weight in hand as shown.
2. Rotate hand to thumb up.
Return to starting position.

Start with 1/2-lb weight, advance to 1-lb weight.
Perform 1 repetition every 4 seconds.
Perform 3 sets of 10 repetitions once every other day.
Rest 1 minute between sets.



D. Exercise with weight

1. Support forearm on table or knee.
Hold weight in hand, thumb up.
2. Lift weight upward.
Return to starting position and repeat.

Start with 1/2-lb weight, advance to 1-lb weight.
Perform 1 repetition every 4 seconds.
Perform 3 sets of 10 repetitions once every other day.
Rest 1 minute between sets.

Therapeutic Review

Lifestyle

- Prevention: Most of the techniques listed in the Prevention Prescription box also off-load affected tendons and may speed healing.
- Establish a time course of healing; most patients recover in weeks to months, but recovery may take up to 1 year or longer. C-1
- Relative rest: Remove or reduce repetitive, heavy activity affecting wrist flexors or extensors. C-1
- Use ice in the first 2 to 4 weeks of pain. B-1

Mind-Body Therapy

- Stress reduction techniques and workplace evaluation are recommended. C-1

Bioenergetic Therapy

- Needle acupuncture may be used. B-1

Pharmaceuticals

- Nonsteroidal antiinflammatory drugs and corticosteroid injections have good efficacy for pain control in the early stages of lateral epicondylosis and medial epicondylosis, but they do not change outcomes in the long term. B-2
  - Topical diclofenac, 3% gel, may be applied twice daily for 1 to 2 weeks.
  - Topical diclofenac may be applied with iontophoresis, using 150 mg at 4 to 8 mA for 20 sessions.
  - Oral ibuprofen, 600 mg, may be taken every 6 hours for no more than 2 weeks.
  - Injection: Methylprednisone, 40 mg in 1 mL of lidocaine, may be injected weekly for up to 4 treatments.

Physical Therapy and Preventive Exercise

- Various exercises may be performed in sets of repetitions with and without weights from twice daily to every other day (see Fig. 67-4). B-1

Orthotics

- Simple wrist splints and elbow straps may be used in conjunction with relative rest. C-1

Prolotherapy

- Prolotherapy appears safe when performed by an experienced injector and is a reasonable treatment option for patients in whom more conservative management has failed. B-2

Platelet-Rich Plasma

- Platelet-rich plasma injection appears safe when performed by an experienced injector and is a reasonable treatment option for patients in whom more conservative management has failed. B-2

Surgery

- Surgery is a reasonable option for patients with severe pain refractory to conservative care. B-2

KEY WEB RESOURCES

Mayo Clinic information on tennis elbow: http://www.mayoclinic.com/health/tennis-elbow/DS00469	This site is a basic but helpful patient-oriented online tool.
Centers for Disease Control and Prevention information on ergonomics: http://www.cdc.gov/niosh/topics/ergonomics/	This site provides information on ergonomic evaluation of computer, laboratory, and industrial settings.
American Association of Orthopaedic Medicine: http://www.aaomed.org	This nonprofit organization provides information and educational programs on comprehensive nonsurgical musculoskeletal treatment including prolotherapy. This searchable site lists members who perform prolotherapy.

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Chapter 68

Atopic Dermatitis

Amanda J. Kaufman, MD

Atopic dermatitis is a pruritic, hereditary skin disease with a lifetime prevalence of 10% to 20%; most cases begin in infancy.[1] Among affected infants, 20% to 40% will have disease that persists into adulthood. The heavy impact of atopic dermatitis on quality of life and medical care costs has led to great interest in improving outcomes. Although conventional therapies are available, they are not always effective, they only suppress disease, and their lifetime use poses potential risks. Investigators have shown keen interest in and have studied integrative therapies to prevent disease and reduce dependence on these medications.

Pathophysiology and Diagnosis

The diagnosis of atopic dermatitis requires three major and three minor features.[1] Major features are as follows:

- Pruritus
- Typical morphology and distribution
- Flexural lichenification in adults
- Facial and extensor involvement in infants and children
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

The 22 minor features illustrate the varying degrees, extent, and distress patients endure. Educating patients about these minor features may lead to less emotional distress through an improved understanding of their condition. The minor features are as follows:

- Itch caused by sweating
- Xerosis
- Eczema (perifollicular accentuation)
- Recurrent conjunctivitis
- Wool intolerance
- Keratosis pilaris
- Palmar hyperlinearity
- Pityriasis alba
- White dermatographism
- Susceptibility to cutaneous infection (*Staphylococcus aureus,* herpes simplex virus and other viruses)
- Nipple dermatitis
- Dennie-Morgan lines
- Elevated immunoglobulin E (IgE)
- Immediate (type I) skin test reactivity
- Food intolerance
- Cataracts (anterior-subcapsular)
- Cheilitis
- Facial pallor or erythema
- Hand dermatitis
- Ichthyosis
- Keratoconus
- Orbital darkening

Genetic, immunologic, and environmental risks collide to influence the course of disease and provide opportunities to mediate the clinical course. Healthy skin in patients with atopic dermatitis has increased density of proinflammatory type 2 helper T (Th2) cells.[1] The skin barrier is impaired, with fewer ceramide lipids and skin barrier proteins, thus causing poor water retention and abnormal permeability. This abnormal skin barrier allows penetration of allergens and microbes that trigger an inflammatory cascade as they stimulate Th2 cells excessively. Affected skin has increased concentrations of inflammatory cytokines and greater eosinophil infiltration. Any stimulation or inflammation sets off the central clinical feature, which is intense itching.

Light stimuli and contact irritants such as sweating, wool, and detergents cause itching. Skin damage caused by scratching releases inflammatory cytokines and further stimulates itch. Reduced barrier function allows entry of *S. aureus, Malassezia* yeasts, *Candida* organisms, and *Trichophyton* dermatophytes, thereby inducing local inflammation. Food allergies, especially to egg, soy, milk, wheat, fish, shellfish, and peanuts, are implicated in one third to one half of children with atopic dermatitis. Aeroallergens can also increase peripheral eosinophilia and serum IgE levels, which lead to increased release of histamine and vascular mediators. These features induce edema and urticaria and thus cause persistence of the cycle of itch, scratch, and rash.

Food allergies, especially to egg, soy, milk, wheat, fish, shellfish, and peanuts, are implicated in one third to one half of children with atopic dermatitis.

The relationship between psychological stress and atopic disorders is bidirectional.[2] Psychosocial stressors increase both self-reported and objective measures. The lack of sleep and physical suffering cause irritability and worsen mood disorders. Self-reporting of itch severity is increased when depression scores are elevated, similar to the relationship with pain scores.

Integrative Therapy

Atopic dermatitis is improved through an integrative approach focusing on improving the barrier function and reducing the itch-scratch cycle. Least invasive therapies are presented first, followed by those with a greater potential for harm. As the disease course waxes and wanes, patients should advance and reduce their regimen as appropriate to allow improved control of flares and reduced use of pharmaceuticals.

Lifestyle and Supportive Care

Hydration

Rehydration of the stratum corneum improves barrier function and reduces the effects of irritants and allergens. Soaking in a lukewarm bath for 10 to 20 minutes is ideal, or lukewarm showers may be taken if preferred. Bath oils can be added to the bath after the skin surface is wet. If even plain water is irritating during acute flares, 1 cup of salt added to the water will help.

Mild Soap or Soap Substitutes

Use mild, neutral-pH soap (Dove, Aveeno, Basis) minimally as needed for the face, axillae, and groin. If these soaps are too irritating, hydrophobic lotions or creams such as Cetaphil can be applied without water, rubbed until foaming, and wiped away with a soft cloth.[1]

Bleach Baths

Dilute bleach baths combined with nasal application of mupirocin with a goal to reduce colonization with *S. aureus* caused dramatic improvement in those areas of the body exposed.[3] Thirty-one children age 6 months to 17 years were treated with cephalexin, 50 mg/kg (maximum 2 g daily) divided three times daily for 14 days, and were then randomized to bathing in a dilute bleach solution (approximately ½ cup to a bathtub of water) twice weekly for at least 5 to 10 minutes and applying mupirocin ointment intranasally for the patient and all household members twice daily for the first 5 consecutive days of each month or placebo. The mean Eczema Area and Severity Score (EASI) of 19.7 was reduced by 10.4 points at 1 month and by 15.3 points at 3 months compared with 2.5 and 3.2 points in the placebo group. These reductions were in exposed areas, but not in head and neck lesions, although the head and neck can also be carefully exposed to the bleach solution.

Moisturizers Following Bathing

Follow bathing by lightly patting the skin with a towel and immediately applying an occlusive emollient over the entire skin surface to retain this moisture. Application within 3 minutes improves hydration, whereas beyond 3 minutes, surface evaporation is drying. Commonly recommended emollients include petroleum jelly, vegetable oil, and Aquaphor. Virgin coconut oil additionally reduces colonization with *S. aureus* and thus provides added benefit.[4] Ceramide-containing emollients have been shown to decrease transepidermal water loss and decrease clinical severity scores. One ceramide formulation (EpiCeram) showed improvement nearly equal to that with fluticasone cream after 28 days of use.[5] Another brand is TriCeram cream, which is also highly effective.

Ceramide, a family of lipid molecules found in cell membranes, can be applied through emollients (e.g., EpiCerem or TriCeram) after bathing, thus decreasing transepidermal water loss while reducing the symptoms of atopic dermatitis.

Urea, alpha-hydroxy acid, and lactic acid products have long been used for their exfoliation and moisturizing properties. A tolerability study of a 5% urea-containing moisturizer compared with the typical 10% formula noted a nearly 20% objective improvement over 42 days of twice-daily use for both groups.[6]

Wet Dressings

Wet dressings are useful for severely affected skin. The constant moisture is therapeutic, the cooling sensation with evaporation reduces itching, and the mechanical barrier prevents scratching. Apply wet cloth with either plain water or Burow solution to recalcitrant lesions, and periodically rewet the compress. Wet dressings increase penetration of corticosteroids. Burow solution can be made 1:40 by dissolving one Domeboro packet or tablet in a pint of lukewarm water. Parents may have success when their children sleep in cotton pajamas dampened in problem areas with another set of pajamas over top.

Avoidance of Allergens

Eliminate known allergens. Eliminate smoke exposure for children with allergies. Dust mite control measures may be helpful in patients with documented sensitivity to dust mites.

In children with animal allergies, consider removing animals from the home. A dog living in the home at the time of birth is associated with a 50% decrease in the incidence of atopic dermatitis at age 3 years.[7] However, parents caring for a dog are less likely to be severely allergic to dog dander.

Loose-Fitting Clothing

Wear loose-fitting clothing made of cotton, silk, or other natural, smooth fibers. Avoid wool. Launder new clothes before wearing to remove formaldehyde and other chemicals. Use liquid detergent, ideally without fabric softeners or optical brighteners, and consider an extra rinse cycle.

Humidity

Controlled humidity and temperature may reduce triggers of cold, heat, and dry air. Humidify in the winter with a goal of 30% to 40% humidity. Air conditioning in the summer decreases sweating as a trigger and prevents the growth of mold.

Nutrition

Prevention Through Breast-Feeding or Hydrolyzed Formula in Infancy

Debate exists on how to counsel atopic families on food exposure in early life. Exclusive breast-feeding for the first 6 months of life was previously thought to reduce atopy, although results of more recent breast-feeding studies have been inconclusive. Debate also exists on the role of food avoidance even in high-risk infants. Some experts point to populations in which very young babies are given tastes of adult food and have a lower incidence of life-threatening allergies. The LEAP (Learning Early about Peanut Allergy) study randomized high risk 4- to 10-month old infants to either exposure or avoidance of peanuts. The study should come to completion in 2013 and give guidance on which approach lowers the incidence of life-threatening peanut allergy. Food allergies are actively being studied to enhance our understanding and to provide a basis for advice to parents. In my practice, mothers with a strong history of atopy who avoid common or known familial triggers in the last month of pregnancy and in the first months of breast-feeding reduce objective measures of disease and increase parental perception of control. Any delay of symptoms or reduction in severity is welcome in these first months of life.

For those infants who cannot breast-feed, hydrolyzed formulas have been found effective for the prevention of atopic dermatitis. A 6-year follow-up to a study of 2252 newborns with familial atopy history who were randomized to various hydrolyzed formulas when breast-feeding was insufficient found a significant risk reduction for allergic disease.[8] Infants were randomized to partially hydrolyzed whey formula, extensively hydrolyzed whey formula, or extensively hydrolyzed casein formula, with regular cow's milk formula as control . The relative risk of development of any allergic manifestation was 0.82, 0.90, and 0.80, and for atopic eczema it was 0.79, 0.92, and 0.71, for the respective study formulas compared with cow's milk formula. A meta-analysis and a more recent study also found that partially hydrolyzed whey formulas appear to be as good at preventing atopic disease as extensively hydrolyzed formulas, and they cost less.[9,10]

Allergy Elimination Diet

Food allergies affect 10% to 40% of children with atopic dermatitis.[1] A study attempting to show a benefit to an allergy elimination diet in a broad sample of children with atopic dermatitis found a benefit only to an egg-free diet in infants with suspected egg allergy positive for specific IgE to eggs.[11] By 5 years old, many of these food allergies resolve. The most common foods causing positive oral challenges are egg, soy, milk, wheat, fish, shellfish, and peanuts. Elimination diets can be stressful on parents. Parents often desire testing to guide them; however, testing is not as reliable as a clinical response. The skin in atopic dermatitis can develop a wheal with a needle prick alone.[1] Serum-specific IgE tests also have significant false-positive rates.[12] The gold standard for diagnosis is a placebo-controlled double-blind oral food challenge because history, prick tests, and specific IgE do not correlate well with clinical reactivity, especially in delayed eczematous skin reactions.[1,11] Diagnostic elimination diets, such as described in this text (see Chapter 84, Food Intolerance and Elimination Diet), should be used before an oral provocation test is considered.[11] Although elimination diets are challenging, parents feel an increased perception of control over the illness when food allergies are found and exposure can be eliminated. A review of the serum radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) and their inherent challenges provides further detailed guidance.[13]

Oolong Tea

With drinking Oolong tea three times a day (made from five teabags daily), 63% of patients had significant objective improvement, and the response persisted at 6 months in 54%.[14] The antiallergenic properties of polyphenols are thought to produce the effect. Drinking 5 to 6 cups of green tea or green tea extract, at 200 to 300 mg three times daily, may provide similar results.

The main difference among green, oolong, and dark tea (all *Camellia sinensis*) is the length of fermentation of the leaf. Green is the shortest and dark the longest.

Mind-Body Therapy

Psychosocial stressors trigger flares of atopic dermatitis, and this connection prompted studies on the effectiveness of mind-body interventions. A Cochrane Review called into question the effectiveness of these interventions.[15] Mixed results showed that at least some patients may benefit from biofeedback, massage therapy, and hypnosis. Cognitive-behavioral therapy and autogenic training are superior to standard care alone and education in reducing use of topical steroids. A study on the benefits of support groups found improved quality of life scores, especially personal relationships and leisure scores.[16] A study of a structured education program on coping skills in children with atopic dermatitis and their parents showed that the intervention improved psychological scores beyond what would be expected with disease improvement.[17] Dr. Ted Grossbart, a Harvard Medical School (Boston) psychologist, created a mind-body program for skin disorders,

and his e-book is available for free (see Key Web Resources). Many therapies with known effectiveness in similar conditions have not been studied. Given the low risk of side effects and the known benefits of mind-body therapies for other measures of well-being, these approaches are worth exploring.

Supplements

Vitamins

Vitamin D and E supplementation may be helpful. In one trial, patients were divided into four groups: those given both vitamin D_3 (1600 units) and vitamin E (600 units synthetic all-rac-alpha-tocopherol), just one, or both compared with placebo for 60 days.[18] Reduction in the symptoms of atopic dermatitis by objective scoring was 64.3% in those taking both vitamin D and vitamin E and 35% in each of the groups taking just one ($P = .004$).

Dosage

Many practitioners recommend supplementation with anti-inflammatory supplements such as vitamin A, 5000 units daily, and zinc, 50 mg daily. Vitamin B_{12} cream, 0.07% used twice daily, was found effective and well tolerated in adults and children with eczema in small studies.[19]

Essential Fatty Acids

Essential fatty acid supplementation may be useful to counterbalance abnormal essential fatty acid metabolism. Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and gamma-linolenic acid (GLA) also improve atopic dermatitis through their antiinflammatory effects. The primary source of DHA and EPA is salmon and other cold-water fish. Good sources of GLA include borage oil (23% GLA), black currant seed oil (17% GLA), and evening primrose oil (8% to 10% GLA).[20]

Many studies showed insignificant improvement with supplementation, although these studies were often limited by small sample size and short duration. Other studies have been more promising. An 8-week study of 53 adults randomized to DHA (5.4 g daily) or isoenergetic saturated fatty acids found significant improvement in the DHA-treated group.[21] Another small study of evening primrose oil with 2 g of linoleic acid and 250 mg of GLA for 3 months significantly improved inflammation in atopic dermatitis.[22]

A meta-analysis of 12 trials of borage oil concluded that the evidence was limited by the small size of trials and their short duration, although borage oil is well tolerated and may have some benefit.[23] A small study in children found that undershirts coated with borage oil significantly reduced erythema, itch, and transepidermal water loss.[24]

Black currant seed oil was tested in the prevention of atopic dermatitis in neonates by randomizing 313 mothers, 81.7% of whom had a personal history of atopy, to black currant seed oil or olive oil placebo from the beginning of pregnancy until the cessation of breast-feeding, followed by supplementation of infants until 2 years old.[25] Although no difference in the groups was observed at 2 years, the prevalence of atopic dermatitis was lower in the group receiving black currant seed oil at 12 months (33% versus 47.3%; $P = .035$).

Dosage

A total of 2000 mg of DHA, EPA, and GLA is likely effective when combined, compared with the doses recommended in single-agent trials. The dose of fish oil (DHA and EPA) is 2 to 4 g daily for an adult. The adult dose of borage oil is 500 mg to 1 g daily, and the adult dose of evening primrose oil is 1 to 2 g daily.

Precautions

Adverse effects of supplements are few, and they are primarily gastrointestinal.

Probiotics

The effects of probiotics were mixed in study results, although this area of research is still in its infancy. Large questions remain to be answered, such as which organisms are effective for which conditions, how best to administer them, and for how long. Although probiotics are exceedingly safe, the current evidence base does not provide significant evidence for their use in treatment. A Cochrane Review left open the possibility that further studies could be promising,[26] and they have been. In a randomized double-blind placebo-controlled prospective trial, 90 toddlers aged 1 to 3 years with moderate to severe atopic dermatitis were treated with a mixture of *Lactobacillus acidophilus* DDS-1 and *Bifidobacterium lactis* UABLA-12 with fructo-oligosaccharide with 5 billion colony-forming units (CFUs) twice a day for 8 weeks, and these children showed an improvement of 33.7% versus 19.4% for placebo ($P = .001$).[27] A cream containing a 5% lysate of *Vitreoscilla filiformis* that was used for 30 days significantly improved objective measurements and pruritus compared with the cream alone.[28] Prenatal and postnatal use of *Lactobacillus rhamnosus* GG among atopic mothers reduced the prevalence of atopic dermatitis in their infants by 50%, with a number needed to treat of 4.5.[29,30] Women with a history of atopy should consider supplementation with *L. rhamnosus* when they are pregnant and breast-feeding, to prevent atopic dermatitis. Other women should consider a 2-month trial of probiotic use.

Dosage

For adults, the dose is 20 billion CFUs daily of a combination probiotic containing *L. rhamnosus,* such as Jarro-dophilus or PB-8. For infants and children, the dose is 5 billion CFUs daily.

Precautions

Patients with extreme immune compromise or those with indwelling catheters should use caution with regard to taking these live organisms.

Botanicals

Much of the long heritage of herbal treatment of atopic dermatitis has not been studied, although several compounds have had small, successful trials, and no safety concerns exist. Ensuring the quality of the compound used is essential to achieve these treatment effects.

Glycyrrhetinic Acid

Derived from licorice root, glycyrrhetinic acid has antiinflammatory actions when it is used topically. Two studies of a 2% glycyrrhetinic acid cream used in a 2-week and 5-week

study noted significant improvements in objective disease scores and itch.[31,32] Atopiclair is a hydrophilic cream containing hyaluronic acid, telmesteine, *Vitis vinifera* (grape), and 2% glycyrrhetinic acid. A vehicle-controlled, randomized study of 218 adults with mild to moderate atopic dermatitis found highly significant response rates with more than 50 days of use.[33] A similarly designed trial of 142 children found Atopiclair statistically more effective than vehicle at 22 days of use.[34] Atopiclair cream is available by prescription and over the counter.

Dosage

Atopiclair cream should be applied to the rash or pruritic area two to three times daily as needed. The 100-g tube is available by prescription only.

Precautions

Atopiclair cream contains a nut oil and thus should not be used in patients with a nut allergy.

Other Botanicals

Honey has been used to reduce inflammation and promote healing. A small study of 21 children ages 5 to 16 years used a honey, beeswax, and olive oil preparation on the left side of the body compared with petroleum jelly (Vaseline) on the right three times daily for 2 weeks; children were randomized to use of corticosteroids or not.[35] In the emollient-only group, 8 of 10 children improved on the honey side, and 2 of 10 improved on the petroleum jelly side. Among the corticosteroid users, 5 of 11 found the honey mixture useful in reducing corticosteroid use.

Chamomile is regarded as gentle and safe, and it has antiinflammatory and antibacterial properties. Cold, wet packs with chamomile tea are traditionally used for bacterial superinfections.[36] A half-side comparison study of chamomile cream or hydrocortisone 0.5%, with vehicle as placebo, showed neither better than placebo, but chamomile fared slightly better than the steroid.[37]

Studies demonstrated the effectiveness of an extract of *St. John's wort* (*Hypericum perforatum*). This botanical has antimicrobial activity and may have beneficial immunologic effects. A study of 28 patients found significant clinical improvement when this extract was applied as a cream, compared with its vehicle.[38]

Twenty-one patients with mild atopic dermatitis who were 5 to 28 years old were randomized to 0.3% *rosmarinic acid* emulsion twice daily or vehicle. These patients had significantly reduced erythema and transepidermal water loss.[39]

Oregon grape root (*Mahonia aquifolium*) has antimicrobial properties and inhibits proinflammatory cytokines.[36] A 10% cream used in 42 adult patients three times daily over 12 weeks demonstrated significant clinical improvement.[40]

Herbavate, a topical preparation that contains the oil extracts of *Calotropis gigantea, Curcuma longa, Pongamia glabra, and Solanum xanthocarpum* in a cream base, showed promise in an open-label 4-week pilot study.[41] These extracts have been used in Indian traditional medicine and Ayurveda.

Commercially available, standardized preparations with demonstrated efficacy should be easy for patients to find either online or in health food stores. One example is the Four Elements Herbals' product Look No X E Ma!, which contains licorice, chamomile, calendula, evening primrose oil, and vitamin E. Compounding pharmacies often can compound several agents into a single product, thus making use less burdensome. Consider compounding glycyrrhetinic acid 2% and St. John's wort (0.3% hypericin or 2% to 5% hyperforin) into a ceramide-containing cream such as CeraVe.

> Familiarize yourself with the products available from your local compounding pharmacist. Use of more than two topical products can be cumbersome for patients, although many products can be compounded together for ease of use. Many commercially available products contain several agents in combination.

Conventional Modalities

Coal Tar

Coal tar preparations have antipruritic and antiinflammatory effects and were used before the development of topical corticosteroids. They are second-line preparations but work well on chronic and lichenified lesions.[1] Tar shampoos can be used for scalp involvement. Adverse effects include contact dermatitis, folliculitis, and photosensitivity. One review found that most studies reported favorable profiles of effectiveness with few side effects (including staining and odor) and also noted that these preparations are cost effective.[42]

Immunotherapy

Allergen immunotherapy is typically indicated for patients with allergic rhinitis or allergic asthma, although trials of subcutaneous or sublingual immunotherapy to house dust mites in persons sensitized with atopic dermatitis showed some promise. Among 28 children 5 to 16 years old who had atopic dermatitis with sensitization to dust mites but without food allergy or asthma compared with 28 children who were given placebo for 18 months, sublingual immunotherapy for dust mites showed improvement in those with mild to moderate disease, but not severe disease.[43] Two children withdrew from the study because of worsening dermatitis.[43] Larger trials are ongoing.

Immunization and Childhood Diseases

Concerns have been raised about the effect of immunizations on atopic dermatitis. Analyses concluded that both natural infection and immunization protect against childhood atopic dermatitis. In a study of 2184 infants with atopic dermatitis and a family history of atopy, exposure to vaccines (diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b, hepatitis B, mumps, measles, rubella, varicella, bacille Calmette-Guérin, meningococci, and pneumococci) was not associated with increased risk of allergic sensitization to food or aeroallergens.[44] On the contrary, immunizations against varicella and pertussis and cumulative numbers of vaccine doses were inversely associated with eczema severity. With varicella, infection has a decreased odds ratio of 0.55 for development of atopic dermatitis.[45] Children who are infected with wild-type varicella zoster infection, as opposed to vaccine, who develop atopic dermatitis have fewer doctor visits for atopic dermatitis (odds ratio, 0.17). One study of measles vaccine (ROUVAX) compared with

placebo that included 12 infants 10 to 14 months old with atopic dermatitis showed improvement in clinical severity in 1 treated child; improvement of some serum markers was also noted.[46] Immunizations have not been found to worsen disease. In fact, exposure has been found to decrease the risk and severity of atopic dermatitis.

Ultraviolet Light

Ultraviolet (UV) light may be helpful for some patients, although this technique is less popular because of acceleration of photoaging and increased risk of skin cancer. A study of narrow-band UVB showed a statistically significant advantage when light therapy was accompanied by synchronous bathing in a 10% Dead Sea salt solution.[47] In one study, narrow-band UVB and medium-dose UVA1 dosed three times a week were equally effective.[48]

Pharmaceuticals

Antimicrobials

Use of antibiotics has not been found effective as treatment for atopic dermatitis.[49] However, bleach baths and mupirocin ointment, as discussed earlier, are tremendously helpful. A study of the effectiveness of pimecrolimus cream measured colonization of *S. aureus,* which correlated with more severe disease, in a cohort of patients whose disease did not respond to corticosteroids.[50] Antibiotics are useful for superinfection and when lesions are not responsive to corticosteroids because subclinical superinfection may be the cause. *Staphylococcus* species and group A beta-hemolytic streptococci are the most common organisms cultured.

Dosage for Superinfection

For superinfection of atopic dermatitis, consider the following: mupirocin or bacitracin ointment twice daily for 7 to 10 days; cephalexin, 250 mg four times daily for 7 days; or dicloxacillin, 250 mg four times daily for 7 days.

Consider herpesvirus superinfection in recalcitrant lesions. Smear or culture swab provides the diagnosis. For herpesvirus superinfection, consider the following: for herpes zoster, acyclovir, 800 mg orally five times daily for 7 to 10 days; for varicella-zoster, acyclovir, 800 mg orally four times daily for 5 days.

Dosage for Fungal Infection

Dermatophyte infections can contribute to head and neck lesions. In patients infected with *Candida albicans* or *Malassezia furfur,* ketoconazole, used topically or taken orally 200 mg twice daily for 10 days, may be helpful.[51]

Antihistamines

Antihistamines may be useful to reduce scratching. Oral antihistamines may be mostly useful for their sedative properties.[1] Doxepin cream can cause sedation if it is used over large areas of the body.

Dosage

Doses are as follows: doxepin cream 5%, a thin layer applied up to four times daily; diphenhydramine, 12.5 to 50 mg orally every 6 hours; hydroxyzine, 10 to 50 mg orally every 6 hours; or loratadine, 10 mg orally daily.

Topical Corticosteroids

The standard medical treatment of atopic dermatitis consists of topical corticosteroids. These drugs are typically used twice daily for up to 2 weeks during an acute flare and then once to twice daily on weekends to maintain remission. Because this disease is more common in young children, concerns arise that long-term use may suppress the hypothalamic-pituitary-adrenal (HPA) axis, cause growth retardation, and have other side effects. Despite these concerns, no other medication is as effective during an acute flare, and use during these times only does not appear to pose a risk.

For quick control of flares, consider using a higher-potency product and then reducing the strength for maintenance or switching down to an herbal preparation. Use only class IV and V corticosteroids on the face, axilla, groin, and intertriginous areas.[1] For children, use class III agents when a more potent agent is desired and titrate downward. For the eyelids, use a class V or VI agent for 5 to 7 days. Apply a thin layer directly after bathing, followed by emollient use. Ointments are generally recommended, although not in warm, humid climates, in which their occlusiveness can cause sweat retention dermatitis. Gels can be used for weeping lesions and on the scalp and bearded skin. A full list of potencies of topical steroids is available in Chapter 69, Psoriasis.

Dosage

Class I (superpotent): clobetasol ointment 0.05% twice daily (also available as a gel)
Class III (upper midstrength): triamcinolone 0.1% ointment twice daily
Class IV (midstrength): hydrocortisone valerate 0.2% ointment twice daily
Class V (lower midstrength): desonide 0.05% ointment twice daily
Class VI (mild): hydrocortisone 1% ointment twice daily

Precautions

Prolonged use of steroid creams can cause skin atrophy or acne, and prolonged use of potent steroids carries a risk of growth retardation in children.

> If systemic steroids are warranted, use in conjunction with an aggressive topical regimen and give as a 14-day taper to avoid a rebound flare.

Topical Immunomodulators

Tacrolimus ointment and pimecrolimus cream, inhibitors of calcineurin, are additional nonsteroid options for treatment of atopic dermatitis. These agents decrease T-cell activation and cytokine release while inhibiting mast cell and basophil degranulation. They have been studied largely as steroid-sparing agents for use after control of an acute flare to maintain remission. Investigators and clinicians were hopeful to find an agent to provide control without the risks of skin thinning and effects on the HPA axis.

After case reports of skin cancer and lymphoma with use of these agents appeared, the U.S. Food and Drug Administration issued a black box warning noting that although a causal relationship had not been established, these agents should be

used with caution. Continued study has not demonstrated an increased risk of malignancy, although longer-term safety studies are ongoing.[52] Patients with atopic dermatitis have an increased risk of lymphoma, and this risk increases with severity of disease. One study found a higher risk in patients treated with topical corticosteroids, and this risk rose with increasing potency and longer duration of use.[53] Avoid the use of topical immunomodulators in immunocompromised patients or in those with known neoplasm. In atypical atopic dermatitis, such as new onset in an adult, skin biopsy can rule out cutaneous T-cell lymphoma or other causes. Encourage sun protection to reduce photocarcinogenesis.

A meta-analysis of tacrolimus use in children found it safe and effective, with no statistical difference between tacrolimus 0.03% and 0.1% preparations and a good response compared with vehicle, 1% hydrocortisone acetate, and 1% pimecrolimus (odds ratio, 4.56, 3.92, and 1.58, respectively).[54] A Cochrane Review found pimecrolimus less effective than moderate and potent corticosteroids and 0.1% tacrolimus.[55] Pimecrolimus studied for prevention had a relapse rate of 9.9% in twice-daily use and 14.7% in daily use.[56]

Use creams as infrequently as possible to maintain remission. Typical use is twice daily for short-term use, no longer than 6 weeks, or intermittently. Tacrolimus used three times weekly is effective in children to maintain remission.[57] Use only on lesional skin and not with occlusive dressings. Use only in children who are older than 2 years old. Adverse effects include burning on application and photosensitivity.

Dosage

Tacrolimus 0.03% ointment is applied twice daily in patients older than 2 years, including adults with mild disease. For adults, tacrolimus 0.1% ointment is applied twice daily, or pimecrolimus 1% cream is applied twice daily.

Other Immunomodulators

Cyclosporine is helpful in patients with severe disease refractory to steroid use. However, cyclosporine should be used only by a provider experienced in its use.

Leukotriene inhibitors (e.g., montelukast) have not been shown to be particularly efficacious as monotherapy for atopic dermatitis, but they may reduce itching.

Therapies to Consider

Traditional Chinese Medicine

Several trials of traditional Chinese medicine herbal blends for atopic dermatitis showed promise. A Cochrane Review concluded that although the studies were small, they showed some evidence of effectiveness.[58] A five-herb concoction was studied in children with moderate to severe disease for 12 weeks, and although no significant difference was noted in clinical severity scores, the treatment group used one-third less corticosteroid and had significantly improved quality of life index scores at the end of treatment and 4 weeks later.[59]

Traditional Japanese Medicine (Kampo)

A case report on treatment with Kampo, traditional Japanese medicine, had color pictures showing resolution of flexural lichenification and is an excellent review of the likely immunomodulatory effects of this therapy.[60] A trial of Shiunko, an herbal mixture commonly used in Kampo for atopic dermatitis, lowered bacterial counts in the areas treated in 4 of 7 people.[61] A trial involving 95 patients using Kampo showed promise, with a moderate to marked effect in more than half and no effect in just 4 patients.[62]

Homeopathy

Homeopathic studies have largely not shown an effect of this therapy in atopic dermatitis, though one small study in children was promising. An open-label trial of 27 children using a homeopathic cream of Oregon grape root (*M. aquifolium*), pansy (*Viola tricolor hortensis*), and gotu kola (*Centella asiatica*) found complete resolution in 6 children and marked improvement in 16.[63]

Prevention Prescription

- Moisturize the skin.
  - Bathe in tepid or lukewarm water up to every day, followed by liberal application of emollients (petroleum jelly, virgin coconut oil, extra virgin olive oil, creams containing ceramide, or other greasy product) to lock in moisture.
  - Limit soap to use only as needed; use a mild, pH-balanced soap such as Dove, Aveeno, or Basis.
- Consider bathing in dilute bleach water (½ cup per tubful) twice weekly for 5 to 10 minutes to reduce staphylococcal colonization.
- Do not scratch! Pat, firmly press, or grasp the skin.
- Avoid triggers.
  - Humidify air in the winter.
  - Reduce exposure to dust mites if sensitive; avoid rugs in bedrooms, wet mop floors, use mattress covers, and launder bedclothes weekly in hot water.
  - Wear smooth, natural fibers that do not rub the skin.
  - Avoid fabric softeners and other chemicals in laundry detergent, use liquid detergent, and consider an extra rinse cycle.
- Discover ways to control emotional stress. Seek low-stress work environments. Mindfulness meditation, massage, or learning self-hypnosis may be helpful. Consider reading *Skin Deep* on www.grossbart.com.
- Pursue an antiinflammatory diet with frequent sources of omega-3 fatty acids such as cold-water fish, walnuts, and flaxseed. Drink green or Oolong tea.
- Consider essential fatty acid supplementation, adding docosahexaenoic acid and eicosapentaenoic acid 2 g daily if your fish intake is inadequate and gamma-linolenic acid in the form of borage oil, 500 mg daily, or evening primrose oil, 1 to 2 g daily.
- Pregnant women with strong history of atopy should consider taking *Lactobacillus rhamnosus* GG prenatally and while breast-feeding. Continue giving it to the infant until age 2 years. If you cannot breast-feed, consider hydrolyzed formulas for atopy prevention for at least the first 4 months of life.
- Consider the benefit from childhood immunizations and natural chickenpox (varicella) infection.
- Moderate amounts of sunshine may be useful and allow you to obtain vitamin D.

Therapeutic Review

Avoidance of Triggers

- Reduce exposure to known allergens. C-1
- Wear smooth, comfortable, breathable clothing. C-1

Improvement in Barrier Function

- Ceramide-containing creams, such as *EpiCeram* or *TriCeram,* have added benefit over other emollients. B-1
- Virgin coconut oil reduces *Staphylococcus aureus* colonization. B-1

Nutrition

- Avoid known food allergies. (The most common foods triggers of atopic dermatitis are egg, soy, milk, wheat, fish, shellfish, and peanut.) A-1
- Infants at high risk who cannot exclusively breast-feed should use hydrolyzed formula (broken down proteins) in the first 4 months of life. Examples of hydrolyzed formulas include Nutramigen LIPIL, Pregestimil, and Alimentum Advance. A-1
- Drink 3 cups of strong oolong tea daily. B-1

Mind-Body Therapy

- Support groups B-1
- Coping skill educational program B-1
- Psychotherapy B-1

Supplements

- Vitamin D_3: 1600 units daily B-1
- Vitamin E: 600 units daily B-2
- Docosahexaenoic acid/eicosapentaenoic acid: 2 to 4 g daily B-1
- Gamma-linolenic acid: 500 mg daily B-1
- *Lactobacillus rhamnosus:* 20 billion CFUs daily for an atopic mother prenatally and postnatally for prevention of atopic dermatitis in the infant B-1

Botanicals

- 2% Glycyrrhetinic acid (Atopiclair or others) applied three times daily A-1
- Topical formulations of *Hypericum perforatum* (St. John's wort), chamomile, rosmarinic acid, or Oregon grape root applied twice daily B-1

Other Creams

- Vitamin B_{12} 0.07% cream used twice daily B-1
- Coal tar preparations applied twice daily to chronic or lichenified lesions B-1

Pharmaceuticals

- Antihistamines
  - Doxepin cream: twice daily to affected areas B-2
  - Diphenhydramine: 12.5 to 50 mg orally every 6 hours B-2
  - Hydroxyzine: 10 to 50 mg orally every 6 hours B-2
  - Loratadine: 10 mg orally daily B-2
- Antimicrobials
  - Dilute bleach baths (½ cup per full bathtub) are recommended twice weekly for 5 to 10 minutes combined with mupirocin 2% intranasally 5 consecutive days each month to reduce *S. aureus* colonization. A-1
  - Consider ketoconazole, 200 mg twice daily for 10 days, for head or neck involvement. B-2
  - Consider skin culture for bacteria and herpes or empirical treatment for recalcitrant lesions. C-2
- Corticosteroids
  - Triamcinolone 0.1% ointment: twice daily for up to 2 weeks for flares, then up to twice daily on weekends to maintain remission A-2
  - Hydrocortisone 1% ointment: used on thin skin at higher risk for adverse events (face, neck, axilla) C-2
- Topical immunomodulators
  - Tacrolimus 0.03% ointment: twice-daily short-term use for patients older than 2 years old A-2
  - Tacrolimus 0.03% ointment: three times weekly to maintain remission in patients older than 2 years old B-2
  - Tacrolimus 0.1% ointment: twice-daily short-term use for patients older than 15 years old A-2
  - Pimecrolimus 1% cream: twice-daily short-term use B-2

KEY WEB RESOURCES	
Eczema and Sensitive-Skin Education: www.easeeczema.org	Patient education and support
KidsHealth: Kidshealth.org; search: eczema	Patient information on eczema for children
Eczema Awareness, Support, and Education (EASE) program: www.eczemacanada.ca	Clear information and downloadable brochures in multiple languages including, "But It Itches So Much!" (for children) and "Eczema: It's Time to Take Control"
Skin Deep: www.grossbart.com	Home of Skin Deep, Dr. Ted Grossbart's mind-body program for healthy skin that is available by free e-book
iHerb.com: www.iherb.com	Online source for difficult to find over-the-counter products at prices often lower than suggested retail price

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Chapter 69

Psoriasis

Apple A. Bodemer, MD

Pathophysiology and Clinical Background

Psoriasis is a chronic inflammatory skin disease characterized by abnormal differentiation and hyperproliferation of the epidermis. Clinically, it manifests as redness and scaling (Figs. 69-1 and 69-2). Psoriasis is fairly common, affecting approximately 2% of the general population. It is more common in white persons and has a bimodal age distribution, with peak onsets between 20 and 30 years and between 50 and 60 years.[1] The cause of psoriasis is multifactorial, with both genetic and environmental components. A family history can usually (but not always) be elicited. If one parent has psoriasis, the risk of a child's having the disorder is approximately 14%. This figure jumps to 41% if both parents have the disorder.[1] Several human leukocyte antigens (HLAs [histocompatibility antigens]) have been associated with psoriasis, including HLA-B13, HLA-B17, HLA-B27, HLA-Cw6, and HLA-DR7. The strongest connection lies with HLA-Cw6, which is associated with earlier-onset disease that is more difficult to treat. Finally, several genetic loci have been linked to the development of psoriasis. Currently, *PSORS1* is considered the major gene associated with psoriasis.[1]

Environmental factors implicated in triggering psoriasis or psoriatic flares are physical trauma (the isomorphic or Koebner phenomenon), infections (e.g., streptococcal pharyngitis), hypocalcemia, stress, and medications such as lithium, beta blockers, antimalarials, interferon (IFN), and rapid tapers of systemic corticosteroids. The effect of pregnancy on psoriasis is not consistent; half of women with psoriasis experience worsening during pregnancy, and half note improvement. Patients infected with human immunodeficiency virus (HIV) tend to have more severe disease, but the incidence of psoriasis is not higher in this population. Finally, rapid weight changes, alcohol consumption, and tobacco use have been associated with psoriasis, but these features have not clearly been shown to be risk factors.

The Koebner phenomenon is when skin trauma or irritation triggers a skin reaction such as a psoriatic plaque. Treatment of itching is important because scratching can trigger flares.

Clinically, psoriasis may manifest in several ways (Table 69-1). In addition to skin findings, nail abnormalities are often present. These include pits, oil slicks, subungual hyperkeratosis, and onycholysis. Nail psoriasis is thought to occur in up to 55% of patients with the disorder. In patients who also have psoriatic arthritis, however, the incidence of nail disease is 86%.[2]

Psoriatic arthritis affects approximately 10% of patients with psoriasis. Generally, skin lesions precede the joint disease by as long as 10 to 20 years; in approximately 10% to 15% of patients, however, the joint disease manifests first.[3] The five classifications of psoriatic arthritis are summarized in Table 69-2. Psoriatic arthritis can be extremely disabling and warrants more aggressive systemic treatment, such as methotrexate or the newer biologic immune response modifiers (see later discussion of systemic pharmaceuticals).

Although psoriasis was initially thought to be caused by abnormalities of keratinocytes, current research indicates that it is an autoimmune-mediated process driven by abnormally activated helper T cells. Activation of these T cells can occur through specific interactions with antigen-presenting cells (APCs) or through nonspecific superantigen interactions (i.e., guttate psoriasis triggered by streptococcal antigens). APC activation requires costimulatory signals. Table 69-3 summarizes the specific costimulatory interactions that are clinically relevant for treatment. Once activated, psoriatic T cells produce a type 1 helper T cell (Th1)–dominant cytokine profile that includes interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-alpha), IFN-gamma, and IL-8. These cytokines act to attract and activate neutrophils, which are responsible for much of the inflammation seen in psoriasis. Other factors leading to neutrophil recruitment and activation are complement split products (C5a) and leukotrienes (arachidonic acid metabolites from the 5-lipoxygenase pathway).[4]

FIGURE 69-1
Auspitz sign. Pinpoint bleeding areas where scale was lifted from psoriatic plaque. (From Weston WL, Lane AT, Morelli JG. *Color Textbook of Pediatric Dermatology.* 4th ed. Philadelphia: Mosby; 2007.)

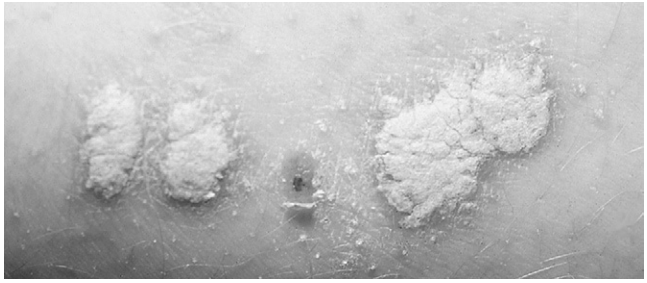

FIGURE 69-2
Psoriatic plaque. Note the sharp demarcation and silvery scale. (From van de Kerkhof PCM, Schalkwijk J. Psoriasis. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology.* 2nd ed. Philadelphia: Mosby; 2008.)

Integrative Therapy

Skin Care

Gentle skin care can help minimize pruritus and skin trauma and can thus prevent the Koebner phenomenon in psoriatic lesions. A helpful measure is bathing in cool to tepid water with gentle cleansers (e.g., Cetaphil soapless cleanser, Aquanil). Additionally, frequent and regular application of emollients, especially while the skin is still damp, will help keep psoriatic skin soft and more manageable. Natural oils such as avocado oil, almond oil, or olive oil can be very helpful and soothing. Colloidal oatmeal in the form of an emollient or bath (e.g., Aveeno) may also help soothe itching and irritation associated with psoriasis.

Oatmeal baths can be made by placing whole oats in a blender and grinding to a fine powder. Water is added to a half cup of the oat flour to make a lose slurry that can be added to a bath. A thicker paste can be made and patted onto psoriatic lesions as a poultice.

Phototherapy

Psoriasis typically improves over summer months, when exposure to ultraviolet radiation (UVR) is greater. People have been taking advantage of this response to UVR for many years. The advent of better-controlled exposure has allowed for more predictable clinical results.

Ultraviolet B

Ultraviolet B (UVB) consists of radiation with wavelengths between 290 and 320 nanometers (nm). UVB is known to decrease DNA synthesis and has immunosuppressive effects. Langerhans cells (the main APCs in the epidermis) are extremely sensitive to UVB, and exposure limits antigen presentation to T lymphocytes. UVB also stimulates keratinocytes to secrete various cytokines, which can further alter the immune response, as well as limit inflammation.[5,6] In 1980, narrow-band UVB (nb-UVB), with a wavelength between 308 and 313 nm, was found to be much more effective than full-spectrum UVB in the treatment of psoriasis.[7,8]

Dosage

Treatment protocols are based on determining a minimal erythema dose (MED), that is, the dose of UVB that elicits barely perceptible erythema. Once an MED is defined, treatments are started at approximately 70% to 75% of the MED and are given three times a week with the goal of maintaining minimally perceptible erythema. Clearance may require up to 30 treatments with broad-band UVB, but it can occur with only one treatment with nb-UVB.[9] Once the skin is clear, some practitioners simply stop phototherapy, but others recommend tapering UVB to a maintenance dose. No clearly defined guidelines exist for accomplishing the tapering.

Precautions

Potential short-term side effects of UVB include erythema, xerosis, pruritus, and higher frequency of herpes simplex outbreaks. Longer-term side effects consist of photoaging and, possibly, increased risk of skin cancers. The carcinogenetic risk of UVB appears to be much less than that associated with ultraviolet A (UVA) combined with psoralen (PUVA; see next section). One multicenter trial examining the risk of carcinogenesis with phototherapy could not find a direct relationship between UVB and nonmelanoma skin cancers.[10] Additionally, a newer study specifically examining the correlation between nb-UVB and skin cancer found no significant association.[11] This therapy is relatively young, however, and further studies will help define the potential long-term risks more definitively.

Ultraviolet A and Psoralen

UVA radiation alone is not effective for the treatment of psoriasis. However, when it is combined with a topical or systemic photosensitizing agent (e.g., psoralen), PUVA becomes a powerful tool for the treatment of psoriasis. Psoralens are furocoumarins found in a wide variety of plants, including lime, parsley, fig, and celery. Synthetic furocoumarins consist primarily of 8-methoxypsoralen (8-MOP) and 5-MOP (available in Europe). Psoralens can be taken orally or used topically. Once absorbed, these compounds incorporate into DNA strands and absorb photons in the

TABLE 69-1. Subtypes of Psoriasis

SUBTYPE	CHARACTERISTICS	ASSOCIATIONS
Chronic Plaque	Erythematous plaques with silvery scale Typically involving scalp, knees, elbows, low back, umbilicus, and gluteal cleft Pruritus variable Nail findings common	Most common; accounting for approximately 90% of all cases of psoriasis
Guttate	Diffuse salmon to red "droplike" papules and plaques with fine scale Typically involving trunk and extremities	Second most common type (2%) Most common in children and young adults Affecting children and young adults Associated with group A *Streptococcus* infections Tends to resolve with eradication of infection Possibly persistent in "strep" carriers Best prognosis for remission
Inverse	Affecting predominantly axillae, groin, and submammary area Less scale than in other types	Prone to secondary bacterial or yeast infections
Erythrodermic	Erythema with scaling over more than 80% of body surface area	Potential complications including high-output cardiac failure, renal failure, and sepsis
Pustular	Confluent pustules on an erythematous base von Zumbusch type: generalized with acute fever, chills, nausea, headache, and joint problems Annular type: subacute or chronic; systemic symptoms possible Acrodermatitis continua of Hallopeau: distal fingers; fingernails possibly floating away on lakes of pus, and permanent nail destruction common	Life-threatening Potential complications including high-output cardiac failure, sepsis, and hypercalcemia Systemic symptoms less common with Hallopeau type
Palmoplantar Pustulosis	Pustules of the palms and soles with yellow-brown macules	Commonly associated with sterile inflammatory bone lesions

TABLE 69-2. Classification of Psoriatic Arthritis

TYPE	CHARACTERISTICS	ASSOCIATIONS
Asymmetric Oligoarticular	Digits of the hands and feet affected first Inflammation of the flexor tendon and synovium occurring simultaneously Usually affecting fewer than five digits	"Sausage digit" (involvement of both DIP and PIP of one digit)
Symmetric Polyarthritis	Clinically identical to rheumatoid arthritis Possibly affecting hands, wrists, ankles, and feet Involvement of DIP Rheumatoid factor negative	Erosive changes seen on radiographs
DIP Arthropathy	Unique to psoriasis Affecting only 5%–10% More prominent in men	Nail involvement with chronic paronychia
Arthritis Mutilans	Osteolysis leading to telescoping of finger with "opera-glass" hand More common in early-onset disease More common in men	Osteolysis (dissolution of the joint) "Pencil-in-cup" deformity on radiographs
Spondylitis with or without Sacroiliitis	Occurring in 5% of patients with psoriatic arthritis More common in male patients Asymmetric involvement of vertebrae	Morning stiffness of lower back the most characteristic symptom

Data from Hammadi AA, Gorevic PD. *Psoriatic Arthritis.* www.emedicine.com/med/topic1954.htm. Accessed 28.08.06.
DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint.

TABLE 69-3. Important Antigen-Presenting Cell–T-Cell Costimulatory Interactions

MOLECULES PRESENT ON APC	MOLECULES PRESENT ON T CELL
Leukocyte function–association antigen-3	Interleukin-2
B7-1 (CD80) B7-2 (CD86)	CD28
Leukocyte function–associated antigen-1	Intercellular adhesion molecule-1

APC, antigen-presenting cell.

UVA range, (320 to 400 nm), thus causing DNA cross-linkage and, ultimately, cell cycle arrest. Additionally, psoralens can interact with reactive oxygen species to cause cell membrane damage.[12]

Dosage

The systemic dose is 0.6 to 0.8 mg/kg 1 to 3 hours before UVA treatment. The initial dose of UVA is commonly based on skin type but ideally should be determined by a patient's specific minimal phototoxicity dose (MPD). For a bath, the regimen is as follows: 15 to 20 minutes of immersion in 0.5 to 5.0 mg 8-MOP per liter of water followed by immediate UVA exposure. The topical dose is 0.01% to 0.1% 8-MOP as a cream, lotion, or ointment before UVA exposure.

Treatments are given two to four times a week, with no more than twice a week during dose changes to allow for appropriate evaluation of overdose. The dose may be increased by 30% if no erythema is noted at the next treatment. Doses should be held stable if minimal erythema is present. If evidence of burn is noted, therapy should be stopped until symptoms resolve.[12]

Precautions

Because psoralens persist for approximately 24 hours, patients must wear protective eyewear and practice sun avoidance with strict photoprotection. Oral psoralens can cause nausea and vomiting, sunburn, and persistent pruritus. These agents should be used extremely carefully or not at all in patients with liver or renal disease, because slower metabolism and excretion can lead to extremely prolonged photosensitivity.

The dose-related risk of skin cancer with PUVA therapy is well known. The risk particularly applies to squamous cell carcinoma and is greatest in fair-skinned people. Subsequent immunosuppressive therapy may lead to a further rise in the risk of squamous cell carcinoma.[13] The risk for development of basal cell carcinomas of the trunk or extremities is moderately higher. An association between PUVA and melanoma has also been identified. One study that examined melanoma diagnosed in patients 15 years after their first PUVA treatment found a higher than expected rate. Patients who received 250 or more treatments appeared to be at the highest risk.[14] More long-term studies are needed to clarify this issue.

Patients with severe psoriasis may use phototherapy along with other systemic therapies. One group found an increased risk of lymphoma in patients concomitantly treated with PUVA and methotrexate for at least 36 months. This risk was higher for those taking higher methotrexate maintenance doses.[10]

Climatotherapy and Balneophototherapy

Climatotherapy means to relocate, either permanently or temporarily, to a climate more favorable to treatment of a disease. *Balneophototherapy* is treatment with water and sun, usually in a spa setting. Dead Sea climatotherapy has long been touted as beneficial for patients with psoriasis. Patients visit resorts at the Dead Sea for 2 to 4 weeks and expose themselves to both the water and sun. One study of 740 German patients treated at the Dead Sea found a 70% complete clearance of symptoms after 4 weeks at one of the clinics.[15] Another study of 100 Danish patients found that symptoms of 75% were clear after 4 weeks, and 68% of those patients remained in remission 4 months later.[16] One proposed explanation for the success of this approach is that the elevation of 400 m below sea level and the thick haze present in the area increase the thickness of the atmosphere. This could attenuate shorter UVB wavelengths and allow a larger proportion of longer-wave UVB to reach the patients. Additionally, the water has a high mineral content. In vitro studies indicated that Dead Sea water has an antiproliferative effect on exposed cells.[17] In addition to the sun and water, these clinics and solariums offer patients an extended retreat from stressful lives; the relaxation likely plays a role in the outcomes as well.

Studies looking at the safety of this type of therapy have found increased actinic damage but not an increase in skin cancers when compared with Israeli patients with psoriasis who were treated by other means.[18,19] Nevertheless, recommending protection of exposed noninvolved skin is prudent.

Nutrition

Antiinflammatory Diet

Although no studies specifically evaluating the benefits of an antiinflammatory diet for psoriasis could be found, one group compared the effects of a low–arachidonic acid diet in patients with rheumatoid arthritis with those of a typical Western diet in a well-matched control group. The average arachidonic acid intake was 49 mg/day in the diet group and 171 mg/day in the control group. A significant positive correlation between arachidonic acid intake and disease activity was found.[20] Although major differences exist between rheumatoid arthritis and psoriasis, this study suggests that minimizing the consumption of proinflammatory substances may help improve inflammatory disease processes (see Chapter 86, The Antiinflammatory Diet).

Fish Oil

Rates of psoriasis and other inflammatory conditions are low in populations consuming high levels of fish oils rich in omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This observation led to laboratory investigations looking for potential mechanisms of action, as well as clinical studies of efficacy.[21] In vitro evidence supports the theory that omega-3 fatty acids should improve psoriasis by inhibition of the inflammatory cytokines IL-6 and TNF-alpha, as well as by decreasing levels of

leukotrienes. Collier et al[22] looked at the effect of consumption of oily fish compared with white fish on chronic plaque psoriasis. These investigators found that the people eating oily fish (6 oz/day for 6 weeks) had significant improvement in their Psoriasis Area and Severity Index score.[22]

Bittiner et al[23] conducted a double-blind placebo-controlled study of patients supplemented with 10 fish oil capsules (1.5 g EPA each) compared with 10 olive oil capsules for 12 weeks and found significantly less itching, scale, and erythema in the group treated with fish oil.

One randomized double-blind placebo-controlled study looked at 20 patients hospitalized for guttate psoriasis who had at least 10% body surface area involvement.[24] These patients were given intravenous infusions of either omega-6 solution or omega-3 solution (2.1 g EPA, 21 g DHA) for 10 days. Improvement from baseline was moderate for the omega-6 group (16% to 25% decrease in severity) and significant for the omega-3 group (45% to 76% decrease in severity). [24] Similar results were also found in another randomized double-blind placebo-controlled study also looking at intravenous infusion of a fish oil–based lipid emulsion in patients with chronic plaque psoriasis.[25] Other randomized and double-blind investigations did not find significant benefits.[26,27]

Some evidence indicates that fish oils can minimize side effects of other systemic therapies. Fish oils may help decrease triglyceride levels and improve cholesterol profiles in patients treated with retinoids.[28] Additionally, fish oils may help reduce the risk of nephrotoxicity associated with cyclosporine.[21]

Dosage

Doses vary depending on the source. Flaxseed, walnuts, and cold-water fish such as mackerel, lake trout, herring, sardines, albacore tuna, and salmon are all rich natural sources of omega-3 fatty acids.

Precautions

Some types of fish may contain high levels of mercury, polychlorinated biphenyls (PCBs), dioxins, and other environmental contaminants. Fish listed by the American Heart Association as having the highest mercury levels are shark, swordfish, tilefish, and king mackerel. PCBs are found in high concentrations in farmed salmon. Choosing wild-caught salmon, trimming fat before cooking, and avoiding overgrilling can help decrease exposure to PCBs. Dioxins can be found in various foods, and dioxin levels are much higher in freshwater fish than in ocean fish.

At doses greater than 3 g/day, fish oils can inhibit coagulation and potentially increase the risk of bleeding. Fish oils should be used carefully in patients taking other blood-thinning agents. Additionally, fish oils may decrease blood pressure and should be used carefully in patients already taking antihypertensives.[29]

Supplements

Zinc

Zinc has been considered a potential therapeutic option for patients with psoriasis. Some investigators have suggested that patients with psoriasis have decreased epidermal zinc levels.[30] McMillan and Rowe[31] compared plasma levels of zinc in 35 patients with psoriasis and in age- and sex-matched controls. These investigators did not find significant differences, but they did note a trend toward lower plasma zinc levels, independent of serum albumin and alkaline phosphatase levels, in patients with more extensive psoriasis.[31] Subsequent studies did not reproduce this finding, and no benefit has been found in clinical studies evaluating zinc supplementation.[32] Nevertheless, some clinicians who have used zinc supplementation for patients with psoriasis feel strongly that it can be beneficial for some patients.

Dosage

The recommended dietary allowance (RDA) is 15 mg/day of elemental zinc.

Precautions

Minor side effects include nausea, vomiting, and a metallic taste in the mouth. Taking more than 40 to 50 mg/day may raise the risk of copper deficiency. At even higher doses, zinc toxicity can manifest as watery diarrhea, irritation and erosion of the gastrointestinal tract, acute renal tubular necrosis, interstitial nephritis, and a flulike syndrome.

Inositol

Lithium is known to worsen psoriasis. Depletion of inositol is known to occur in people taking lithium. The role of inositol as a mechanism of action in bipolar disease is not completely clear, but supplementation of inositol for people taking lithium has been shown to reduce some of the side effects of lithium without diminishing its clinical usefulness. In 2004, Allan et al[33] conducted a randomized placebo-controlled cross-over study and found that Psoriasis Area and Severity Index scores were improved when patients taking lithium (300 to 1200 g/day) also took inositol (6 g/day) for 10 weeks. These investigators did not see a worsening of bipolar disorder, but this outcome was not formally evaluated in this study.[33]

Dosage

The dose is 6 g/day.

Precautions

Inositol appears to be safe. However, patients who have bipolar disorder should undergo close monitoring of their psychiatric state during inositol supplementation.

Topical Botanicals

Capsaicin

Itching is a common complaint in psoriasis. The neuropeptide substance P has been shown to be elevated in psoriatic skin.[34] This compound up-regulates the expression of adhesion molecules important in the activation and recruitment of leukocytes.[35] Additionally, substance P is known to elicit itching when it is applied to normal skin.[36] Capsaicin is an extract of chili peppers that acts by depleting substance P locally. A double-blind placebo-controlled study looking at the potential use of capsaicin four times daily for 6 weeks found that the treatment group trended to have better global improvement, greater pruritus relief, and a reduction in psoriasis severity scores. None of the differences in parameters, however, reached statistical significance.[37]

Dosage
The dose is 0.025% or 0.075% capsaicin cream, applied three or four times/day.

Precautions
Patients typically experience burning during initial applications. The burning disappears with consistent use. Patients must be careful to wash hands after application and to avoid rubbing capsaicin into their eyes.

Aloe Vera
Topical aloe extract seems to reduce the desquamation, erythema, and infiltration associated with psoriatic plaques. Results from controlled studies have been variable. One small study of patients with mild psoriasis compared the application of a 0.5% extract in hydrophilic cream three times a day for 4 weeks with a placebo and found improvement of psoriatic plaques in the treatment group.[38] Another double-blind placebo-controlled study with right-left comparison in 40 patients found a slightly better response in the placebo group.[39] Although aloe is very safe, topical sensitization can occur.

Glycyrrhetinic Acid (Licorice)
In the skin, cortisol is inactivated by the enzyme, 11beta-hydroxysteroid dehydrogenase. This enzyme is dramatically inhibited by glycyrrhetinic acid, a compound found in licorice. Through this mechanism, topical glycyrrhetinic acid has been shown to potentate the action of hydrocortisone.[40] Glycyrrhetinic acid is available in 1% and 2% formulations and appears to be safe when it is used topically. No studies have specifically investigated the use of this compound in psoriasis.

Systemic Botanicals

Curcumin
The active component of turmeric, curcumin, is known to inhibit proinflammatory pathways critical to psoriasis.[41] One study looked at patients who were given 500-mg capsules of a curcuminoid complex that contained 95% curcuminoids.[42] These patients were instructed to take three capsules three times a day for 12 weeks, followed by 4 weeks of observation. Only eight people completed the study. Although two had an excellent response, the very small sample size and the complicated nature of some of these patients' cases make the results difficult to interpret. Larger and better-controlled studies are needed.

Milk Thistle (Silybum marianum)
Although milk thistle has not been suggested to play a role in psoriasis treatment, this botanical has been purported to protect against the hepatotoxicity seen with methotrexate. Milk thistle has been shown to act as an antioxidant by scavenging free radicals and inhibiting lipid peroxidation. Investigators have also suggested that it may protect against DNA injury and increase hepatocyte protein synthesis.[43]

Dosage
The dose is 140 mg (70% silymarin) two or three times/day.

Precautions
Diabetic patients taking silymarin require careful monitoring of blood glucose because this botanical may cause hypoglycemia secondary to increased insulin sensitivity.[42]

Milk thistle can be protective against hepatotoxicity in patients using methotrexate to control psoriasis.

Topical Pharmaceuticals

Keratolytics
Keratolytics such as salicylic acid (2% to 10%), urea (up to 40%) and alpha-hydroxy acids (glycolic and lactic acids) are useful for decreasing the thickness of psoriatic plaques. Along with providing added comfort, thinner plaques allow for enhanced penetration of other topical agents.

Precautions
Salicylic acid should not be applied extensively on the body, especially in children. Systemic absorption can lead to salicylism, which is characterized by tinnitus, nausea, and vomiting.

Tar
Coal tar is created from the gasses produced during the distillation of coal. These are condensed and undergo ammonia extraction, resulting in a thick dark liquid. Coal tar contains 10,000 different chemical compounds, including polycyclic aromatic hydrocarbons, phenols, and nitrogen bases. Similar products that contain fewer carcinogenic compounds can be created from wood. Because of the large number of compounds available, determining a precise mechanism of action for tar is difficult. It does appear to have antiproliferative and antiinflammatory activities.[44,45]

Dosage
Patients should use 5% to 20% preparations.

Precautions
Use of tar in patients who are also treated with UV radiation has been shown to lead to a higher incidence of skin cancer. Other side effects are phototoxicity, contact allergy, irritant dermatitis, and acneiform eruptions.

Anthralin
Anthralin is a synthetic derivative of chrysarobin, which is found in Goa powder from the bark of the araroba tree of South America.[46] The mechanism of action is not well understood, but it has been shown to inhibit cell growth and promote cell differentiation.

Dosage
A 0.5% to 1% preparation is applied for 10 to 30 minutes, and is then washed off, once to twice daily.

Precautions
Irritation to normal skin can be minimized by protection with petrolatum or zinc oxide paste around psoriatic plaques. Anthralin is messy and can stain hair, skin, nails, clothing, and bedding a brownish to purplish color. The hair discoloration can be minimized by using neutral henna powder to coat the hair.

Calcipotriene (Dovonex)
Vitamin D receptors are present on many different cells, including keratinocytes and Langerhans cells. The bioactive form (1,25-dihydroxycholecalciferol) has been shown to inhibit

keratinocyte proliferation and promote keratinocyte differentiation.[47] Calcipotriene is a synthetic analogue of the natural active form of Vitamin D. It is locally metabolized very rapidly, thus leading to less interference with calcium metabolism.

Dosage
A 0.005% cream, ointment, or lotion is applied twice daily.

Precautions
Self-limited irritant dermatitis is the most common complaint. Photosensitivity can develop in patients who receive UVB after calcipotriene is applied. Hypercalcemia is the most significant potential risk, but this is not a problem as long as the dose is kept at less than the recommended 100 g/wk.[48]

> The benefits of phototherapy and topical vitamin D analogues in the treatment of psoriasis also warrant 25-hydroxyvitamin D serum screening to make sure adequate oral supplementation is provided to maintain levels between 40 and 60 ng/mL.

Tazarotene Gel
Tazarotene is a topical retinoid (vitamin A derivative) that can be applied once daily. It acts to increase differentiation of keratinocytes.

Dosage
A 0.05% or 0.1% gel may be used with a topical steroid.

Precautions
Local skin irritation and pruritus are common side effects. Tazarotene may be teratogenic, so it should be used extremely carefully by women of childbearing age.

Topical Steroids
Corticosteroids have antiinflammatory, immunosuppressive, and antiproliferative properties. These activities are mediated by alterations in gene transcription. The efficacy of an individual topical corticosteroid is related to its potency and its ability to be absorbed into the skin.

Dosage
See Table 69-4 for information on potencies of different topical steroids.

Precautions
Topical corticosteroids are associated with tachyphylaxis, which is decreased efficacy with continued use. Combining topical steroids with other topical medicaments minimizes this problem. Local side effects are more common with higher potency; they include skin atrophy, acne, and localized hypertrichosis. Systemic absorption can occur with frequent or long-term use over large areas and can cause side effects similar to those of oral steroids (e.g., hyperglycemia, adrenal suppression).

Systemic Pharmaceuticals

Methotrexate
Methotrexate is a folic acid antagonist. It blocks the formation of the building blocks needed for DNA synthesis and leads to cell cycle arrest. It also has immunosuppressive effects. Finally, methotrexate acts as a potent antiinflammatory by raising tissue adenosine levels.[49] Methotrexate is particularly useful in patients with psoriatic arthritis.

Dosage
Methotrexate comes as a 2.5-mg pill or as solutions of 2.5 or 25.0 mg/mL. Typically, a 5- to 10-mg test dose is given, and complete blood count and liver function values are measured 7 days later. A dose of 10 to 15 mg/wk is usually enough to control psoriasis. Methotrexate is given weekly either as a single dose or divided into three doses given 12 hours apart.[49]

Precautions
Multiple side effects are associated with methotrexate. The most common is gastrointestinal upset, and the most dangerous is pancytopenia. Both can be decreased by adding 1 mg of folic acid daily. Other significant concerns are hepatotoxicity, pulmonary fibrosis, induction of malignancy, and teratogenicity. The concern for induction of malignancy is much greater when methotrexate is combined with PUVA; the risk of skin cancer and lymphoma appears to be increased (see the earlier section on PUVA). These potential complications require frequent monitoring with complete blood count, as well as renal and liver function tests. Liver biopsy to evaluate for fibrosis is indicated after a cumulative dose of 1.5 to 2.0 g. Additionally, the dose needs to be adjusted if the creatinine clearance value is less than 50 mL/minute.

Cyclosporine
Cyclosporine was initially isolated from the soil fungus *Tolypocladium inflatum*. It inhibits IL-2 gene transcription and leads to decreased T-cell proliferation and activation. Cyclosporine also inhibits the transcription of various proinflammatory cytokines.[50,51] It is useful in all types of psoriasis, but because of its rapid effect, cyclosporine is particularly useful in widespread pustular or erythrodermic psoriasis.

Dosage
Treatment should start at 5.0 mg/kg/day and slowly taper by 0.5 mg/kg/day until the minimum dose required to prevent recurrences is reached.

Precautions
Potential side effects include renal dysfunction, hypertension, hypertrichosis, gingival hyperplasia, gastrointestinal upset, neurologic effects (headache, tremor, paresthesias), electrolyte imbalances, sleep disturbances, acneiform eruptions, hypertriglyceridemia, decreased seizure threshold, and bone marrow suppression. Monitoring consists of measurements of blood pressure, renal function parameters including urinalysis, complete blood count, liver function tests, and blood chemistry analysis including magnesium, potassium, and uric acid.

Because cyclosporine is metabolized by the cytochrome P-450 CYP3A4 enzyme system, it has many potential drug interactions. The clinician should review a complete medication and herbal list with each patient before cyclosporine therapy is initiated.

TABLE 69-4. Potencies of Topical Steroids

CLASS	BRAND NAME	GENERIC NAME
1: Superpotent	Clobex Lotion, 0.05%	Clobetasol propionate
	Cormax Cream/Solution, 0.05%	Clobetasol propionate
	Diprolene Gel/Ointment, 0.05%	Betamethasone dipropionate
	Olux Foam, 0.05%	Clobetasol propionate
	Psorcon Ointment, 0.05%	Diflorasone diacetate
	Temovate Cream/Ointment/Solution, 0.05%	Clobetasol propionate
	Ultravate Cream/Ointment, 0.05%	Halobetasol propionate
2: Potent	Cyclocort Ointment, 0.1%	Amcinonide
	Diprolene Cream AF, 0.05%	Betamethasone dipropionate
	Diprosone Ointment, 0.05%	Betamethasone dipropionate
	Elocon Ointment, 0.1%	Mometasone furoate
	Florone Ointment, 0.05%	Diflorasone diacetate
	Halog Ointment/Cream, 0.1%	Halcinonide
	Lidex Cream/Gel/Ointment, 0.05%	Fluocinonide
	Maxiflor Ointment, 0.05%	Diflorasone diacetate
	Maxivate Ointment, 0.05%	Betamethasone dipropionate
	Psorcon Cream, 0.05%	Diflorasone diacetate
	Topicort Cream/Ointment, 0.25%	Desoximetasone
	Topicort Gel, 0.05%	Desoximetasone
3: Upper Midstrength	Aristocort A Ointment, 0.1%	Triamcinolone acetonide
	Cutivate Ointment, 0.005%	Fluticasone propionate
	Cyclocort Cream/Lotion, 0.1%	Amcinonide
	Diprosone Cream, 0.05%	Betamethasone dipropionate
	Florone Cream, 0.05%	Diflorasone diacetate
	Lidex-E Cream, 0.05%	Fluocinonide
	Luxiq Foam, 0.12%	Betamethasone valerate
	Maxiflor Cream, 0.05%	Diflorasone diacetate
	Maxivate Cream/Lotion, 0.05%	Betamethasone dipropionate
	Topicort Cream, 0.05%	Desoximetasone
	Valisone Ointment, 0.1%	Betamethasone valerate
4: Midstrength	Aristocort Cream, 0.1%	Triamcinolone acetonide
	Cordran Ointment, 0.05%	Flurandrenolide
	Derma-Smoothe/FS Oil, 0.01%	Fluocinolone acetonide
	Elocon Cream, 0.1%	Mometasone furoate
	Kenalog Cream/Ointment/Spray, 0.1%	Triamcinolone acetonide
	Synalar Ointment, 0.025%	Fluocinolone acetonide
	Uticort Gel, 0.025%	Betamethasone benzoate
	Westcort Ointment, 0.2%	Hydrocortisone valerate
5: Lower Midstrength	Cordran Cream/Lotion/Tape, 0.05%	Flurandrenolide
	Cutivate Cream, 0.05%	Fluticasone propionate
	Dermatop Cream, 0.1%	Prednicarbate
	DesOwen Ointment, 0.05%	Desonide
	Diprosone Lotion, 0.05%	Betamethasone dipropionate
	Kenalog Lotion, 0.1%	Triamcinolone acetonide
	Locoid Cream, 0.1%	Hydrocortisone
	Pandel Cream, 0.1%	Hydrocortisone
	Synalar Cream, 0.025%	Fluocinolone acetonide
	Uticort Cream/Lotion, 0.025%	Betamethasone benzoate
	Valisone Cream/Ointment, 0.1%	Betamethasone valerate
	Westcort Cream, 0.2%	Hydrocortisone valerate
6: Mild	Aclovate Cream/Ointment, 0.05%	Alclometasone dipropionate
	DesOwen Cream, 0.05%	Desonide
	Synalar Cream/Solution, 0.01%	Fluocinolone acetonide
	Tridesilon Cream, 0.05%	Desonide
	Valisone Lotion, 0.1%	Betamethasone valerate
7: Lowest Potency	Hydrocortisone	
	Dexamethasone	
	Methylprednisolone	
	Prednisolone	

From The National Psoriasis Foundation: Potencies of topical steroids. www.psoriasis.org/treatment/psoriasis/steriods/potency.php.

Acitretin

Acitretin is an oral retinoid with antiproliferative and anti-inflammatory effects. It can reduce lymphocyte proliferation and decrease arachidonic acid metabolism, thus leading to decreased neutrophil chemotaxis. Acitretin has been especially useful for rapid control of pustular psoriasis.

Dosage

The dose is 10, 25, or 50 mg/day. Acitretin should be taken with food.

Precautions

Acitretin, like all retinoids, is highly teratogenic. It can cause drying of skin and mucous membranes, which some investigators have suggested may be improved by adding 800 units of vitamin E daily.[52] Decreased night vision may occur, as well as pseudotumor cerebri, especially if acitretin is given with tetracycline antibiotics. Arthralgias, myalgias, bony changes (hyperostosis), poor wound healing, and gastrointestinal symptoms are all potential side effects. Serum cholesterol and triglyceride values may be elevated in 25% to 50% of patients, who must be monitored throughout therapy. Liver transaminase values may be elevated in up to 33% of patients, but toxic hepatitis is very rare.[53,54]

Monitoring should include pregnancy tests, lipid measurements, liver function tests, complete blood count with platelets, renal function tests, and creatine phosphokinase concentrations.

Biologic Immune Response Modifiers

Biologic immune response modifiers are directed specifically at neutralizing cytokines and blocking costimulatory messages important for the activation of T cells (see Table 69-3).

Alefacept (Amevive) is a fusion protein that blocks the costimulatory signal between leukocyte function–associated antigen 3 (LFA-3) and CD2 needed for antigen-mediated T-cell activation. This agent is given as an intramuscular injection of 15 mg once weekly for 12 weeks. The injection schedule may be repeated after 12 weeks of observation. Alefacept is contraindicated in patients who have active infections or malignant diseases.

Etanercept (Enbrel) is a humanized chimeric monoclonal antibody to TNF-alpha. It is given subcutaneously as 50 mg once or twice weekly. It should not be given to patients who have an active infection or a personal or family history of multiple sclerosis.

Efalizumab (Raptiva) is a monoclonal antibody directed against CD11a (a component of LFA-1). It blocks the costimulatory interaction between LFA-1 and intercellular adhesion molecule-1 (ICAM-1), thus preventing T-cell activation. This medication can be self-administered as a subcutaneous injection of 1 to 4 mg/kg each week, with the weekly dose not to exceed 200 mg. Mild to moderate flulike symptoms may occur initially, but they tend to resolve after the first few treatments.

Infliximab (Remicade) is a monoclonal antibody that neutralizes TNF-alpha by binding to both soluble and transmembrane TNF-alpha. It induces apoptosis of TNF-alpha–expressing cells and inhibits other proinflammatory cytokines, thus leading to a decrease in keratinocyte proliferation. It is given intravenously at a dose of 5 mg/kg over 2 to 3 hours at weeks 0, 2, and 6 and then every 8 weeks. The development of antibodies is of concern and can result in infusion reactions. Infliximab should not be used in people with heart failure. In addition to regular careful monitoring (see later), patients taking infliximab must undergo additional screening for liver function.

Ustekinumab (Stelara) is a human monoclonal antibody that blocks both IL-12 and IL-23, which cause naive $CD4^+$ T cells to differentiate into types 1 and 17 helper T cells, key mediators in psoriasis. This agent is given as a subcutaneous injection at either 45 or 90 mg at weeks 0 and 4 and followed by one dose every 12 weeks. It appears to have efficacy and safety profiles similar to those of other biologics.[55] It is a very new medication, and we will learn more about its optimal use and safety as more studies are done.

All the biologic immune response modifiers require thorough baseline evaluation. This includes a history and physical examination (with special attention to liver, neurologic or cardiac disease, infection, and malignancy), complete blood count, chemistry screen with liver function tests, viral hepatitis screening, and screening for latent tuberculosis. Patients all require screening for tuberculosis annually and blood chemistry with liver function testing every 2 to 6 months. The exception is Alefacept, which requires this testing only at the beginning of each course and in patients with signs of liver damage. Alefacept also requires monitoring of $CD4^+$ T cell count at baseline and every 2 weeks. Efalizumab requires monitoring of complete blood count monthly for the first 3 to 6 months and then every 3 months thereafter. Both etanercept and infliximab require blood counts every 2 to 6 months. Patients are generally advised to have any necessary vaccinations before they begin treatment with the biologic immune response modifiers.[56]

Mind-Body Therapy

That patients with psoriasis experience greater stress as a consequence of their disease is well known. A large survey study including members of the National Psoriasis Foundation documented that psoriasis has profound emotional, social, and physical effects on quality of life.[57] Additionally, emotional factors—particularly stress—have been shown to have a strong correlation with onset and exacerbation of psoriasis.[58,59]

The mechanism of action for the effect of stress on psoriasis is beginning to be understood more clearly. Garg et al[60] found that the epidermal barrier is impaired by psychological stress. These investigators showed that injury to the epidermis promotes higher levels of keratinocyte growth stimulators, such as substance P and vasoactive intestinal peptide. Additionally, epidermal injury increases neural proliferation that, in turn, may stimulate Langerhans cell activity. These researchers suggested that psychological stress may change the level of tolerance for physical insult or may prolong epidermal recovery time. This effect could lower the threshold for disease initiation or interfere with treatment.[60]

Stress levels have also been found to affect treatment outcomes. Fortune et al[61] examined 112 patients with psoriasis before they started PUVA phototherapy and compared stress level with time to clearance of symptoms. These investigators

found that high-level worry was the only significant predictor of time taken for PUVA to clear psoriasis. Patients in the high-level worry group cleared 19 days later (1.8 times slower) than did patients in the low-level worry group. Severity of disease, rates of positive family history, and levels of alcohol intake at the onset of the study were not significantly different between the two groups.[61] This information suggests that improving stress levels may enhance results from more conservative or traditional therapies. Other studies looking at various psychogenic interventions supported this suggestion as well.[62,63]

Improving stress levels may enhance results from more conservative or traditional therapies.

Meditation

A small study found that patients who listened to a mindfulness meditation–based stress-reduction tape during PUVA or UVB therapy for psoriasis demonstrated significantly faster improvement than did patients who had no access to the tape. Clearance occurred 1 month earlier for the patients receiving UVB and the relaxation tape compared with the UVB-only group and 6 weeks earlier in the PUVA and relaxation tape group than in the PUVA-only group.[64] Another small study looked at symptoms of psoriasis as rated by dermatologists after treatment with 12 weeks of meditation (n = 5) or meditation plus imagery (n = 4) compared with controls (n = 9). A significant difference was noted between the treatment groups and the control group, but imagery did not yield more improvement than meditation alone.[65] The study was very small and had flaws; nevertheless, the results suggested that some patients may be able to decrease symptoms of psoriasis with meditation.

Hypnosis

A 3-month randomized blind controlled trial looked at the efficacy of active (suggestion of disease improvement) versus neutral (no mention of disease) hypnosis for the treatment of psoriasis in patients classified as highly or moderately hypnotizable. Although the groups were very small, highly hypnotizable patients showed significantly greater improvement regardless of their assigned treatment group. This observation suggests that patients who are highly hypnotizable may benefit from adding hypnosis to their treatment plan.[66]

Therapies to Consider

Traditional Chinese Medicine

According to traditional Chinese medicine (TCM), the main cause of papulosquamous disorders is an inadequate supply of nutrients to the skin. The inadequacies include external pathogenic wind-heat and wind-cold, accumulation of blood-heat resulting from dietary or emotional influences, qi stagnation and blood stasis from retention of pathogenic wind, damp, and heat, and yin deficiency of the liver and kidneys.[67]

Topical Preparations

Xu Yihou[67] discussed topical therapies only briefly in his text. He recommended combinations that emphasize gentle, nonirritating ointments used to decrease the scale and thickness of psoriatic plaques. An abundance of combination topical TCM preparations is available. Many actually contain corticosteroids, which would explain their efficacy.[68] Additionally, reports exist of contamination with heavy metals, toxins, and other pharmaceuticals. Such contamination can have significant adverse effects, as exemplified by the report of salicylate toxicity after the use of an herbal preparation containing oil of wintergreen over a large body area with occlusion.[69]

Systemic Herbs

A full description of all the Chinese herbs and combinations that can be useful for patients with psoriasis is beyond the scope of this chapter. Tse[70] reviewed clinical trials in both the English and Chinese literature that pertained to the use of Chinese herbal medicines for psoriasis from 1966 to 2001. He found only 7 poorly performed controlled trials but was also able to gain information from the 20 noncontrolled trials he identified. Of the 174 different herbs used in these trials, Tse specified 10 herbs that were commonly encountered and discussed their potential mechanisms of action. They were *Rehmannia glutinosa* (dried root), *Angelica sinensis* (root), *Salvia miltiorrhiza* (root), *Dictamnus dasycarpus* (root cortex), *Smilax glabra* (underground stem), *Oldenlandia diffusa* (whole plant), *Lithospermum erythrorhizon* (root), *Paeonia lactiflora* (root), *Carthamus tinctorius* (flower), and *Glycyrrhiza uralensis* (root).

Precautions

Many herbal preparations are not well regulated, and the risk of hepatotoxicity can be significant, either from the herbal components themselves or from contaminants.[71]

Acupuncture

As with the prescription of herbs, the acupuncture points used depend on the pattern of psoriasis. The main points discussed by Xi Yihou[67] focused on correcting blood-heat (BL18, BL23, BL12, and BL15) and wind-dryness from blood deficiency (BL17, BL19, BL12, BL13, and BL20). He also provided guidance on selecting points on the basis of location of the disease: LI4, LI11, TB6, and GB20 are useful for the scalp and arms; SP6, SP10, and GB34 treat the trunk, buttocks, or genital area; SP6, SP10, and ST36 treat lower limbs; and GV14, LI11, SP6, and SP10 are good for generalized lesions.

In a case series, 61 patients with psoriasis not responsive to more conventional therapies were treated with acupuncture.[72] After an average of 9 sessions (range, 1 to 15), 30 patients experienced complete or almost complete clearance of the skin lesions, 14 had two-thirds clearance, 8 experienced one-third clearance, and 9 had minimal or no improvement.[72]

One controlled clinical trial compared electrostimulated acupuncture with a sham procedure (described as "minimal acupuncture") in 56 patients with psoriasis.[73] No difference in response between the two groups was found.[73] Acupuncture without electrostimulation is used extensively in TCM, and this study was not designed to evaluate the potential benefit of plain needle acupuncture. Acupuncture is very difficult to study, and perhaps a more appropriate control would be to compare acupuncture performed on nontreatment points with acupuncture performed on points that are considered therapeutic.

Precautions

Acupuncture is quite safe, but because the needles are inserted into the skin, the Koebner phenomenon could potentially occur.[74] Clearly, more work is needed in this area if we are to gain a better understanding of its usefulness in the treatment of psoriasis.

> Assessment of traditional Chinese medicine (TCM) as a system is very difficult within a Western framework. The classification of disease in TCM is based on a different point of view, and because each patient is evaluated and treated individually with various combinations of herbs and acupuncture, creating standardized protocols to measure treatment outcomes is difficult.

Homeopathy

Like TCM, the system of homeopathy looks at psoriasis as the local expression of a systemic disturbance. Each patient is evaluated individually, and treatments are given on the basis of a constitutional approach. Because each patient is viewed as having a unique imbalance, the specific remedy chosen depends greatly on the patient. The practitioner must be well trained and have a deep understanding of homeopathy. Certification is not uniformly required, so one should look for practitioners who are accredited by one of the following organizations: Council for Homeopathic Certification (CHC), American Board of Homeotherapeutics (ABHt), Homeopathic Academy of Naturopathic Physicians (HANP), and North American Society of Homeopaths (NASH).

Precautions

With homeopathic treatments, patients may experience an exacerbation of symptoms before resolution. This exacerbation is known as a healing crisis.

Prevention Prescription

- We currently do not have a way to prevent psoriasis. Although some situations are known to exacerbate psoriasis, flares are often unpredictable. Some things patients with psoriasis can do include the following:
  - Maintain a balanced lifestyle.
  - Minimize stress.
  - Maintain a stable weight.
  - Avoid alcohol overuse.
  - Avoid tobacco.
  - Eat a well-balanced diet.
  - Treat skin infections early.
  - Avoid medications known to exacerbate psoriasis (i.e., lithium, beta blockers, antimalarials, interferon, and rapid tapering of systemic corticosteroid dosage).

Therapeutic Review

General Measures

- Gentle skin care: Avoid hot water for bathing and use gentle cleansers and emollients and colloidal oatmeal. A1

Phototherapy

- Narrow-band ultraviolet B or ultraviolet B A2
- Ultraviolet A alone or with psoralen (PUVA) A2
- Climatotherapy and balneophototherapy B2

Nutrition and Supplements

- Antiinflammatory diet: See Chapter 86, The Antiinflammatory Diet. C1
- Fish oil or oily fish: This is also useful as an adjuvant to decrease side effects of systemic retinoids and cyclosporine. Consider 2 to 3 g/day. B2
- Zinc: No good evidence has indicated a benefit in psoriasis; however, some clinicians do report a benefit. The dose is 15 to 30 mg/day. C2
- Inositol: This may be useful in patients with lithium-induced psoriasis. The dose is 6 g/day, with monitoring of psychiatric disease in patients with bipolar disorder. B2

Topical Botanicals

- Capsaicin for itching: A 0.025% or 0.075% cream is applied three or four times/day. Patients may experience stinging or burning during initial applications. A2
- Aloe vera: This may help decrease scaling and redness. C1
- Glycyrrhetinic acid 1% to 2% formulation: This may enhance the effect of topical steroids by inhibiting their degradation. C1

Systemic Botanicals

- Curcumin: The effective dose is unclear. One study looked at 150 mg three times a day. C1
- Milk thistle: The dose is 140 mg (70% silymarin) two to three times/day. It is best used as a hepatoprotective agent in patients taking hepatotoxic medications. C1

Topical Pharmaceuticals

- Keratolytics, to decrease scale and plaque thickness:
  - Salicylic acid (2% to 10%) twice daily A2
  - Urea (up to 40%) twice daily A2
  - Alpha-hydroxy acids (glycolic and lactic acids) twice daily A2
- Tar: 2% to 20% preparations A2

Continued

- Anthralin: 0.5% to 1% preparation applied for 10 to 30 minutes once or twice daily, to protect normal skin from irritation 
- Calcipotriene (Dovonex): 0.005% cream, lotion, or ointment twice daily, limited to no more than 100 g/week 
- Tazarotene gel (Tazorac): 0.05% to 1% gel applied at bedtime 
- Topical steroids: See Table 69-4. Clinician should pay attention to the location treated and watch for side effects. 

Systemic Pharmaceuticals

- Methotrexate: 10 to 15 mg/week; single weekly dose or divided into three doses given 12 hours apart 
- Cyclosporine: started at 5.0 mg/kg/day, with dosage tapered by 0.5 mg/kg/day to the lowest required dose 
- Acitretin (Soriatane): 10, 25, or 50 mg daily 
- Biologic immune response modifiers:
  - Alefacept (Amevive): 15 mg/week intramuscularly for 12 weeks 
  - Etanercept (Enbrel): 50 mg once or twice a week subcutaneously 
  - Efalizumab (Raptiva): 1 to 4 mg/kg once a week subcutaneously 
  - Infliximab (Remicade): 5 mg/kg over 2 to 3 hours intravenously at weeks 0, 2, and 6 and then every 8 weeks thereafter 
  - Ustekinumab (Stelara): 45 or 90 mg as a subcutaneous injection at weeks 0 and 4 and then every 12 weeks thereafter 

Mind-Body Therapy

- Meditation: Great for stress reduction or minimization 
- Hypnosis: Most potential benefit for hypnotizable patients 

Therapies to Consider

- Traditional Chinese medicine: Please see the text *Dermatology in Traditional Chinese Medicine*, by Xu Yihou,[67] for more detailed and complete information on and understanding of traditional Chinese medicine. 
- Homeopathy 

KEY WEB RESOURCES

Information About Traditional Chinese Medicine Practitioners

National Certification Commission for Acupuncture and Oriental Medicine: www.nccaom.org

American Academy of Medical Acupuncture: www.medicalacupuncture.org

Information About Homeopathic Practitioners

Council for Homeopathic Certification (CHC): www.homeopathicdirectory.com

American Board of Homeotherapeutics (ABHt): http://homeopathy.org/specialty-board.html

Homeopathic Academy of Naturopathic Physicians (HANP): www.hanp.net

North American Society of Homeopaths (NASH): www.homeopathy.org

General Web Sites for Psoriasis

National Psoriasis Foundation: www.psoriasis.org

Mayo Clinic: www.mayoclinic.com/health/psoriasis/DS00193

American Academy of Dermatology: http://www.aad.org/education-and-quality-care/medical-student-core-curriculum/psoriasis/

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Chapter 70

Urticaria

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Pathophysiology

Urticaria, also known as hives, is a common problem affecting approximately 20% of the general population at some point in their lives. It is characterized by wheals—discrete areas of swelling, erythema, and pruritus that are often surrounded by a pale halo. Individual lesions typically come and go over the course of 24 hours, but recurrent crops can appear for weeks. *Acute urticaria* refers to outbreaks of wheals occurring on at least 2 days a week for up to 6 consecutive weeks. When the process lasts for 6 weeks or longer, it is considered *chronic urticaria.* Patients who have less frequent outbreaks are classified as having recurrent urticaria.[1] The skin findings and symptoms of urticaria are the result of increases in inflammatory and vasoactive mediators such as histamine, prostaglandins, leukotrienes, proteases, and cytokines. These mediators are primarily found in mast cells and basophils. Although the main physiologic event is mast cell degranulation, any mechanism that elevates these mediators can result in urticaria.

Mast cell degranulation can occur through both immunologic and nonimmunologic pathways. Immunologic mechanisms include allergic mast cell degranulation, which is a type I hypersensitivity process elicited by antigen-mediated cross-linking of immunoglobulin E (IgE) receptors. Additionally, autoantibodies either to IgE or to the high-affinity IgE receptor (FceRI) can bind to mast cells and result in degranulation.

Nonimmunologic processes cause degranulation without interacting with the IgE receptor. This category involves agents that can directly bind to mast cells to elicit degranulation (e.g., opiates, radiocontrast media), as well as other compounds that can induce the production of factors that bind to other receptors on the mast cell to cause degranulation. C1 esterase inhibitor deficiency can lead to higher levels of mediators important in urticaria. This defect causes uninhibited activation of the complement system that leads to an increase in bradykinin, which is a vasoactive inflammatory mediator.[2] Some compounds, such as aspirin, can alter the balance of prostaglandin and leukotriene synthesis, and others, including nettle plants, can directly implant vasoactive mediators into the skin.[3]

Determining the causative factor in a case of urticaria is often very frustrating. No specific origin is ever determined in 50% to 80% of patients. The most commonly implicated causes of acute urticaria are infections (especially viral infections of the upper respiratory tract), drugs (such as penicillins, sulfonamides, salicylates, nonsteroidal antiinflammatory drugs, and opiates), and foods (particularly shellfish, fish, eggs, cheese, chocolate, nuts, berries, and tomatoes). Chronic urticaria can be caused by these same agents but is more likely to be secondary to physical stimuli (e.g., dermatographism, pressure, vibration, heat, cold, exercise, sun, water), stress, autoimmune diseases (most commonly thyroid disorders), and other chronic medical diseases, such as connective tissue disease, cryoglobulinemia or cryofibrinogenemia, rheumatoid arthritis, amyloidosis, and cancer (Table 70-1).[1]

The most important factor in a good evaluation is the history. Thorough questioning may help patients recognize associations between stimuli and symptoms. Detailed diaries of a patient's activities, exposures, and ingestants can be invaluable in helping identify an association with urticarial outbreaks. Random screening laboratory tests have proved to be of little value.[4] In selected patients, however, laboratory investigations directed by the history and physical findings may be considered. The tests may include stool examination for ova and parasites, antinuclear antibody titer, screening for hepatitis B and C, thyroid function and thyroid antibody measurements, complete blood count with differential, and, possibly, an age-directed screen for malignant disease.[5]

Understanding the difference between urticaria and urticarial vasculitis is important. Urticarial vasculitis looks identical to other forms of urticaria, but individual lesions typically last for more than 24 hours and may be purpuric. Patients

TABLE 70-1. Histamine-Rich and Histamine-Releasing Foods

Histamine-Rich Foods	Avocados Fermented drinks Cheese Emmenthal Harzer Gouda Roquefort Tilsiter Camembert Cheddar Fish Anchovies Mackerel Herring Sardines Tuna Processed meat Ham Salami Sausage Jams and preserves Sauerkraut Sour cream Spinach Tomatoes Vinegar Yeast extract Yogurt
Histamine-Releasing Foods	Alcohol Bananas Chocolate Eggs Milk Some nuts Papaya Shellfish Strawberries Tomatoes

Data from Wantke F, Gotz M, Jarisch R. Histamine-free diet: treatment of choice for histamine-induced food intolerance and supporting treatment for chronic headaches. *Clin Exp Allergy.* 1993;23:982–985.

often complain more of burning than of itching.[6] Additionally, systemic symptoms such as arthralgia, gastrointestinal pain or a digestive disturbance, pulmonary obstructive disease, or renal disease may be present.[7] Urticarial vasculitis has been associated with connective tissue diseases (most commonly systemic lupus erythematosus), infections (viral hepatitis), and, rarely, with medications or hematologic disorders. The evaluation and treatment of urticarial vasculitis are beyond the scope of this chapter.

Integrative Therapy

General Principles

When a cause of urticaria is recognized, treatment can be as simple as avoiding the causative agent. In many cases of urticaria, however, the trigger is never identified. Even if the trigger is known, some patients may be unable to avoid the reaction. In these situations, many options are available for the management of urticaria.

The patient must be informed that a causative agent may never be found and that urticaria can be a chronic disease. He or she should understand that the skin reaction itself is not dangerous but is often very frustrating and difficult to live with. Chronic idiopathic urticaria can be a very unsatisfying disorder to manage, and the health care practitioner may become easily frustrated with the patient. Practitioners must not let this happen and must be open and supportive of the patient, with the recognition that urticaria is most frustrating for those who live with it.

General conservative measures can increase comfort during an exacerbation. They include staying in a cool, calm environment, wearing loose, comfortable clothing, and taking lukewarm to cool baths with added baking soda, cornstarch, or colloidal oatmeal (Aveeno). Many topical preparations can help calm the itching associated with urticaria, including menthol-containing products, aloe, and topical steroids.

Nutrition

Dietary Limitations

In the setting of acute urticaria without an inciting agent after ingestant and activity diaries have been analyzed, trying an elimination diet may be useful (see Chapter 84, Food Intolerance and Elimination Diet). Although food is a rare cause of chronic urticaria (approximately 1% of cases), it may still be helpful to try eliminating histamine-rich and otherwise antigenic foods from the affected patient's diet (see Table 70-1).[8] An Italian research group evaluated patients with chronic idiopathic urticaria before and after a 3-week, low-histamine, hypoallergenic diet. Although their sample size was small, these investigators did find significant decreases in both symptoms and plasma histamine levels after the low-histamine diet ($P = .05$).[9]

Antiinflammatory Diet

Research into the role of an antiinflammatory diet in patients with urticaria is lacking. Intuitively, it seems that if general inflammation can be minimized, urticaria—which is driven by inflammatory mediators—should improve. However, many antiinflammatory diets focus on foods rich in omega-3 fatty acid, including fish and nuts, which are known to cause or exacerbate urticaria in some patients. This type of diet should be tried only in patients who have already determined that their urticaria is not exacerbated by the recommended foods (see Chapter 86, The Antiinflammatory Diet).

Botanicals

Many different botanicals have been reported to be useful in the treatment of urticaria. They vary with sources, including canthaxanthin, field scabious, Japanese mint, kudzu, peppermint, alfalfa, bilberry extract, cat's claw, chamomile, echinacea, ginseng, licorice, nettle, yellow dock, and sarsaparilla. Many of these remedies have no evidence of efficacy from controlled studies. This section focuses only on the botanicals for which at least some in vitro evidence supports potential mechanisms of action to explain their possible benefit for patients with urticaria.[10]

Quercetin

The bioflavonoid quercetin can be found in many foods, including red wine, black tea, green tea, onions, apples, berries, citrus fruit, and brassica vegetables. Its antiinflammatory effects are thought to be mediated by inhibition of leukotriene and prostaglandin synthesis, as well as by inhibition of histamine release from mast cells and basophils.[10,11] Although theoretically quercetin should help ameliorate symptoms of urticaria, no studies looking specifically at its use in urticaria could be found.

Dosage

The dose is 400 mg by mouth twice daily before meals.

Precautions

None are known.

Quercetin works by stabilizing mast cells, and butterbur inhibits histamine and leukotrienes. These botanicals may work synergistically on the allergic type of reaction seen in urticaria.

Butterbur (Petasites hybridus)

Butterbur lowers serum levels of histamine and leukotrienes.[12] It also decreases priming of mast cells in response to contact with allergens.[13] One study found butterbur to be as effective as cetirizine (Zyrtec) for allergic rhinitis, without sedation.[14] No studies have been conducted specifically on the use of butterbur in urticaria. Because of its positive mechanism of action on the mediators of this condition, however, butterbur should be considered in those patients who are intolerant of the sedating side effects of antihistamines.

Dosage

The dose is 50 to 100 mg of extract twice daily with meals (extract should be standardized to contain a minimum of 7.5 mg of petasin and isopetasin).

Precautions

The major concern with butterbur is its hepatotoxic pyrrolizidine alkaloid content. This herb should not be used in patients with liver disease, and liver function parameters should be monitored in any patient who uses it over a long period.

Sarsaparilla

The sarsaparilla root contains quercetin. Please see the earlier section on quercetin for more details.

Dosage

The dose of dried root is 1 to 4 g or 1 cup of tea three times/day. The dose of liquid extract (1:1 in 20% alcohol or 10% glycerol) is 8 to 15 mL three times/day.

Precautions

Gastrointestinal irritation or temporary kidney impairment may occur when sarsaparilla is used in excessive doses.

To prepare sarsaparilla tea, simmer 1 to 4 g of dried sarsaparilla in 8 to 12 oz of water for 5 to 10 minutes.

Stinging Nettle (Urtica dioica)

The leaves of the stinging nettle contain flavonoids, including quercetin, rutin, and kaempferol. Please see the earlier section on quercetin for more details.

Dosage

The dose is 300 mg three times/day (up to seven times/day).

Precautions

Possible side effects include gastrointestinal complaints, sweating, diarrhea, and rash. Stinging nettle may worsen glucose control in patients with diabetes, lower blood pressure, and act as a diuretic.[15]

Peppermint

Luteolin-7-orutinoside from the peppermint leaf may inhibit histamine.[16] Additionally, menthol volatile oil found in peppermint is useful as a soothing topical preparation for itchy skin.

Dosage

The dose of peppermint oil is 0.2 to 0.4 mL three times/day between meals. Enteric-coated tablets are available.

Precautions

Topical use of peppermint oil can cause contact dermatitis and hives. Oral peppermint can relax the gastroesophageal sphincter and possibly worsen symptoms of gastroesophageal reflux disease. Some people have peppermint sensitivity leading to burning mouth syndrome or pruritus ani. Other side effects of peppermint that may be seen at very high doses are cramping, diarrhea, drowsiness, tremor, muscle pain, slow heart rate, and coma. Additionally, peppermint oil appears to inhibit several cytochrome P-450 enzymes, thus resulting in several potential drug interactions. Pure menthol is toxic and should never be taken internally.

Menthol-Containing Products for Topical Use

- Aveeno Skin Relief Moisturizing Lotion: menthol and colloidal oatmeal
- Sarna Anti-Itch Lotion: 0.5% menthol and 0.5% calamine
- Gold Bond Medicated Body Lotion: 0.15% menthol (Extra Strength has 0.5% menthol)
- PrameGel: 0.5% menthol and 1% pramoxine
- Watkins Menthol Camphor Ointment: 2.8% menthol and 5.3% camphor
- Eucerin Itch-Relief Spray: 0.15% menthol

Ginkgo biloba

Ginkgo biloba contains ginkgolides, which are strong inhibitors of platelet-activating factor. Some early evidence indicates that platelet-activating factor may be implicated in some cases of cold-induced urticaria.[17] No studies have looked at the use of *Ginkgo biloba* in urticaria, but this botanical may be useful in some patients with cold-induced urticaria.

Dosage

The dose is 120 mg/day of standardized extract.

Precautions
Because of its antiplatelet activity, *Ginkgo biloba* may potentiate other anticoagulants, and concomitant use requires extreme care. Other side effects may include gastrointestinal upset and dizziness.

Valerian Root
Valerian has long been used as an anxiolytic and may be useful in patients whose urticaria is induced by high levels of emotional stress. No studies have specifically looked at this use of valerian.

Dose
The dose is 200 to 300 mg/day for generalized anxiety.

Precautions
No known contraindications exist. Possible side effects may include upset stomach, headache, and itching.

Pharmaceuticals

Antihistamines
The four known histamine receptor subtypes are H_1, H_2, H_3, and H_4. H_1 receptors are found throughout the body and are involved in evoking pain and pruritus, vascular dilatation, vascular permeability, bronchoconstriction, and stimulation of cough receptors. H_2 receptors are widely distributed as well and have functions similar to those of the H_1 receptors, with increased activity in the gastrointestinal system leading to higher secretion of gastric acid and mucus. In allergic processes, H_2 receptors act indirectly by altering the cytokine milieu. H_3 and H_4 receptors have been described, and their expression appears to be limited to neural and hematopoietic tissues, respectively.[18]

Antihistamines are the mainstays of treatment for patients with urticaria. Pharmacologic control is typically initiated with H_1-receptor antagonists. These agents can be broken down into the first-generation, more sedating drugs (chlorpheniramine, diphenhydramine, hydroxyzine, and promethazine) and the newer, less sedating medications (fexofenadine, cetirizine, loratadine). Because additional factors are involved in the development of urticaria, antihistamines may not completely control symptoms, but they can be expected to improve symptoms in most patients. Antihistamines should be used on a regular basis, rather than as needed, to reduce inflammation and prevent symptom development.[19]

Many studies of the various antihistamine medications showed that efficacy is equivalent for the sedating and nonsedating classes.[20,21] No specific drug works consistently better, but some patients may have a better response to one than to another. If one agent does not adequately control symptoms, switching medications or adding a second antihistamine is appropriate. In fact, combining two nonsedating agents is not an uncommon practice and can be very useful.[22] Additionally, some patients may have good response to a combination of H_1 and H_2 antagonists.[23,24]

The tricyclic antidepressant doxepin has potent antihistamine properties that make it useful for patients with chronic urticaria.[25] Doxepin is very sedating and therefore is best used either in patients who have symptoms primarily at night or in combination with nonsedating antihistamines during the day.[26]

Dosage of First-Generation H_1-Receptor Antagonists
The dose of hydroxyzine is 50 mg at bedtime or up to four times/day. The dose of diphenhydramine is 25 to 50 mg every 6 to 8 hours. For chlorpheniramine, the dose is 4 to 8 mg twice daily. The dose of promethazine is 12.5 to 25 mg every 6 to 8 hours.

Dosage of Second-Generation H_1-Receptor Antagonists
The dose of loratadine (Claritin) is 10 mg daily or twice daily. The dose of fexofenadine (Allegra) is 60 to 180 mg daily or twice daily. For cetirizine (Zyrtec), the dose is 10 mg daily or twice daily.

Dosage of H_2-Receptor Antagonists
The dose of ranitidine (Zantac)is 150 to 300 mg twice daily. For famotidine (Pepcid), the dose is 20 to 40 mg one or twice daily. The dose of cimetidine (Tagamet) is 200 to 400 mg once or twice daily.

Dosage of Doxepin
The dose of doxepin is 10 to 75 mg, taken at bedtime.

Precautions
The possible side effects of first-generation H_1-receptor antagonists include central nervous system depression, cardiac arrhythmias, electrolyte imbalance, dry mouth, constipation, blurred vision, dysuria, and drug interactions.

Second-generation H_1-receptor antagonists have no significant adverse effects. Loratadine may interact with some antidepressant medications.

The side effects of H_2-receptor antagonists are generally mild and reversible. Common side effects include constipation, diarrhea, fatigue, headache, insomnia, muscle pain, nausea, and vomiting. Cimetidine has some antiandrogenic activity, and high doses may rarely lead to breast enlargement in men or impotence. Cimetidine is an H_2 blocker that is typically used to block stomach acid, but it can be tried in recalcitrant urticaria. Its use in urticaria is considered off-label.

Doxepin is extremely sedating and has a potential for significant drug interactions. Other possible side effects are cardiac conduction disturbances (QT prolongation), orthostatic hypotension, and anticholinergic effects (dry mouth, blurry vision, constipation, urinary retention).

The tricyclic antidepressant doxepin has potent antihistamine properties that make it useful for patients with chronic urticaria.

Leukotriene Inhibitors
Leukotrienes are secondary inflammatory mediators in the pathogenesis of urticaria. Inhibitors of these compounds include zafirlukast, montelukast, and zileuton. These agents are used successfully in asthma and, theoretically, should work for chronic urticaria as well. Case reports have shown somewhat mixed results.[27,28] These agents are most useful when they are combined with traditional histamine receptor antagonists.[26]

Dosage
The dose of zafirlukast (Accolate) is 20 mg twice daily. For montelukast (Singulair), it is 10 mg daily. The dose of zileuton (Zyflo) is 600 mg up to four times/day.

Precautions
Use these agents cautiously in patients with liver disease, and consider potential drug interactions.

Corticosteroids
Corticosteroids are very effective for rapid resolution of urticarial symptoms. Because side effects can be significant, the use of these drugs should be limited to occasional short, tapering dosages for severe exacerbations. These agents should be used cautiously and sparingly, with reliance on other therapies for maintenance control. Short, rapidly tapered dosages of corticosteroids are generally safe and well tolerated, but repetitive tapered dosages or long-term use can lead to significant side effects and complications.

Dosage
The dose of prednisone is 60 mg/day for 2 to 3 days, then tapered over 1 to 2 weeks.

Precautions
Common side effects include euphoria or depression, gastrointestinal distress, hypertension, sodium and fluid retention, impaired wound healing, higher risk of infection, osteoporosis, and skin atrophy. Growth retardation may occur in children. More serious side effects are adrenocortical insufficiency, cataracts, glaucoma, Cushing syndrome, hyperglycemia, and tuberculosis reactivation. Additionally, many potential drug interactions are associated with corticosteroids.

Cyclosporine
Cyclosporine is a strong immune suppressant that can be useful for patients with severe debilitating urticaria that has been recalcitrant to other therapies. It blocks the transcription of interleukin-2, which is required for T-cell activation. Among other effects, cyclosporine blocks the release of histamine from mast cells. Side effects are severe and significant, so appropriate monitoring is essential. Long-term treatment is not ideal, although some patients may require long-term low-dose therapy. Fortunately, many patients experience a period of improvement or even remission after 4 to 12 weeks of treatment.[29]

Dosage
Many dosage regimens have been described. All use cyclosporine at does at or less than 5 mg/kg/day for various durations. One regimen described specifically for chronic and debilitating urticaria is as follows: 3 mg/day divided into two doses for 6 weeks, followed by 2 mg/kg/day divided into two doses for 3 weeks, followed by 1 mg/kg/day divided into two doses for 3 weeks.[30]

Precautions
Cyclosporine is contraindicated in patients with uncontrolled hypertension, severe renal disease, serious infections, or a current or prior history of malignant disease.

Potential side effects include renal dysfunction, hypertension, hypertrichosis, gingival hyperplasia, gastrointestinal upset, neurologic effects (headache, tremor, paresthesias), electrolyte imbalances, acneiform eruptions, hypertriglyceridemia, bone marrow suppression, and sleep disturbances. Monitoring includes urinalysis, complete blood count, liver function tests, and blood chemistry analysis including magnesium, potassium, and uric acid.

Because cyclosporine is metabolized by the cytochrome P-450 CYP3A4 enzyme system, it has many potential drug interactions. The clinician should review a complete medication and herb list with each patient before cyclosporine therapy is initiated.[31]

Mind-Body Techniques

Background
Several studies showed that psychological stress can trigger or exacerbate flares of urticaria.[32,33] Although the mechanism is not well understood, the release of neuropeptides is thought ultimately to lead to elevations of histamine or greater sensitivity to histamine.[34] Human skin mast cells have been shown to release histamine in response to stimulation from various neuropeptides, including substance P, vasoactive intestinal polypeptide, and somatostatin.[35] Much more work needs to be done before we have a clear understanding of the relationship between the neural impact of stress on inflammation and urticaria.

Hypnosis
Most information on the effectiveness of hypnosis is in the form of case reports. The flare reaction to histamine prick testing has been shown to be significantly decreased with hypnosis.[36,37] One investigation looking at the use of relaxation techniques in patients who were classified as hypnotizable and those classified as unhypnotizable found that both groups experienced improvement in symptoms; however, only patients classified as hypnotizable had fewer clinical lesions.[38] In spite of the limited evidence, hypnotherapy may be a beneficial alternative—either alone or in combination with other therapies—for some patients with urticaria.

> Hypnosis is a therapy that should be encouraged for chronic urticaria. The evidence is promising, and potential for side effects is minimal.

Traditional Chinese Medicine
Within the framework of traditional Chinese medicine (TCM), urticaria is thought to be caused primarily by wind-heat, which obstructs energy channels and networks and causes red inflammation on the skin. When excess wind is present in the body, it can wander through the skin and cause itching. Wind-heat can arise through several different mechanisms. Invasion of pathogenic wind is often combined with pathogenic cold or heat. Emotional disturbances and irritability cause heat accumulation in the heart and blood that makes one more susceptible to invasive wind. Damage to the spleen and stomach (resulting from a diet that is unhygienic or heavy in fish, seafood, or spicy foods) impairs the function of these organs and leads to increased dampness. When dampness accumulates internally, it can be transformed into wind-heat.

Each situation leading to the accumulation of wind-heat can be specifically treated with various herbal concoctions that are beyond the scope of this chapter. Acupuncture can also be used alone or in combination with herbal remedies. The main general acupuncture points used for urticaria vary according to the source but include PC6 Neiguan, GB20 Fengchi, and ST36 Zusanli[39] or LI11 Quchi, SP10 Xuehai, SP6 Sanyinjiao, and S36 Zusanli.[40] Because TCM treatments are highly individualized for each patient and specific symptom variations, these very general acupuncture points may differ significantly from patient to patient. The assistance of a well-trained TCM physician should be sought, especially if one is interested in pursuing TCM herbal therapies.

Wide variation exists from state to state regarding certification, so when choosing an Oriental Medical Doctor (OMD), one should ask whether the person has passed the National Certification Commission for Acupuncture and Oriental Medicine herbal examination. If someone is interested in acupuncture alone, the American Academy of Medical Acupuncture is a good additional source of well-trained practitioners.

Homeopathy

Like TCM, homeopathy looks at urticaria as the local expression of a systemic disturbance. Each patient is evaluated individually, and treatments are given on the basis of the constitutional approach. Because each patient is viewed as having a unique imbalance, the specific remedy chosen depends greatly on the patient. Two patients with urticaria may be successfully treated with vastly different therapies. Approximately 20 remedies are commonly employed to help patients with urticaria, including Natrum Muriaticum (a derivative of sodium chloride), Apis Mellifica (derived from the honey bee), Urtica Urens (derived from the stinging nettle plant), silica, and Kali Carbonicum (derived from potassium carbonate).

To give a patient an appropriate cure, a practitioner must be well trained and have a deep understanding of homeopathy. Certification is not uniformly required, so one should look for practitioners who are accredited by one of the following organizations: the Council for Homeopathic Certification (CHC), the American Board of Homeotherapeutics (ABHt), the Homeopathic Academy of Naturopathic Physicians (HANP), and the North American Society of Homeopaths (NASH).

Precautions

With homeopathic treatments, patients may experience an exacerbation of symptoms before resolution; this exacerbation is known as a healing crisis.

Prevention Prescription

- If a cause is identified in a particular patient, recurrences can be limited by having the patient
  - Avoid exposure to known triggers.
  - Limit stress.
  - Eat a healthy, balanced diet with a low histamine content.

Therapeutic Review

This is a summary of therapeutic options for urticaria. Laboratory investigation should be directed by the history and physical findings. Particular attention to associations with systemic disease is warranted in patients with chronic urticaria.

General Measures

- Identify and avoid any precipitating factors, if possible. Activity and ingestant diaries may be particularly useful in this endeavor. A1
- Use topical measures, including a cool, calm environment, loosely fitting, comfortable clothes, baths with cornstarch, colloidal oatmeal (Aveeno), or baking powder. B1

Nutrition

- Avoid allergenic foods and foods high in histamine (see Table 70-1). B1
- Consider an elimination diet (see Chapter 84, Food Intolerance and Elimination Diet). C1

Botanicals and Supplements

- Quercetin: 400 mg orally twice daily before meals C1
- Butterbur (Petadolex): 75 mg orally twice daily C2
- Sarsaparilla: 1 to 4 g as dried root or tea three times daily; liquid extract (1:1 in 20% alcohol or 10% glycerol): 8 to 15 mL three times daily C2
- Stinging nettle: 300 mg three times daily C2
- Peppermint: 0.2 to 0.4 mL oil three times daily between meals or equivalent in enteric-coated tablets C2
- *Ginkgo biloba* for cold-induced urticaria: 120 mg/day standardized extract C2
- Valerian root for stress-related urticaria: 200 to 300 mg/day C2

Pharmaceuticals

- Antihistamines: H_1-receptor blockers alone or in combination with H_2-receptor blockers A2
- First-generation
  - Hydroxyzine: 50 mg one to four times daily

- Diphenhydramine: 25 to 50 mg every 6 to 8 hours
- Chlorpheniramine: 4 to 8 mg twice daily.
- Promethazine: 12.5 to 25 mg every 6 to 8 hours
- Second-generation
  - Loratadine (Claritin): 10 mg once or twice daily
  - Fexofenadine (Allegra): 60 to 180 mg once or twice daily
  - Cetirizine (Zyrtec): 10 mg once or twice daily
- H_2-receptor antagonists
  - Ranitidine (Zantac): 150 to 300 mg twice daily
  - Famotidine (Pepcid): 20 to 40 mg one to twice daily
  - Cimetidine (Tagamet): 200 to 400 mg one to four times daily
- Doxepin: 10 to 75 mg before bed
- Leukotriene inhibitors 
  - Zafirlukast (Accolate): 20 mg twice daily
  - Montelukast (Singulair): 10 mg daily
  - Zileuton (Zyflo): 600 mg up to four times daily
- Corticosteroids: 60 mg/day for 2 to 3 days, then tapered over 1 to 2 weeks 
- Cyclosporine: 3 mg/kg/day for 6 weeks, 2 mg/kg/day for 3 weeks, and 1 mg/kg/day for 3 weeks. Appropriate monitoring is essential. 

Mind-Body Therapy

- Relaxation: Good for everyone! 
- Hypnosis, especially for people classified as hypnotizable 

Traditional Chinese Medicine

- Please see the text *Dermatology in Traditional Chinese Medicine*, by Xu Yihou,[35] for more detailed and complete information on and understanding of TCM.
- Please also see Key Web Resources for Web sites listing traditional Chinese medicine practitioners.

KEY WEB RESOURCES

General Overview of Disease and Treatment

American Academy of Dermatology: http://www.aad.org/public/publications/pamphlets/skin_urticaria.html

Mayo Clinic: http://www.mayoclinic.com/health/chronic-hives/DS00980

Web Sites for Information about Traditional Chinese Medicine Practitioners

National Certification Commission for Acupuncture and Oriental Medicine: www.nccaom.org

American Academy of Medical Acupuncture: www.medicalacupuncture.org

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Chapter 71

Recurrent Aphthous Ulceration

David Rakel, MD

Recurrent aphthous ulcers (RAUs), also called aphthous stomatitis and canker sores, are the most common oral mucosal lesions, affecting 20% of the population in North America. They appear as recurrent ulcers with circumscribed margins with erythematous halos and gray or yellowish floors (Fig. 71-1).

RAUs affect the nonkeratinized or poorly keratinized mucosa of the mouth and oropharynx. No specific test is available for RAUs, and diagnosis is made from the patient's history and clinical findings.

Pathophysiology

RAUs appear to be multifactorial in origin, with a strong component of immune mediation. Histologically, there is an increase in immunoglobulin (Ig)E–bearing lymphocytes along with an increase in mast cells and tumor necrosis factor-alpha (TNF-alpha) in the prodromal stages.[1] Cytotoxic action of lymphocytes and monocytes seem to cause the ulceration, but the exact trigger is not clear.

The three main clinical variations are as follows:

Minor aphthous ulcers: Commonly less than 5 mm in diameter, these are the most common form (80%). Typically one to five ulcers may be present at any one time, and they usually heal without scarring in 7 to 14 days.

Major aphthous ulcers: These ulcers, which are less common, are larger and deeper than minor aphthous ulcers, tend to have irregular edges, and are more painful. They affect the lips, soft palate, and oropharynx and can take up to 6 weeks to heal, often leaving a considerable scar. Major and minor RAUs can be associated with Behçet's syndrome and human immunodeficiency virus (HIV) infection.

Herpetiform RAUs: From 1 to 3 mm in diameter, herpetiform RAUs often occur in groups of 10 to 100 that commonly coalesce to form large, irregular areas of ulceration. These are not as deep as major aphthous ulcers. They heal without scarring in 7 to 14 days and, in spite of their name, are not associated with herpesvirus or other viral origin.

Minor and major RAUs usually begin in childhood or early adolescence and have a tendency to resolve naturally later in life. Herpetiform RAUs appear later than minor and major RAUs, usually in the third decade (Box 71-1).

Integrative Therapy

Nutrition

Several nutritional deficiencies have been associated with RAUs. Nutrients vitamin B_{12}, iron, and folic acid have been the most studied and are commonly deficient in patients with RAUs.[2] Laboratory evaluation for red cell folate, serum vitamin B_{12}, and ferritin levels should be included in any evaluation of RAUs.

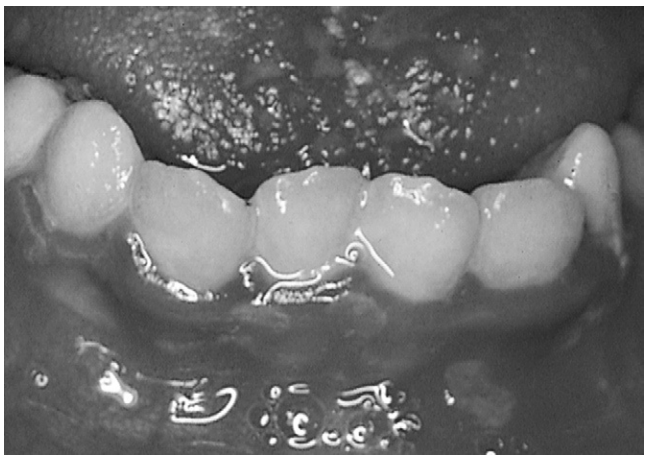
Vitamins B_1,[3] B_2, B_6, and B_{12} have also been found to be deficient in some patients with RAUs.[4]

> Laboratory evaluation for red cell folate, serum vitamin B_{12}, and ferritin levels, as well as complete blood count, should be ordered in the evaluation of recurrent aphthous ulceration. HIV infection should be considered if the patient is at risk for this infection.

Diet

A few patients with RAUs have gluten-sensitive enteropathy and improve considerably with a gluten-free diet.[5] The diagnosis is usually made by jejunal biopsy or by assay of tissue transglutaminase IgA with a positive antiendomysial antibody. Although no evidence in the literature shows that gluten-free diets help patients with RAUs who do not

FIGURE 71-1
Recurrent aphthous ulcers. The ulceration seen on the labial mucosa is surrounded by a characteristic erythematous halo. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 5th ed. St. Louis: Mosby; 2007.)



BOX 71-1. Etiology of Recurrent Aphthous Ulceration

The origin of recurrent aphthous ulceration seems to be multifactorial and can include one or several of the following factors:

- Familial and genetic basis
- Nutritional deficiencies: vitamins B_1, B_2, B_6, and B_{12}, folic acid, iron
- Stress
- Stopping smoking
- Menstruation
- Food allergies (cow's milk and gluten most common)
- Sensitivities to toothpastes (sodium lauryl sulfate)
- Medications
  - Antineoplastic (methotrexate, daunorubicin, doxorubicin, hydroxyurea)
  - Angiotensin-converting enzyme inhibitors (captopril most common)
  - Antimicrobials
  - Barbiturates
  - Griseofulvin
  - Nonsteroidal antiinflammatory drugs (NSAIDs)
  - Sulfonamides
  - Quinidine
  - Penicillamine
- Physical trauma
- Systemic conditions
  - Celiac disease
  - Crohn's disease
  - Human immunodeficiency virus infection
  - Neutropenia and other immune deficiencies
  - Neumann bipolar aphthosis
  - Behçet's syndrome
  - MAGIC (mouth and genital ulcers with inflamed cartilage)

have gluten sensitivity,[6] anecdotal observations indicate that some patients without gluten sensitivity may benefit from a gluten-free diet.[7] For the patient with recurring ulcers, a 2- to 4-week therapeutic trial of gluten avoidance is a reasonable option to assess effect.

The role of food allergies in the pathogenesis of RAUs is controversial. Several foods—milk, chocolate, coffee, nuts, strawberries, pineapple, citrus fruits, tomatoes, azo dyes—and food additives—monosodium glutamate (MSG), benzoic acid, tartrazine (yellow dye no. 5), and cinnamaldehyde—have all been suggested as a cause of RAUs[8,9] (see Chapter 84, Food Intolerance and Elimination Diet).

Honey

Honey has been found to be helpful in healing stasis ulcers of the legs as well as preventing mouth ulcers in patients receiving radiation therapy. In 40 patients with head and neck cancer who were receiving radiation, those who took 20 mL of honey 15 minutes before therapy and at 15-minute intervals at the time of therapy, and then again 6 hours after therapy, had significantly fewer mouth ulcers than the saline-treated control group.[10]

Supplements

Glutamine

Glutamine, the most abundant amino acid in the body, is essential for maintaining intestinal function, immune response, and amino acid homeostasis during times of severe stress. Glutamine supplementation has been found to improve nutritional and immunologic status and reduce complications in critically ill patients.[11] Not everyone benefits from supplementation, however. Those who are most nutritionally deficient are thought to have the best clinical response.[12] Supplementation with glutamine is beneficial during times of skeletal muscle wasting because most of glutamine is produced in skeletal muscle, and glutamine depletion raises the incidence of oral and gastrointestinal ulcerations. This amino acid has been found to reduce the duration and severity of oral stomatitis in patients undergoing chemotherapy.[13]

Dosage

Glutamine can be purchased in powdered form. The patient should mix 4 g in water, swish in the mouth, and swallow four times daily. If glutamine is used with chemotherapy, it should be taken on the day of chemotherapy and then used for 4 days after completion of each treatment.

Precautions

Grittiness of the oral solution may be unpleasant. Glutamine is otherwise well tolerated. It may cause mania in patients with bipolar disease.

Vitamin B_{12}

A randomized double-blind trial using 1000 mcg of sublingual vitamin B_{12} taken daily before sleep for 6 months in 58 patients with RAU showed that those in the treatment arm of the trial had significant reduction in ulcer formation, and 74% (compared with 32% in the placebo group) reported "no aphthous ulcer status" after 6 months. The response was not predicted by baseline serum vitamin B_{12} levels, and study subjects with normal levels still responded to therapy.[14]

Dosage
The dose of vitamin B_{12} is 1000 mcg sublingually daily for ulcer prevention.

Precautions
Vitamin B_{12} therapy is safe. The body excretes any excess into the urine, with the resulting classic bright yellow coloration seen with B-vitamin supplementation.

Botanicals

German Chamomile (Matricaria recutita)
Chamomile is used for its antiinflammatory properties in the treatment of dyspepsia, leg ulcers, and oral mucositis. When used as a mouthwash, it has been found to prevent oral mucositis associated with radiation therapy and chemotherapy.[15]

Dosage
Make an oral rinse with 10 to 15 drops of German chamomile liquid extract in 100 mL warm water, and use three times daily.

Precautions
The plant has allergic potential but is otherwise safe.

Licorice (Glycyrrhiza)
Licorice, which has antiinflammatory action, has been used as a mouthwash and is available in oral disks.[16] A randomized double-blind study using a *Glycyrrhiza* oral patch compared with placebo patch showed significantly faster resolution of ulcers in the *Glycyrrhiza*-treated group at 8 days.[17]

Dosage
To use licorice as a mouthwash, mix ½ teaspoon licorice extract with ¼ cup water, swish, gargle, and expel the mouthwash four times daily for symptomatic aphthous ulcers.

A product called CankerMelt contains 30 mg *Glycyrrhiza* extract. The disk is applied to the ulcer and allowed to dissolve over time; then a new disk is applied every 6 hours.

Precautions
If the mouthwash is not swallowed, side effects are rare. Licorice can cause sodium retention and hypokalemia if it is swallowed. Care should be taken with the use of licorice in patients with hypertension, because licorice ingestion can worsen the condition.

Although research is limited, many patients find pain relief from the tannins found in tea leaves *(Camellia sinensis)*. A brewed black or green tea bag can be applied to the ulcer as needed.

Homeopathy

Several homeopathic remedies have been used historically to treat RAUs. Unfortunately, all the evidence for their use is anecdotal. A classical homeopath would look for a constitutional remedy that fits the whole patient. Symptomatic remedies that may help are as follows:

Mercurius solubilis is indicated if the RAUs are associated with foul breath and increased salivation.

Borax is indicated if the RAUs are brought on by citrus or acidic foods. The mouth usually feels dry even though some saliva may be present.

Arsenicum album is indicated in patients with RAUs that are brought on by stress and eased with hot drinks.

Dosage
All the preceding remedies are best given initially at a potency of 6X or 6C four times daily (the X and C refer to the potency, which is the extent of dilution of the remedy). They should be discontinued when the RAUs begin to improve (see Chapter 111, Therapeutic Homeopathy).

Mind-Body Therapy

Stress, both emotional and physical, triggers RAUs. Emotional and environmental stress may precede 60% of first-time aphthous ulcer cases and be involved in 21% of recurrent episodes.[7] The pathogenesis may involve the known alteration of the immune response from stress or the depletion of B vitamins, or the cause may be unknown.

Meditation and stress reduction techniques, such as guided imagery and hypnosis, have been shown to be useful in the management of RAUs.[18,19]

Lifestyle

Toothpaste
Sodium lauryl sulfate is a common detergent used in toothpastes that has been shown to precipitate RAUs.[20] Other ingredients may also affect RAUs, so a good question to ask patients with newly developed RAUs is whether they have recently changed toothpaste. *CloSYS, Tom's of Maine, The Natural Dentist, Burt's Bees,* and *Squigle* are examples of brands of toothpaste that do not contain sodium lauryl sulfate.

Pharmaceuticals: Antiinflammatory Agents

Amlexanox
The only prescription medication approved by the U.S. Food and Drug Administration (FDA) for treatment of aphthous stomatitis is amlexanox (Aphthasol) 5% paste. It accelerates healing through an unknown mechanism that inhibits inflammatory mediators (histamine, leukotrienes) from mast cells, neutrophils, and mononuclear cells. This agent has no direct analgesic properties.

Dosage
Apply 0.5 cm to the sore with fingertip four times daily after meals and at bedtime. Start at the onset of symptoms, and stop with resolution. If no resolution has occurred in 7 days, reevaluation is warranted. Amlexanox is dispensed in a 5-g tube.

Precautions
This agent may cause minimal burning on application. Rash, diarrhea, nausea, and worsening stomatitis have been reported in less than 1% of cases.

Triamcinolone and Dexamethasone

Steroids such as triamcinolone and dexamethasone reduce inflammatory mediators but do not decrease the frequency of RAU occurrence.

Dosage

For triamcinolone acetonide 0.1% in carboxymethyl cellulose paste (Kenalog in Orabase), apply 0.5 cm to the sore two or three times daily. Start at the onset of symptoms and stop with resolution. If no resolution has occurred in 7 days, reevaluation is warranted. This agent is dispensed in a 5-g tube.

For dexamethasone (Decadron) oral solution 0.5 mg/5 mL, rinse the mouth with 1 teaspoon (5 mL) for 2 minutes and spit out, three times daily after meals and once at bedtime.

Precautions

Thrush may occur.

Pharmaceuticals: Analgesic Agents

A helpful approach is to avoid spicy, salty, and vinegar-containing foods that may irritate and increase pain of the ulcers. The following analgesic agents may also be useful.

Viscous Lidocaine (Xylocaine 2% solution)

This agent provides anesthetic properties that diminish pain while eating.

Dosage

To use viscous lidocaine (Xylocaine 2% solution), swish 15 mL and expel, every 3 hours or before meals as needed for pain relief. Do not use more than eight doses daily. This agent is dispensed in 50-, 100-, and 450-mL bottles.

Precautions

Care should be taken not to ingest large amounts of viscous lidocaine internally because of its potential cardiotoxicity. Benzocaine gel (10% to 20%) is a safer alternative, particularly for use in children.

Pharmaceuticals: Mouthwashes

Chlorhexidine Gluconate

Chlorhexidine gluconate 0.12% oral solution (Peridex or Periogard oral rinse) is a mouthwash that has been shown to reduce the incidence, duration, and discomfort of RAUs.[21] It does not, however, appear to be as effective as the other pharmaceutical topical agents.[22]

Dosage

Swish 15 mL for 30 seconds and expel, twice daily. Chewing sugarless gum after using this mouthwash can help reduce tooth discoloration.

Precautions

This agent can cause stinging when it is first used, reversible discoloration of the teeth and tongue after 1 week of use, transient disturbances of taste, and burning sensation of the tongue.

Tetracycline–Fluocinolone Acetonide–Diphenhydramine Mouthwash

For more severe cases, a formula containing tetracycline, fluocinolone acetonide, and diphenhydramine can be used. Tetracycline is thought to work through antimicrobial as well as antiinflammatory mechanisms. Fluocinolone and diphenhydramine work through antiinflammatory and anesthetic mechanisms. I have found this mixture to be very helpful in severe cases of RAUs resulting from immunosuppressant therapy.

Dosage

This formula requires the help of a pharmacist for mixing. Most pharmacies are able to comply with these directions. The following should be mixed together to make a total of 150 mL:

Tetracycline: At a concentration of 500 mg/5mL (which pharmacist makes by dissolving a 500-mg capsule in 5 mL of water) for a total of 60 mL

Diphenhydramine syrup (Benadryl): 12.5 mg/5 mL for a total of 60 mL

Fluocinolone acetonide 0.01% solution (Synalar): A total of 30 mL

Swish 10 mL and expel four times daily until the ulcers resolve. Do not use for more than 7 days at a time.

Precautions

Tetracycline should not be given to children younger than 9 years old because it stains the teeth. Fluocinolone, like most steroids, can cause thrush if it is used for extended periods.

For severe cases, a trial of tetracycline–fluocinolone acetonide–diphenhydramine mouthwash is indicated before using systemic therapy.

Systemic Pharmaceuticals

For cases resistant to topical therapy, consider the following systemic pharmaceuticals, in descending order as discussed here.

Colchicine

Colchicine has been used for stomatitis associated with Behçet's disease.[23] It has also been found to be beneficial for RAUs in patients without this disorder and is even more effective when combined with systemic steroids.[24]

Dosage

The dose is 0.6 mg orally twice daily. It may be increased to three times daily as tolerated with regard to gastrointestinal side effects.

Precautions

The most common side effects are gastrointestinal, consisting of diarrhea, nausea, and cramping. Colchicine can also cause thrombocytopenia and aplastic anemia.

Systemic Steroids

No good studies have been conducted on the use of systemic steroids for RAUs. These agents should be used cautiously in immunocompromised hosts.

Dosage
The dose of prednisone is up to 40 to 60 mg/day for 5 days. If longer use is needed, taper the dosage over 10 to 14 days.

Precautions
In patients with HIV infection, adverse reactions include cushingoid facies, thrush, reactivation of herpes simplex virus, and accelerated progression of Kaposi sarcoma.[25]

Thalidomide
Thalidomide has pronounced efficacy in healing oral aphthae. In two trials involving difficult cases, thalidomide completely healed 48% to 55% of ulcers, compared with 7% to 9% in patients receiving placebo. This effect was temporary, however; many of the patients treated had recurring symptoms.[26]

Dosage
The dose is 200 mg/day orally.

Precautions
Because of the potential for teratotoxicity and irreversible peripheral neuropathy, this treatment should be used only for the most serious, intractable cases.

Because of the elevation of tumor necrosis factor-alpha (TNF-alpha) in recurrent aphthous ulceration, some people with resistant cases related to autoimmune conditions may benefit from a TNF inhibitor drug such as infliximab, etanercept, or adalimumab. These medications also have significant risk resulting from inhibition of immune function.[27]

Cautery With Silver Nitrate
The use of silver nitrate sticks to provide chemical cautery was found to reduce pain significantly compared with placebo, but it did not reduce healing time. The study involved only one application. Clinicians contemplating this therapy should consider pretreating the ulcer with 2% viscous lidocaine and then painting the ulcer with the silver nitrate stick until it turns completely white.[28]

Therapies to Consider

Traditional Chinese Medicine
Chinese medicine views RAU as a condition caused by heat in the stomach; it can also be caused by yin deficiency or toxic heat. Treatment is with Topical Watermelon Frost or internally with formulas that cool stomach heat and clear toxic heat, such as Dao Chi Pian or Niu Huang Jie Du Pian. Although no reliable studies on the use of traditional Chinese medicine in the treatment of RAUs have been conducted, referral to a Chinese medicine practitioner is a valid approach if other treatments are not indicated or are unsuccessful.

Prevention Prescription
- Have patients:
  - Avoid oral trauma from biting, dental procedures, brushing, and eating of rough foods.
  - Avoid toothpaste that contains sodium lauryl sulfate.
  - Ensure adequate nutrition by consuming seven to nine servings of fruits and vegetables daily.
  - Avoid trigger foods; cow's milk and wheat (gluten) are most common.
- Consider a B-100 complex vitamin daily for recurring cases.
- Help patients learn how to change their interpretation of stressful information and events to reduce physical consequences (see Chapter 93, Relaxation Techniques, and Chapter 98, Recommending Meditation).
- Avoid the use of medications associated with recurrent aphthous ulcers (see Box 71-1).

Therapeutic Review
The most important issue in dealing with recurrent aphthous ulcers (RAUs) is to exclude systemic conditions, particularly Behçet's syndrome (mouth, genital, and eye ulcers). Because the origin of RAUs is multifactorial, a simple list of treatments is not applicable; a good history helps focus on the triggers and can lead to a specific treatment plan. The following is a guide to the most common causes and treatments of RAU.

Laboratory Evaluation
- Identification of nutritional deficiencies should be the first step in treating RAUs.
- Order measurements of serum ferritin, red cell folate, and serum vitamin B_{12}. Replace these nutrients if the patient is deficient.
- Giving 250 mg of vitamin C with the iron is often helpful to assist in iron absorption.

Nutrition
- If you suspect celiac disease, assess the patient for tissue transglutaminase immunoglobulin A and antiendomysial antibodies.
- Identify any foods that trigger the RAUs and consider elimination (see Chapter 84, Food Intolerance and Elimination Diet).
- Consider using honey, 20 mL before, during, and after radiation therapy of the head and neck to reduce the severity of mouth ulcerations. C 1

Supplements

- B vitamins (vitamins B_1, B_2, B_6, B_{12})
  - Because the cost and potential harm of B vitamins are low, a 3-month trial of one B-50 complex vitamin pill daily can be used to see whether the frequency of RAUs is reduced. A B-50 complex vitamin contains approximately 50 mcg or mg of each B vitamin.
  - Vitamin B_{12}, 1000 mcg sublingually daily for 6 months, has been found to reduce the incidence of ulcers. B1
- Glutamine
  - Mix 4 g of powder in water, swish, and swallow four times/day.
  - This is best for RAUs resulting from severe disease or injury or in patients undergoing chemotherapy. B1

Botanicals

- Licorice *(Glycyrrhiza)* mouthwash: Mix ½ teaspoon of licorice extract in ¼ cup of water; swish and expel four times/day.
- CankerMelt disks contain 30 mg *Glycyrrhiza* extract. The disk is applied to the ulcer and allowed to dissolve over time; then a new disk is applied every 6 hours. B2

Homeopathy C1

- Mercurius solubilis is indicated if the RAUs are associated with foul breath and increased salivation. Use 6X or 6C potency four times/day until healing begins.
- Borax is indicated if the RAUs are brought on with citrus or acidic foods. The mouth usually feels dry even though some saliva may be present. Use 6X or 6C potency four times/day until healing begins.
- Arsenicum album is indicated in patients whose RAUs are brought on by stress and eased with hot drinks. Use 6X or 6C potency four times/day until healing begins.

Mind-Body Therapy C1

- Because stress is often a component of RAUs, stress reduction techniques, such as meditation and guided imagery, are usually advisable to include in management (see Chapter 93, Relaxation Techniques).

Pharmaceuticals

- Topical therapy
  - Amlexanox (Aphthasol) 5% paste: 0.5 cm applied to sore four times daily B1
  - Triamcinolone acetonide 0.1% in carboxymethyl cellulose paste (Kenalog in Orabase): 0.5 cm applied to sore three to four times daily B1
  - Viscous lidocaine (Xylocaine 2% solution): 15 mL swished every 3 hours as needed for pain B2
  - Chlorhexidine gluconate 0.12% oral solution (Peridex or Periogard oral rinse): 15 mL rinsed and expelled twice daily B2
  - Tetracycline 500 mg/5 mL to make 60 mL, fluocinolone acetonide solution (Synalar) 30 mL, and diphenhydramine syrup (Benadryl) 60 mL, mixed together to make 150 mL: 10 mL swished and expelled four times daily C2
- Systemic therapy
  - Colchicine: 0.6 mg twice daily, increased to three times daily as tolerated in terms of gastrointestinal side effects B2
  - Prednisone: 40 to 60 mg/day for 5 days C2
  - Thalidomide: 200 mg/day; used only for most severe cases B3

Cautery

- Premedicate with 2% viscous lidocaine and paint the ulcer once with silver nitrate stick until it turns white.
- This technique helps reduce pain but not ulcer duration. B2

KEY WEB RESOURCES

Dentist.net: http://www.dentist.net/sls-free-toothpaste.asp	This consumer site sells sodium lauryl sulfate–free toothpastes.
OraHealth: http://www.orahealth.com/	This company developed oral adhering disks that allow the medicinal application of specific treatments for recurrent aphthous ulcers. Information on obtaining CankerMelts can be found here.

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Chapter 72

Seborrheic Dermatitis

Alan M. Dattner, MD

Pathophysiology

Seborrheic dermatitis (SD) involves a predisposition toward a specific inflammatory desquamative reaction pattern in typically oily areas rich in *Malassezia*. An overabundance of or an inappropriate immune reaction to the common skin and follicular microflora species known as *Malassezia* (formerly *Pityrosporum*) has been both demonstrated and disputed in the literature.[1] Since the identification of seven major strains of *Malassezia* in 1996, studies have begun to demonstrate which species are most predominant in SD in different populations. *Malassezia globosa* and *Malassezia restricta* predominate, according to some reports,[2,3] and various other strains are reported to be associated with SD as well. Evidence both for and against an association with increased or altered sebum production has been presented, but increased sebum production leading to greater growth of *Malassezia* seems to be a contributor.

Seborrhea is aggravated by Parkinson disease and by drugs that induce parkinsonism; clinical improvement is obtained with levodopa treatment of Parkinson disease. Aggravation by emotional stress and changes associated with cases of partial denervation suggest a neurohumoral influence as well. Some drugs have been implicated in inducing SD. Infantile SD, or Leiner disease, has been reported to respond to biotin and essential fatty acids (EFAs). The observation of an increase in both frequency and severity of SD among patients with acquired immunodeficiency syndrome (AIDS) has renewed interest in this otherwise benign disorder. These findings suggest that immune alterations may play some role in SD. *Malassezia* metabolites including free fatty acids released from triglycerides of sebaceous origin are also thought to induce the inflammation seen in SD.[4]

Malassezia is a genus of fungi found to cause seborrhea and skin depigmentation commonly associated with tinea versicolor. It requires fat to grow and thus is common in sebaceous glands.

Because *Malassezia* species are present in most people, one should ask why SD develops in some people and not others. Besides the specific species, sebum production, and particular circumstances just mentioned, reactions initiated by both the keratinocytes and immune system can account for this difference. Some of the response in SD may be related to direct interactions between *Malassezia* organisms and keratinocytes that generate cytokines such as interleukin-8 (IL-8).[5] Activation of innate immunity through Toll-like receptors (TLRs) also seems to play a role. Keratinocytes infected with *Malassezia furfur* up-regulate TLR-2, as shown by RNA analysis.[6]

Another possible explanation of the mechanism of SD may come from the observation that symptomatic *Candida* vulvovaginitis does not develop unless an aggressive response by polymorphonuclear leukocytes occurs.[7] A similar excessive neutrophilic hypersensitivity may play a role in SD because a neutrophilic infiltrate is a characteristic histopathologic finding in SD.

My own interpretation of the pathophysiology is that the trigger involves cytokines and TLRs, as already described, as well as a specific hyperactive cross-reactive immune response to some antigenic component of *Malassezia* that contributes greatly to the inflammation. The cross-reactive stimulation is a hyperactive response to the *Malassezia* organisms resulting from primary stimulation of the lymphocytes by *Candida* and other gut fungal microflora products. Patients with scalp psoriasis and seborrhea have been shown to have elevations of *Candida* organisms in the feces and on the tongue, a finding suggesting higher gut levels.[8] Elevations of *Candida* in the stool and *Candida* phospholipase A, as well as the improvement of seborrhea with oral nystatin (which tends to remain in the gut), further argue for a role for *Candida* cross-stimulation in SD.[9] This phenomenon of primary stimulation and secondary response has been demonstrated in vitro[10] and in the clinical setting.[11]

I believe that the immune response to the organism is biphasic, leading to both a tolerance to some components (epitopes) of yeast and a hyperactive response to others.

Cross-reactivity among *Malassezia, Candida,* and other yeasts relative to immunoglobulins has been well demonstrated.[12,13] Such a biphasic response would explain the mixed results in the literature showing both hyporeactivity and hyperreactivity to *Malassezia* antigens in patients with SD. The first component allows some overgrowth of *Malassezia* and related organisms (i.e., yeasts in gut and on skin). The hyperactive response precipitates a cascade of immune-mediated activity leading to the erythema and desquamation characteristic of the disease. Resident microflora (especially *Candida*) and ingested antigens from related microflora (i.e., yeasts and molds and their byproducts) provide the cross-reactive stimulus leading to both the tolerance and the hyperreactivity. Consideration of this etiologic hypothesis changes the way one treats chronic SD, described later.

The proinflammatory response disposition comes in part from a metabolic shift toward the production of proinflammatory prostanoids, caused by the common dietary oils rich in arachidonic acid. Antiinflammatory precursors, such as the omega-3 EFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are insufficient. A study of psoriasis, a related skin disease, demonstrated a higher ratio of arachidonic acid to omega-3 EFAs in patients receiving fish oils than in a control group. Supplementing with fish oil reduced arachidonic acid and malondialdehyde (another inflammatory molecule that is a marker of oxidative stress) and was associated with clinical improvement.[14] Arachidonic acid is a precursor to the proinflammatory leukotriene B_4 (LTB_4), which has been well documented to play a role in the pathogenesis of the psoriatic lesion.

The mixed nature of those findings may result in part from a lack of control of other critical factors influencing both lipid metabolism (e.g., oxidant status of the patient and relative intake of proinflammatory lipid precursors) and biochemical influences on the delta-5 and delta-6 desaturases, which are key in the metabolic pathway toward proinflammatory or antiinflammatory prostanoids. An additional key factor is that carbohydrate excess leads to excess insulin release. The excess insulin both inhibits the delta-6 desaturase and causes long-term release of proinflammatory cytokines,[15] thus favoring the inflammatory disease process despite the antiinflammatory effects of ingested EFAs. Most published studies do not address this important variable, which is best managed by encouraging a diet low in simple carbohydrates. In my experience, such a diet leads to positive results in a significant proportion of patients with SD as well as in patients with other inflammatory disorders of the skin (see Chapter 86, The Antiinflammatory Diet).

Integrative Therapy

Changing to antiinflammatory oils, controlling yeast on the skin and in the bowel, and calming the nervous system are mainstays in controlling seborrheic dermatitis.

Nutrition

Omega-3 Essential Fatty Acids

Omega-3 unsaturated fatty acids should be substituted for other dietary fats. Saturated, heat-altered, and partially hydrogenated fats should be eliminated from the diet because they lead to production of proinflammatory prostaglandin E_2 (PGE_2) prostanoids. In addition, they block the delta-6 desaturase that catalyzes the formation of antiinflammatory leukotriene precursors. Extra fats contribute to the unfavorable ratio of proinflammatory lipids in the cell membrane and contribute to weight gain because of their caloric content. Other indicators of a need for omega-3 oils are dry skin in winter, dryness around the nailfold area, a lack of dietary intake of such oils, depression, and a high ratio of arachidonic acid to omega-3 EFAs in the plasma or red blood cell membrane. EPA appears to be the primary antiinflammatory component of omega-3 unsaturated fatty acids.

An excellent source of omega-3 unsaturated EFAs is EFA-enriched fish oil capsules or liquid. Krill oil, cod liver oil and other cold-water fish oils are also good sources. Eating four to five portions weekly of oily cold-water fish is also recommended. Flaxseed oil, which contains alpha-linolenic acid, is also a potential source, but it must undergo chain elongation involving an extra step requiring the delta-6 desaturase, and some people cannot use this oil effectively. Canola oil and walnut oil are lesser sources of omega-3 unsaturated EFAs.

Oils can be either taken as supplements or worked into the diet as foods. For example, flaxseed oil can be used in making smoothies or salad dressing. These oils should not be heated because the unsaturated bonds that make them useful are unstable on heating. Because of their unsaturated nature, they should be accompanied by vitamin E in the diet. Similarly, other factors contributing to high oxidative stress in the individual patient should be corrected, or counterbalanced with additional antioxidants, to maximize the effectiveness of these oils. Omega-3 fish oil can induce glucose intolerance in diabetic patients. To counter this effect and to reduce the proinflammatory mediators from carbohydrate-stimulated insulin elevation, a proper balance of carbohydrate intake with protein intake and exercise should be achieved.

Dosage

The dosage is based on the severity of presentation, a history of inadequate dietary intake of omega-3 EFAs, and a low red blood cell membrane ratio of EPA to arachidonate. Whereas daily intake of five capsules (approximately 1 teaspoon) of flaxseed oil or EPA-DHA fish oils may be helpful, some patients may need as much as 15 mL (3 teaspoons) daily for a short time, mixed into a shake to make it palatable. Vitamin E, 400 to 800 units/day, should be taken to protect these unsaturated oils from oxidation. At least 1000 mg of EPA should be in the product used.

Precautions

Fish oils have been known to prolong bleeding time through the anticoagulant effect of PGE_3 for which they are precursors. Use of large doses in pregnant women has also been associated with elevated birth weight of their infants.

Yeast Elimination

For patients who require additional measures to control their seborrhea, a yeast and mold elimination diet should be instituted. The basis of this diet is the elimination of bread, cheese, wine and beer, excessive carbohydrates (especially sugar and simple starches), and other foods containing or produced by yeast or fungus. This diet has been touted as

highly effective in the popular literature, and the success of different variations is probably related both to yeast reduction and to relief of different food allergies in patients with yeast sensitivities. Probiotics such as *Lactobacillus acidophilus* and *Bifidobacterium bifidus* should be taken before or during meals to help repopulate the normal flora of the gut. Patients who cannot give up bread should be counseled to eat true sourdough bread, the leavening agent for which is derived from limited cultures of different yeasts captured from the air.

Supplements

Vitamins

Oils, which can be used as either foods or supplements, have already been discussed. Vitamin E, at 400 units/day, should be added as an antioxidant to protect the oils. Adequate levels of magnesium, zinc, vitamin C, and vitamin B_6 should be maintained by supplementation if intake of any of these nutrients is insufficient in the diet, to enhance the function of the delta-6 desaturase. Vitamin B_6 cream, 50 mg/g, compounded in a water-based cream by a compounding pharmacy, has been used for treatment of SD of the scalp.[16,17]

Biotin is especially useful in infantile SD,[18] and it may have a role in the treatment of adult seborrhea as well. Besides contributing to the generation of antiinflammatory prostanoids through activation of the delta-6 desaturase (as do other vitamins mentioned here), biotin is reputed to retard the formation of the mycelial form of *Candida.* Other B vitamins shown to be helpful in seborrhea are vitamin B_6, folate,[19] and vitamin B_{12}.[20]

Dosage

One or two tablets/day of a high-potency multivitamin with mineral (even for those with a three- to six-tablet/day recommendation on the bottle label) can be used for B-vitamin supplementation in most patients. If clinical improvement is not seen, extra biotin up to 7.5 mg/day, and vitamin B_6 or pyridoxal 5-phosphate 20 to 50 mg/day can be added; zinc picolinate 25 to 50 mg/day and vitamin C 500 mg one to three times daily are also useful.

Probiotics

To address the yeast overgrowth, adding probiotic bacteria such as *Lactobacillus acidophilus* and *Bifidobacterium,* or the yeast *Saccharomyces boulardii* to the diet is nearly as important as proper diet in restoring normal gut flora and reducing the yeast population. Caprylic acid can be added to inhibit attachment of the yeast to the intestinal wall.

Dosage

GI Flora (Allergy Research Group, Alameda, Calif) is an economical, effective source of multiple probiotic strains; the dose is one or two capsules with meals. Ultra Flora DF and Ultra Flora IB, one capsule per day (Metagenics, San Clemente, Calif), are other useful sources. Doses for caprylic acid are begun at one capsule three times daily before meals and are gradually increased to two capsules/meal.

If the patient has known overgrowth of yeast in the gastrointestinal tract, consider Caprystatin (Ecological Formulas, Concord, Calif; telephone 800-888-4585), which contains caprylic acid, a short-chain fatty acid that inhibits *Candida* growth and prevents attachment of yeast to the intestinal wall. Start with one capsule three times per day before meals, and increase the dose as necessary. Some patients, especially those who have associated fatigue or hypersensitivities, may have a die-off reaction and have some symptoms worsen before they improve. Follow these patients closely to be sure that they are not reacting to something in the treatment regimen. Resume the program at a slower rate if symptoms occur.

Precautions

A source of fiber is important to add, to ensure that bowel movements are occurring at least one or more times per day during yeast reduction therapy, so that allergenic moieties are not absorbed from the dying organisms. Fiber also promotes healthy mucosa along the gastrointestinal tract in which bacteria live.

Probiotics should not be given to a patient with a compromised immune system because of the slight risk of infection.

> Many companies that produce probiotics claim to offer the absolute best species, combinations, or strains of bacteria. Clinicians are advised to start with an affordable *Lactobacillus acidophilus* or *Bifidobacterium bifidus* preparation and then add others to their personal pharmacopoeia as evaluation of a specific product is found to be convincing and its effects are confirmed to be beneficial. Different patients do better with different probiotic bacteria. *Bifidobacterium bifidus* is thought to be more beneficial initially.

Botanicals

For topical treatment, any application that reduces yeast on the skin may be helpful. Various essential oils may be useful for their incorporation in scalp sebaceous lipids and antimicrobial action against *Malassezia.* Tea tree oil, honey, and cinnamic acid have been shown to reduce *Malassezia* and SD.[21] Tea tree oil and cinnamic acid, as well as other essential oils, however, can cause contact dermatitis, especially in inflamed skin, and honey is messy to use on the scalp. *Monarda fistulosa,* a distinctive-smelling herb from the mint family, has also been reported to yield an essential oil that is effective against seborrhea.[22]

Many different antifungal herbs and combination products with probiotics are available on the market today, and a comprehensive evaluation of these products is beyond the scope of this chapter. A few are mentioned here, but most that are effective in significantly reducing the yeast population in the gut will work. The use of fiber products such as psyllium and of other vegetable fiber is essential to maintain rapid passage of treated organisms through the bowel.

Grapefruit seed extract and *Artemisia annua* can also be added to reduce the yeast population. Some newer herbal preparations constituted for this purpose are available. Pau d'arco tea is another product with reported antiyeast activity. Application of aloe has been shown to be useful in seborrhea.[23]

Dosages

Tea tree oil may be used in adults on an occasional basis, applied sparingly to the areas of intense scaling after wetting the scalp. Because it is a potent allergen, I do not recommend it for regular, ongoing use. Aloe vera *(Aloe barbadensis)* gel may be applied directly from the cut leaf of the plant. Avocado may contain oils and sugars[24] that are helpful in controlling SD.

Mind-Body Therapy

SD is more prevalent in patients with depression.[25] Perhaps the improvement seen in the summer is the result either of reduced depression or of the effects of increased sunlight on melatonin release.[26] Addressing depression or seasonal affective disorder with light therapy, visits to a sunnier climate, psychotherapy, Bach Flower Remedies, supplements, or medications may be considered in a patient with SD in whom the disease severity varies with his or her affective state.

Pharmaceuticals

Shampoos

The two mainstays of topical treatment of SD are tar shampoos and antiyeast shampoos. Antiyeast shampoos consist, in order of potency, of zinc pyrithione, selenium sulfide 1% (over-the-counter shampoos), selenium sulfide 2.5% (prescription), and ketoconazole shampoos (available over the counter in some countries). Tar shampoos have antiinflammatory and antiyeast activity.

Dosage

A more recent treatment for fungal infections is ciclopirox 1% shampoo (Loprox), which is also approved for use in SD. Side effects include pruritus (itching), burning, erythema (redness), seborrhea, and rash. This product comes in a gel and a shampoo. Use the shampoo twice a week for 4 weeks or apply the gel twice daily for 4 weeks.

Tar shampoo (Tegrin, T/Gel) is used three times per week initially and then once per week.

Keratolytic Treatments

Oils are applied to the scalp to loosen scale. Olive oil is particularly useful in this regard, especially in infants with thin hair. Wetting the scalp and applying a warm oil turban for an hour, with 6% salicylic acid mixed into the olive oil, may remove more adherent scale. Patients must remove the oil with dishwashing liquid detergent before they apply a therapeutic shampoo.

Other salicylic acid preparations may also be used for the same purpose when thick, adherent scale is difficult to remove. Urea preparations may be used for the same purpose. These preparations also need time to act and generally require shampoo for removal. After thick scale is removed, a therapeutic agent can be applied to penetrate the scalp more deeply. Keratolytics such as salicylic acid have antifungal properties as well.

Dosage

Consider the following treatment to help reduce scaling. Olive oil is compounded with 6% salicylic acid. The oil is applied under a towel turban for 1 hour, and then scales are removed with a soft brush.

Topical Corticosteroids

Topical corticosteroids are another mainstay of conventional treatment of SD. Even 1% hydrocortisone cream brings temporary improvement in SD of the face and nasolabial folds in a previously untreated patient. Liquids, gels, and even a foam vehicle are available, with a more potent fluorinated corticosteroid used to avoid the hair and reach the scalp.

Dosage

Patients should apply 1% to 2.5% hydrocortisone cream sparingly once or twice daily for 1 to 2 weeks.

Precautions

Frequent or repeated application of corticosteroids results in tachyphylaxis (a progressively diminished response), requiring more potent steroids to obtain the same response. In addition, some patients behave as though they are addicted to the topical steroids. The problem becomes worse, and the corticosteroid is needed more and more often in higher strengths to control the redness and scaling. Repeated use on the face, especially of stronger corticosteroids, and even the use of hydrocortisone on the thin tissues of the eyelids, can result in atrophy of the skin with permanent show-through of the underlying capillaries or the development of problematic steroid acne.

Other Creams

Ketoconazole (Nizoral) cream applied sparingly twice daily is extremely helpful for management of SD of the face and hairline. It inhibits the *Malassezia,* gives dramatic clinical improvement, and does not cause the atrophy resulting from prolonged corticosteroid use. Other antifungal creams, including ciclopirox (Loprox) and nystatin cream, are also useful.

Dosage

Ketoconazole cream 2% is applied twice daily to affected areas, sparingly.

Lithium Succinate

Lithium succinate 8% ointment has been reported to be helpful in SD. An antiyeast effect has been confirmed in vitro,[27] as well as in patients.[28] The ointment is applied twice daily. The relationship between lithium as a drug for depression, which has been implicated as a cause of seborrhea, and direct application of lithium as a treatment for seborrhea is interesting to contemplate. A common mediator pathway for both disorders may exist.

Oral Antifungals

Oral antifungals should be used only when the seborrhea is serious enough to warrant the risk of taking the drug or when the underlying condition of overgrowth has not responded to diet and herbal treatment alone.

Nystatin

Oral nystatin is useful to reduce the *Candida* population in the gut. It has the benefit of being poorly absorbed and therefore remaining in the gut. It works by causing defective yeast cell wall formation, resulting in release of intracellular contents, which has in turn been blamed for the aggravation of symptoms constituting a Herxheimer-type reaction (flulike feeling from die-off effect of yeast) in some patients after a large dose.

Ketoconazole and Fluconazole

Ketoconazole (Nizoral) is well absorbed, exerts an antiyeast effect in the gut and skin, and is excreted in high concentrations in the sweat. Other oral antifungal agents, such as fluconazole (Diflucan), have also been used for severe cases of seborrhea. An antiyeast regimen should be instituted gradually, starting with diet, *Lactobacillus acidophilus,* and supplements and botanicals before oral pharmaceuticals are used. The first reason is to avoid rapid kill-off of a large number of organisms, which may result in a die-off effect, or Herxheimer-type reaction. The second reason is to reduce the intestinal yeast population less drastically. If the gut ecology is altered to favor a more gradual reduction in yeast population, a rebound growth of yeast resistant to the most powerful agents available will be less likely to occur. Although these agents may be effective in the short term, I question whether it is responsible practice to use these agents without initially or simultaneously altering the ecologic conditions that favor yeast overgrowth.

Dosage

The dose of nystatin is increased slowly from 500,000 units once daily to 2 million units three times daily; this dose is then maintained until the patient's condition is improved and stable and appropriate dietary changes have been effected. Dosing should begin with one capsule (500,000 units) per day of the powder, with addition of an extra capsule every 2 or 3 days until a total dose of four capsules three times daily (6 million units/day total) is achieved. Doses for the pure powder should begin with ⅛ teaspoon/day increased to 1 teaspoon/day (6 million units/day total) in the same gradual manner. This dose should be continued for 1 to 3 months or tapered for 1 to 2 weeks after symptoms clear.

For fluconazole (Diflucan), the dose is 100 to 200 mg/day for 10 to 14 days. (Many drug interactions and cautions are cited in the package insert.) Seborrhea is not a listed indication and should only be used in cases with severe underlying yeast issues.

The dose of ketoconazole (Nizoral) is 100 to 200 mg/day. Ketoconazole should be used only if other indications exist and liver enzyme values are monitored. In general, this drug should be avoided, or the liver can be protected with silymarin (milk thistle). Seborrhea is not a listed indication and should only be used in cases with severe underlying yeast issues.

Precautions

Adverse effects include elevation in liver enzymes, hepatic failure (uncommon with oral ketoconazole and less likely with fluconazole), a Herxheimer-type die-off phenomenon (especially with nystatin), and overgrowth of resistant organisms.

Before an oral antifungal is considered, intestinal yeast growth should be reduced with dietary measures. This will help prevent the growth of resistant strains of yeast and lead to improved response from the oral antifungal.

Therapies to Consider

Homeopathy

A homeopathic dilution of tobacco was reported to clear SD in a patient with tobacco sensitivity. I mention this not to recommend this specific remedy but rather to emphasize the potential benefits of choosing an appropriate homeopathic or other remedy that addresses prominent underlying imbalances in the patient. Other homeopathics, including Natrum Muriaticum, Arsenicum Album, and Bryonia, may be considered, but homeopathics should be prescribed according to other characteristics of the patient besides local presentation.

Food Allergy

As in patients with atopic dermatitis, addressing food allergy by removing the offending foods from the diet may benefit some patients with recalcitrant SD (see Chapter 84, Food Intolerance and Elimination Diet).

Energy-Based Treatments

When addressing a variety of apparent causal factors is not sufficient, the clinician must address ways in which the seborrhea may be an expression of some deeper autonomic or psychological pattern. Psychotherapy may be useful if it is powerful and targeted. Classical homeopathy addressing mental and emotional symptoms may touch this level. Newer forms of treatment that use acupressure meridian activation or tapping to release patterns of sensitivity in the autonomic nervous system, including Lang desensitization and Neuromuscular Therapy (NMT), may be considered by the practitioner skilled in these techniques.

Prevention Prescription

- Use a Mediterranean-type diet based on olive oil and fresh vegetables.
- Supplement with omega-3 essential fatty acids from fish oil, northern fish, and flaxseed.
- Reduce the intake of bread, cheese, wine, beer, and yeast.
- Reduce the intake of sugar, refined carbohydrates, and heated oils.
- Shampoo the scalp at least twice a week, with an antidandruff shampoo when necessary.

Therapeutic Review

The following is an outline of therapeutic options for the treatment of seborrheic dermatitis. Determining which factors lead to the disease presentation in a given patient may improve the chances of success of a given therapy. For more severe or resistant cases, a progressive, sequential approach with multiple therapeutic avenues is recommended, with either intensification of treatments or addition of systemic pharmacologic agents, as indicated by the clinical response.

Antidandruff Shampoos

- Zinc pyrithione, selenium sulfide (Selsun), tar, or ketoconazole (Nizoral) shampoo is used for 5 minutes two or three times/week.
- If the patient has used one type with no clinical improvement, another can be tried. B1

Antiyeast Creams

- Ketoconazole cream 2% (Nizoral) or another pharmacologic or herbal substitute works well on the face and nonscalp areas. B1

Supplements

- Eicosapentaenoic acid and docosahexaenoic acid (fish oils) can be added at 1 to 2 g/day and titrated to clinical improvement. B2
- Other sources of omega-3 essential fatty acids—oily cold-water fish, such as salmon and sardines, three to five servings/week, and flaxseed oil, 1 teaspoon/day—can be used.
- Vitamin E 400 units/day should be given with these oils to prevent oxidation. C1
- Vitamin B complex, vitamin B_6 500 mg, and biotin up to 8 mg/day may be beneficial in patients with resistant cases. C1
- Caprylic acid is taken at 100 to 200 mg two to three times/day.

Nutrition

- A diet low in yeast and simple carbohydrates, especially one that eliminates bread, cheese, wine, beer, fermented foods, and starches, is helpful in patients with persistent cases.
- Some improvement may result from removal of other food allergens. C1
- Adding probiotic bacteria such as *Lactobacillus acidophilus,* one capsule/meal, or live-culture yogurt may also help. C2

Botanicals

- The antiyeast botanicals grapefruit seed extract and *Artemisia annua* may be used at two to six capsules/day. C1
- Undecenoic acid, derived from the castor bean, is another antiyeast product (Formula SF 722 [Thorne Research, Sandpoint, Idaho]), used at two to six capsules/day. C1

Pharmaceuticals

- Nystatin is used in slowly increasing doses from 0.5 to 6 million units/day. B2 C2
- Fluconazole (Diflucan) is taken at 100 to 200 mg/day for 2 weeks, for resistant cases. This agent is best used after dietary, herbal, and supplement methods have been employed to reduce the yeast flora and to attenuate the ecologic factors favoring yeast growth.
- Triamcinolone solution or betamethasone valerate foam (Luxiq) once or twice daily can be used to relieve pruritus and inflammation. A2

KEY WEB RESOURCES

Holistic Dermatology: www.holisticdermatology.com	Information on alternative treatments for numerous skin conditions, including seborrheic dermatitis
Medscape: http://emedicine.medscape.com/article/1108312-treatment	Conventional medications for seborrhea
American Academy of Dermatology EczemaNet: http://www.aad.org/public/publications/pamphlets/common_seb_dermatitis.html	Photographs and a description of conventional treatments for seborrheic dermatitis
Wikipedia: http://en.wikipedia.org/wiki/Seborrhoeic_dermatitis	Overview of seborrheic dermatitis, including treatment

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Chapter 73

Acne Vulgaris and Acne Rosacea

Sean H. Zager, MD

Pathophysiology and Clinical Presentation

Acne vulgaris, known by most as acne, represents the most common disease of the skin as it affects approximately 45 million individuals in the United States and as many as 80% to 90% of adolescents.[1,2] Worldwide spending on prescription and over-the-counter acne treatments is estimated to be tens of billions of dollars each year, making it one of the fasting growing markets in the dermatologic industry to date.[3] Although the majority of cases are seen through the teenage years and in young adulthood, acne may be manifested at any time during the life span. Whereas it is not typically associated with significant physical comorbidity, acne may have severe social and psychological sequelae, necessitating a multidimensional approach to care.[4]

Acne rosacea, commonly referred to as rosacea, is a skin disorder that primarily affects individuals older than 30 years.[5] It is a condition that affects approximately 10% of fair-skinned people and tends to run in families. It has a higher prevalence in women and among individuals of northern European descent.[6,7] Although rosacea may sometimes appear similar to acne vulgaris and have comparable psychoemotional consequences, the two conditions represent distinct pathophysiologic processes.

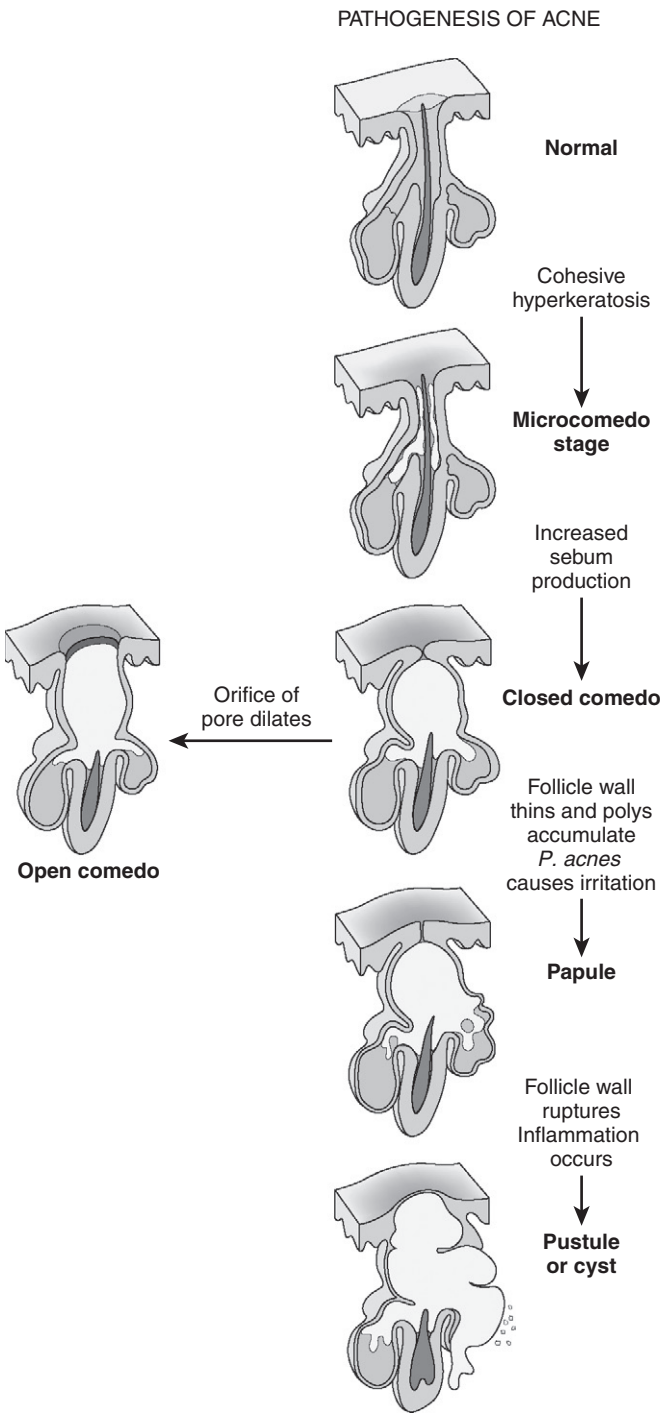
Acne Vulgaris

Acne vulgaris is a disease of the pilosebaceous unit of the skin, where the hair follicle meets the sebaceous gland in the dermis. The sebaceous gland functions to facilitate desquamation and lubrication of the skin. In the development of acne vulgaris, a cascade of five main factors contributes to a dysregulation of the pilosebaceous unit:

1. Increased levels of androgens are produced not only by the adrenal glands and gonads but also by the sebaceous glands in the skin. Elevated androgenicity is a physiologic consequence of puberty and a pathophysiologic consequence of conditions such as polycystic ovary syndrome, congenital adrenal hyperplasia, Cushing syndrome, and androgen-secreting tumors.[8]
2. Proliferation and impaired desquamation of keratinocytes lining the orifice of the follicle pore follow and lead to the development of a hyperkeratotic plug. This occurs within the follicular canal and causes the formation of a microcomedo.
3. Increased sebum is produced within the sebaceous gland, also because of increased androgen production. This results in the evolution of a closed comedo (a whitehead) and, if the orifice of the pore dilates, an open comedo (a blackhead).
4. The gram-positive anaerobic bacterium *Propionibacterium acnes* propagates in its sebum-rich growth medium. Although *P. acnes* is typically a normal component of skin flora, it thrives in an anaerobic environment abundant with lipids as a nutrient source.
5. A local inflammatory process develops as neutrophils and other host immune cells accumulate. Papules form, and with the rupture of the pilosebaceous follicle into the surrounding dermis, more severe pustular, nodular, and cystic acne lesions may appear (Fig. 73-1).

There is a wide spectrum of susceptibility to the proliferation of *P. acnes* and the factors that facilitate it. Inheritance studies, such as those comparing dizygotic and monozygotic twins,[9,10] demonstrate a significant role of genetics in the pathogenesis of acne. Suggested mechanisms include an increased tendency of 5-alpha-reductase to convert testosterone to the tissue-active metabolite dihydrotestosterone and a possible hypersensitivity of androgen receptors within sebaceous glands.[11,12] Whether through genetic predispositions (e.g., polycystic ovary syndrome, Cushing syndrome) or environmental exposure, increased levels of hormones

FIGURE 73-1
The pathogenesis of acne vulgaris. (From Habif TP. Acne, rosacea, and related disorders. In: Habif TP, ed. *Clinical Dermatology*. 5th ed. Philadelphia: Saunders; 2009.)



such as insulin and cortisol are also shown to promote acne development.[8]

Acne Rosacea

Like advanced cases of acne vulgaris, acne rosacea should be viewed as a chronic condition with cycles of exacerbation and remission. The pathophysiologic mechanism of rosacea is not yet well elucidated, and the therapeutic aims should emphasize control rather than cure. With regard to etiology, the following theories have been proposed:

1. Dysbiosis or invasion of foreign organisms triggering immune hyperreactivity
   a. *Demodex folliculorum* is a skin mite that feeds on sebum. It has been found in higher density in the facial skin of those affected by rosacea compared with unaffected subjects.[13] Further, it has been postulated that this mite may have symbiotic relationships with bacteria that spur inflammation and are susceptible to antibiotics used in the management of rosacea.[14]
   b. Data are conflicting about the relationship between the bacterium *Helicobacter pylori* and the pathogenesis of rosacea. With treatment of *H. pylori* infection, there is evidence of concomitant improvement of rosacea symptoms; as well, studies show no notable change.[15,16]
   c. Small bowel bacterial overgrowth has also been put forth as a trigger of rosacea. One study found that bacterial overgrowth in the small intestine was more common in those with rosacea and that eradication of the overgrowth decreased rosacea symptoms.[17]
2. Structural or functional dysregulation
   a. Reduced levels of hydrochloric acid in gastric secretions have been linked to rosacea.[18] Hypochlorhydria, secondary to genetic defect or environmental cues such as proton pump inhibitors, is evidenced to cause small bowel overgrowth.[19] Rosacea may represent one consequence of this aberrant condition.
   b. Vascular instability including accelerated angiogenesis and capillary dysfunction, mast cell prevalence, and connective tissue hypertrophy may also contribute to the inflammatory process of rosacea.[20,21]

The four major subtypes of acne rosacea and the common clinical features of each are as follows:

1. Erythematotelangiectatic rosacea (vascular rosacea): flushing, telangiectasias, and persistent erythema of the central face
2. Papulopustular rosacea: inflammatory papules and pustules; erythema of the central face
3. Ocular rosacea: burning, itching, and dryness of the eyes; conjunctival injection, blepharitis, periorbital edema, and photosensitivity
4. Phymatous rosacea: connective tissue hypertrophy or nodularity most notable at the distal nose (known as rhinophyma) but also seen on the chin, forehead, cheeks, and ears (Fig. 73-2)

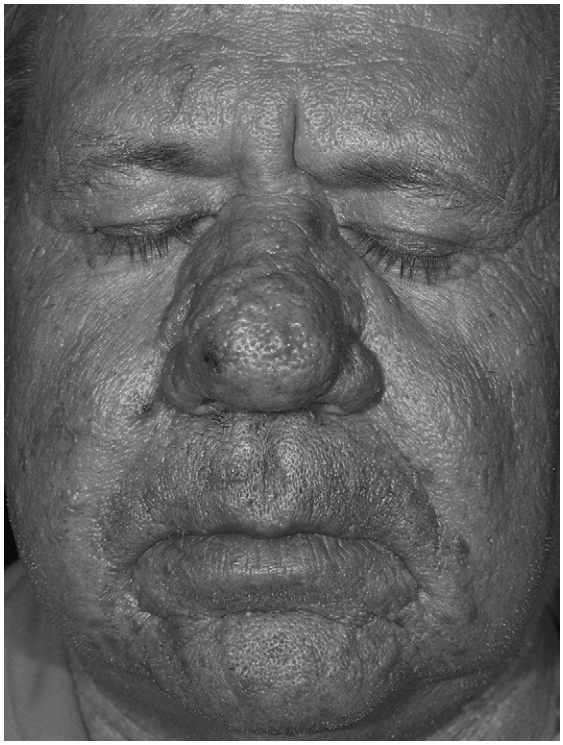
These subtypes often overlap. Typical environmental triggers for rosacea include extremes of temperature, stress, and particular foods and beverages; some of these are touched on in later sections of the chapter.[22]

Integrative Therapy

Hygiene

In approaching the patient with acne vulgaris or rosacea, it is reasonable to begin with a focus on simple behavioral considerations for prevention—whether it is primary, secondary, or tertiary. It is essential to engage in a dialogue about proper skin care. Ensure that patients are rinsing twice daily with lukewarm water and a non–soap-based cleanser. To avoid

FIGURE 73-2
Rhinophyma in phymatous rosacea. (From Habif TP. Acne, rosacea, and related disorders. In: Habif TP, ed. *Clinical Dermatology*. 5th ed. Philadelphia: Saunders; 2009.)



microabrasion of the skin, instruct patients to rinse with their hands instead of washcloths or other rough materials and to do so gently without scrubbing. Water-based, noncomedogenic lotions, cosmetics, and hair products are preferable to those that are oil based, and picking at acne lesions should be discouraged. The mechanical trauma of picking at lesions may lead to follicular wall rupture, releasing inflammatory cells into the surrounding dermis and increasing the likelihood of scarring.

Finally, particularly in patients with rosacea, environmental conditions must be considered. Sun and wind exposure and extremes of temperature have been noted to aggravate rosacea symptoms.[23] In one study, bacteria were isolated from the facial skin of affected subjects. At higher temperatures, these bacteria were noted to secrete greater amounts of a specific lipase that may be implicated in the inflammatory process of rosacea.[24]

Stress Management

Psychoemotional stress is an important contributor to and effect of acne vulgaris and rosacea. In a survey of 1066 rosacea patients, 79% identified emotional stress as an exacerbating factor and 64% ranked it within their top three triggers.[24] In a study of high-school students, a significant difference was noted in severity of acne vulgaris during periods of high stress (midterm exams) and low stress (summer break).[25]

It has also been shown that many patients with acne vulgaris or rosacea experience considerable levels of ensuing stress in association with depression, anxiety, anger, and low self-esteem.[4,26,27] Treatment strategies must therefore include attention to patients' social, psychological, and emotional well-being in addition to physical manifestations.

In response to these clinical needs, the field of psychodermatology has emerged. One mind-body technique, biofeedback-assisted guided relaxation imagery, was evidenced to improve acne vulgaris.[28] Cognitive-behavioral and biofeedback therapies have also been used to help patients decrease their frequency of picking at acne lesions.[29] Given the close reciprocal relationship between psychoemotional stress and both acne vulgaris and rosacea, other relaxation practices, such as breathing exercises, meditation, and massage therapy, may be recommended as part of a treatment plan (see Chapter 89, Breathing Exercises; Chapter 93, Relaxation Techniques; and Chapter 98, Recommending Meditation).

Diet

Nutritional factors play an important role in the pathogenesis of acne. A diet with a low glycemic load, favoring protein over carbohydrates and fats, has been shown to significantly decrease (inflammatory and noninflammatory) lesion counts in acne vulgaris.[30] A low glycemic–load diet has also been associated with a reduction in calorie intake, body mass index, and insulin resistance. Improved insulin sensitivity leads to a decrease in androgen production and a concordant improvement in the symptoms of acne vulgaris[30–34] (see Chapter 85, The Glycemic Index/Load).

Large population studies have furthermore demonstrated a worsening of acne symptoms with greater consumption of dairy products.[35,36] This may be a consequence of an increased carbohydrate-to-protein ratio, exposure to exogenous androgenic hormones, or triggering of proinflammatory processes by dairy allergy or lactose intolerance. Hence, in addition to adhering to a diet favoring protein over carbohydrates and fats, patients with acne should limit consumption of animal products treated with exogenous androgenic hormones. Instead, they should seek U.S. Department of Agriculture (USDA)–certified organic meats and dairy products. It may also prove beneficial to review the details of an antiinflammatory diet (see Chapter 86, The Antiinflammatory Diet) and to consider a trial of an elimination diet (see Chapter 84, Food Intolerance and Elimination Diet) that excludes dairy products.

A diet rich in omega-3 fatty acids—found in high quantities in salmon, mackerel, sardines, and flaxseed oil—has been linked to improvement in acne symptoms. Probably through the reduction of both proinflammatory compounds (such as leukotrienes and prostaglandins) and androgen production, omega-3 fatty acids discourage the opportunity for and sequelae of *P. acnes* proliferation.[37–40] Indeed, epidemiologic investigation reveals that communities consuming higher levels of omega-3 fatty acids have less prevalence of acne.[38,41] Although it is best to consume them in food in which they naturally occur, omega-3 fatty acids may be supplemented in the diet. Typical daily doses are 1 tablespoon of flaxseed oil per 100 pounds of body weight or 1 to 2 g of fish oil in capsule form. One small study did show marked improvement in acne symptoms and mental outlook after 2 months of omega-3 fatty acid supplementation.[42]

In addition, decreased serum levels of vitamin A have been associated with worsening acne severity.[43] Hence, patients with acne may be counseled to eat more vegetables rich in vitamin A, such as carrots, sweet potatoes, spinach, kale, and winter squash.

With regard to acne rosacea, affected patients should be screened for potential food allergies or intolerances that may contribute to exacerbations. Dietary triggers typically include alcohol, spicy foods, hot beverages, marinated meats, dairy products, and certain fruits and vegetables.[22] A careful elimination diet should be performed as part of tailoring a treatment plan specific to the needs of each individual patient.

Supplements

Brewer's Yeast (Saccharomyces cerevisiae)

Brewer's yeast is a medicinal yeast often used in brewing and baking. It is commonly used as a remedy for acne vulgaris in Western Europe. Brewer's yeast is known to contain chromium and is thereby thought to decrease insulin resistance.[44,45] One strain of brewer's yeast, known as Hansen CBS 5926, has been recognized as an inhibitor of bacterial growth.[46] In one study of 139 subjects with acne, more than 80% saw significant improvement in symptoms with brewer's yeast supplementation.[47]

Dosage

The recommended intake of dried brewer's yeast is 2 g three times daily. The recommended dose of isolated Hansen CBS 5926 strain of brewer's yeast, freeze-dried, is 750 mg daily.[46]

Precautions

Brewer's yeast may cause migraine headaches or flatulence in sensitive individuals. It can lead to hypertension if it is used in conjunction with monoamine oxidase inhibitors and will have decreased efficacy if it is used with antifungal medications.[44,47]

Zinc

Zinc is a metallic chemical element that serves as an essential cofactor in many biochemical reactions involved in the maintenance of skin health and general immune function, local hormone activation, and production of retinol-binding protein. Zinc has been noted to be bacteriostatic against *P. acnes* and to inhibit the production of inflammatory cytokines. Although sample sizes have been small, most studies show that zinc supplementation does have a therapeutic effect on acne symptoms.[3,18,48–52]

Dosage

The recommended dose of zinc gluconate is 30 mg/day.

Precautions

Oral zinc supplementation can result in gastrointestinal symptoms including nausea, vomiting, and diarrhea.[53] These adverse effects may be mitigated by taking zinc just after meals. Prolonged zinc supplementation can also lead to copper deficiency with resultant sideroblastic anemia and neutropenia.[54] Thus, as a rule of thumb, clinicians should supplement 2 mg of copper for every 30 mg of zinc.

Vitamin A

Vitamin A is a retinol and fat-soluble vitamin that has been studied in the treatment of acne, given its capacity for immune modulation and reduction of follicular hyperkeratinization. In one study of patients supplemented with 100,000 units of vitamin A daily, there was no significant improvement in acne severity, and a number of subjects complained of symptoms compatible with hypervitaminosis A.[55] In another trial using higher doses of vitamin A (between 300,000 and 500,000 units daily), therapeutic effects were noted. In this study, however, the majority of patients experienced cheilitis and xerosis; a number suffered from headache (causing two patients to quit the study), fatigue, and nausea—all symptoms associated with hypervitaminosis A.[56]

Dosage

Tolerable upper intake level (the maximum dose that is unlikely to carry a risk of adverse side effects) is 10,000 units daily and less for children.[57] As mentioned earlier, significantly higher doses have been used in the treatment of acne vulgaris.

Precautions

Given its questionable therapeutic effect and demonstrated potential for toxicity, oral supplementation with vitamin A is *not recommended*. High doses appear to be required for symptomatic control, and hypervitaminosis A has short- and long-term health risks. These risks include headaches, myalgias, fatigue, nausea and vomiting, dry skin and mucous membranes, hair loss, hepatitis, reduced bone mineral density, and teratogenicity.

Botanicals

Tea Tree Oil (Melaleuca alternifolia)

An essential oil from the leaves of the native Australian tea tree, tea tree oil is commonly used as a topical antimicrobial. In two blinded, randomized controlled trials, application of 5% tea tree oil was shown to significantly improve acne severity compared with placebo and was comparable to 5% benzoyl peroxide. Although tea tree oil had a slower onset of action than that of benzoyl peroxide, it was better tolerated with less skin irritation.[58,59]

Dosage

Tea tree oil, 5% to 15% solution or gel, is applied topically once daily.

Precautions

Topical tea tree oil is generally well tolerated, but it has been noted to cause local skin irritation and allergic contact dermatitis in some patients.[60]

Pharmaceuticals: Topical Preparations

Azelaic Acid

A naturally occurring dicarboxylic acid produced by the yeast *Malassezia furfur,* azelaic acid is found in wheat, rye, and barley. It is antibacterial as well as anticomedonal through its capacity for keratolysis.[61] In two blinded, randomized controlled trials, the therapeutic effect of azelaic acid on acne

severity was demonstrated to be significant and on par with that of topical benzoyl peroxide and clindamycin .[62] In addition, azelaic acid is helpful in treating the hyperpigmentation that results from acne-associated inflammation.[61,63] For patients with acne rosacea, azelaic acid has been shown to be comparable to topical metronidazole in the reduction of inflammatory lesions and erythema.[64]

Dosage

Azelaic acid, 20% cream or 15% gel, is applied topically twice daily.[61–64]

Precautions

Azelaic acid may cause local skin irritation and changes in pigmentation. Of note, it has been shown that whereas azelaic acid decreases the postinflammatory hyperpigmentation seen with acne, it does not alter skin tanning or hyperpigmentation that occurs with exposure to ultraviolet light.[61,65]

Salicylic Acid

Salicylic acid occurs naturally as a phenolic phytohormone; its name comes from the Latin word *salix,* which means willow tree. It is chemically similar to the active component of aspirin and has a comedolytic effect by disrupting the pilosebaceous unit and causing desquamation. Salicylic acid is found in many over-the-counter products, including lotions, creams, and pads. It is generally considered to be less potent but better tolerated than topical retinoids in the treatment of acne vulgaris. As a 2% preparation, salicylic acid has been demonstrated to be more effective than 10% benzoyl peroxide for acne control, although this may be due to better patient compliance given the superior side effect profile of salicylic acid.[3,66–68]

Dosage

Salicylic acid, applied topically one or two times daily, is commonly used as an over-the-counter preparation in concentrations up to 2%. It may also be obtained by prescription in concentrations between 2% and 10%.

Precautions

The most frequent adverse effect of salicylic acid is local skin irritation and peeling, which are likely when concentrations of 2% or higher are used. Risk of hyperpigmentation is less common, and salicylate toxicity is rare, noted with application over large body surface areas for prolonged periods.[3,69]

Retinoids

In the conventional care of acne vulgaris, topical retinoids are included in the initial management of most patients. As vitamin A derivatives, they are useful for treatment of both comedonal and inflammatory acne lesions because they oppose hyperkeratinization and obstruction of the follicular pore as well as the release of proinflammatory compounds.[70,71] In addition, they are helpful in reducing acne-associated postinflammatory hyperpigmentation.[72] Of the topical retinoids currently available, no significant difference in efficacy has been established, and each should lead to visible improvement of acne vulgaris after 8 to 12 weeks of treatment. In the approach to patients with acne rosacea, studies highlight notable risks and benefits of topical retinoid application.[73–75]

Dosage

Tretinoin, 0.01% to 0.1%, is applied once nightly or every other night if it is not well tolerated. Adapalene, 0.1%, is applied once nightly or every other night if it is not well tolerated. Tazarotene, 0.05% to 0.1%, is applied once nightly or every other night if it is not well tolerated.

Precautions

Topical retinoids may lead to local irritation and drying of the skin. They may also increase sun sensitivity and should therefore be applied at night. Whereas no topical retinoids are recommended in pregnancy, tazarotene must be avoided as it is classified as pregnancy category X. Finally, topical retinoids should *not* be used to treat acne rosacea given their potentially harmful effects, including the promotion of epithelial thickening, neovascularization, and telangiectasia formation.[74,75]

Antibiotics

The use of topical antibiotics is generally indicated for the treatment of mild to moderate inflammatory (papular or pustular) lesions of acne vulgaris and rosacea. Particularly in those cases recalcitrant to other measures of care, topical antibiotics are prescribed in combination with topical retinoids and in combination with one another.

> The topical antimicrobial benzoyl peroxide is unique in that it serves to reduce rather than to increase the antibiotic resistance of *P. acnes*. When it is prescribed in combination with other topical antimicrobials, such as erythromycin and clindamycin, benzoyl peroxide is noted to elevate treatment efficacy significantly and to decrease antibiotic resistance. In turn, given the rising antibiotic resistance of *P. acnes*, patients with acne vulgaris should not be prescribed antibiotics as monotherapy. Instead, the use of topical or oral antibiotics should be accompanied by topical benzoyl peroxide, a topical retinoid, and a continuing dialogue on lifestyle modifications and adjuvant therapies as outlined earlier.[76–81]

Of note, benzoyl peroxide should not be applied at the same time as tretinoin because it may cause tretinoin to oxidize and become less effective. Basic descriptions of topical antibiotics commonly used in the treatment of acne vulgaris and rosacea are included in Table 73-1.

Pharmaceuticals: Systemic Preparations

When considering systemic pharmaceuticals in association with acne, the astute clinician should be aware of the range of oral medications that may induce or worsen acne vulgaris. Many of these are listed in Table 73-2.

Antibiotics

Oral antibiotics are reserved for the treatment of moderate to severe inflammatory acne lesions, specifically for refractory pustular, cystic, and nodular lesions of acne vulgaris and for rosacea with nodular lesions or ocular involvement.[82,83] Because they directly inhibit bacterial growth, oral antibiotics demonstrate relatively rapid clinical benefit, usually visible within 6 to 8 weeks. This, however, is at the cost of

TABLE 73-1. Topical Antibiotics Commonly Used for Acne Vulgaris or Acne Rosacea

PREPARATION AND DOSAGE	INDICATION	SIDE EFFECTS
Benzoyl peroxide 2.5% to 10%, applied topically once or twice daily	Acne vulgaris and glandular or phymatous subtypes of acne rosacea	Significant itching, redness, or drying of skin Contact dermatitis May bleach clothing
Clindamycin 1%, applied topically once or twice daily	Acne vulgaris and acne rosacea	Local irritation and drying of skin Very rare incidence of pseudomembranous colitis Will stain clothing
Erythromycin 1.5% to 2%, applied topically once or twice daily	Acne vulgaris and acne rosacea	Local irritation and drying of skin Will stain clothing
Sulfacetamide 5% or 10% lotion, with or without sulfur, applied topically twice daily	Acne vulgaris and acne rosacea	Local irritation, itching, redness Rare occurrence of hypersensitivity reactions Contraindicated in individuals allergic to sulfa
Metronidazole 0.75% or 1.0% cream, applied once or twice daily	Acne rosacea	Significant skin irritation and dryness

From Hull SK. Acne vulgaris and acne rosacea. In: Rakel D, ed. *Integrative Medicine*. 2nd ed. Philadelphia: Saunders; 2007.

TABLE 73-2. Oral Medications That Induce or Exacerbate Acne Vulgaris

Androgens (e.g., testosterone, danazol)	Isoniazid
Glucocorticoids (e.g., prednisone)	Cyclosporin
Corticotropin	Azathioprine
Lithium	Disulfuram
Phenytoin	Iodides, bromides
Phenobarbital	Epidermal growth factor receptor inhibitors

greater side effects, including increasing antibiotic resistance and risk of inflammatory bowel disease.[84] The following oral preparations are those most commonly used in the treatment of both acne vulgaris and rosacea.

Dosage

Erythromycin and tetracycline are administered at 250 to 500 mg twice daily. Doxycycline and minocycline are administered at 50 to 100 mg twice daily.

Precautions

As is typical with the use of systemic antibiotics, these medications may lead to vaginal candidiasis, reduced effectiveness of oral contraceptives, and gastrointestinal distress. Tetracycline should be taken on an empty stomach; along with doxycycline and minocycline, it may cause photosensitivity. Like tetracycline itself, these tetracycline derivatives are contraindicated in pregnancy and in children younger than 9 years, given their potential to reduce bone growth and to discolor developing teeth. Antibiotic resistance may be minimized by continually assessing for clinical response and discontinuing systemic antibiotics when inflammation resolves. Topical benzoyl peroxide and retinoid application should carry on, and if the clinical need again arises, the same oral antibiotic should be used as long as it is effective.

Retinoids

Systemic retinoids are extremely effective in the treatment of severe refractory nodular acne that is often to the point of scarring. This therapeutic option is unique in that it can permanently alter acne pathogenesis, yet its side effect profile has raised concern.

Dosage

Isotretinoin, 0.5 to 1 mg/kg/day, is administered once or in two divided doses daily. Duration of treatment is usually 20 weeks or for a cumulative dose of 120 mg/kg.[85]

Precautions

Oral retinoids are highly teratogenic. In turn, the Food and Drug Administration has implemented the iPLEDGE program (www.ipledgeprogram.com), which requires registration by licensed providers, participating pharmacies, and patients who agree to specified responsibilities before they may prescribe, distribute, or use the medication. For example, female patients of childbearing age must use two separate forms of birth control from 1 month before until 1 month after treatment.[86] In addition, oral retinoids may cause hepatotoxicity, mucocutaneous irritation, myalgias, hypertriglyceridemia, and pseudotumor cerebri. Depression and suicidality have been questioned but not conclusively evidenced as further adverse effects.[85,87]

Oral Contraceptives

Combined oral contraceptive pills (OCPs) decrease serum androgen levels and sebum production. They are a reasonable addition to a treatment regimen for female patients with moderate to severe acne vulgaris whether or not they have comorbid hyperandrogenism. All of the typical adverse effects of OCPs (e.g., nausea, weight gain, thromboembolic events) should be considered. There is some evidence that OCPs containing the progestin drospirenone are among the most efficacious and best tolerated as a part of acne management.[88–91]

Dosage

Some combinations that contain drospirenone include drospirenone–ethinyl estradiol (Yasmin, Gianvi, Ocella,Yaz). Oral contraceptive pills are taken as 1 tablet daily.

Phototherapy, Laser Therapy, and Surgery

In the treatment of acne vulgaris, limited evidence supports the efficacy of various light and laser therapies. It has been demonstrated that red-blue light therapy may be more effective than 5% benzoyl peroxide in the short term (4 to 12 weeks) and that pulsed dye laser therapy after 5-aminolevulinic acid application may transiently reduce inflammatory acne lesions.[81,92,93] Better quality, long-term studies are clearly needed. With respect to acne rosacea, laser therapy has shown promise in the reduction of associated telangiectasias and erythema.[94,95] Surgical techniques used in the reshaping of significant rhinophyma include heated scalpel, electrocautery, dermabrasion, and radiofrequency electrosurgery.[75]

Therapies to Consider

Other therapeutic options for which limited data are available include topical alpha-hydroxy acids, such as glycolic acid, and retinaldehyde for improved control of acne symptoms and associated postinflammatory hyperpigmentation.[96–98] One study demonstrated the efficacy of topical green tea for reducing acne severity.[99] Botanical preparations in Ayurvedic medicine, such as *Sunder vati,* and Japanese kampo remedies, such as *Mahonia aquifolium,* may also be useful adjunctive treatments of acne vulgaris.[100–105] The pharmaceutical spironolactone has been used to treat acne, but a systematic review of the literature found no evidence that it is effective.[106] For acne rosacea, topical application of permethrin,[107] the herbal extract *Chrysanthellum indicum,*[108] and the bioflavonoid silymarin with methylsulfonylmethane (MSM)[109] may lead to symptomatic improvement. Finally, as a topical or oral therapy, niacinamide has been noted to be of benefit in both acne vulgaris and rosacea.[52,110]

Prevention Prescription

- Maintain proper skin care: rinse gently, twice daily with warm water and a non–soap-based cleanser. Avoid scrubbing with abrasive materials, oil-based lotions and cosmetics, and picking at acne lesions.
- Reduce psychoemotional stress by getting adequate amounts of sleep and engaging in regular relaxation practices, such as meditation, guided imagery, breathing exercises, and massage therapy.
- For acne vulgaris, maintain a diet with a low glycemic load, rich in protein and omega-3 fatty acids and low in carbohydrates and saturated fats.
- Also for acne vulgaris, eat USDA-certified organic meats and dairy to limit consumption of animal products treated with exogenous androgenic hormones.
- Limit exposure to pharmaceutical medications that may cause eruption of acne vulgaris (see Table 73-2)
- Particularly in acne rosacea, avoid potential environmental triggers such as extremes in temperature as well as dietary triggers that may best be identified by way of a dedicated elimination diet.

Therapeutic Review

Mind-Body Medicine (for acne vulgaris and rosacea)

- Practice stress management and relaxation techniques — B1

Nutrition (for acne vulgaris)

- Maintain a diet low in glycemic load — B1
- Limit or eliminate dairy consumption — B1
- Maintain a diet high in omega-3 fatty acids with the option of flaxseed or fish oil supplementation — C1

Supplements (for acne vulgaris)

- Brewer's yeast: 2 g three times daily — B2
- Zinc gluconate: 30 mg daily — B2

Botanicals (for acne vulgaris)

- Tea tree oil: 5% to 15% solution or gel, applied topically once daily — B2

Pharmaceutical Preparations (for acne vulgaris and rosacea)

- Azelaic acid: 20% cream or 15% gel, applied topically twice daily for acne vulgaris or rosacea — B2
- Salicylic acid: applied topically one or two times daily for acne vulgaris — B2
- Retinoids: applied topically once nightly for acne vulgaris — A2
- Topical antibiotics (benzoyl peroxide, clindamycin, erythromycin, sulfacetamide, metronidazole) for acne vulgaris and rosacea (see Table 73-1) — A2
- Oral antibiotics (erythromycin, tetracycline, doxycycline, minocycline) for acne vulgaris and rosacea — A2
- Isotretinoin: 0.5 to 1 mg/kg/day, taken orally once or in two divided doses daily for acne vulgaris — A3

Surgical Therapy (for acne rosacea)

- Laser therapy for associated erythema and telangiectasias — B2
- Various surgical techniques for rhinophyma, a consequence of phymatous rosacea — C3

KEY WEB RESOURCES	
www.rosacea.org	Run by the National Rosacea Society, this is a Web site that includes links to information for patients, physicians, and researchers as well as to the Rosacea Review Newsletter, a glossary of terms, and a weblog.
www.glycemicindex.com	Maintained by the University of Sydney, this Web site provides descriptions of glycemic index and load, a food measurement database, literary resources, newsletters, press releases, and research efforts.
www.ipledgeprogram.com	This online resource provides information about the iPLEDGE program as well as the use and risk of isotretinoin. It is geared toward prescribing providers and patients and allows a search of participating pharmacies.

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