21st Edition

HARRISON'S®

PRINCIPLES OF INTERNAL MEDICINE

LOSCALZO
FAUCI
KASPER
HAUSER
LONGO
JAMESON

VOLUME 1

Mc Graw Hill

TREATMENT

Back Pain

Management is considered separately for acute and chronic low back pain syndromes without radiculopathy, and for back pain with radiculopathy.

ACUTE LOW BACK PAIN WITHOUT RADICULOPATHY

This is defined as pain of <12 weeks duration. Full recovery can be expected in >85% of adults with ALBP without leg pain. Most have purely "mechanical" symptoms (i.e., pain that is aggravated by motion and relieved by rest).

The initial assessment is focused on excluding serious causes of spine pathology that require urgent intervention, including infection, cancer, or trauma. Risk factors for a serious cause of ALBP are shown in Table 17-1. Laboratory and imaging studies are unnecessary if risk factors are absent. CT, MRI, or plain spine films are rarely indicated in the first month of symptoms unless a spine fracture, tumor, or infection is suspected.

The prognosis of ALBP is generally excellent; however, episodes tend to recur, and as many as two-thirds of patients will experience a second episode within 1 year. Most patients do not seek medical care and improve on their own. Even among those seen in primary care, two-thirds report substantial improvement after 7 weeks. This high likelihood of spontaneous improvement can mislead clinicians and patients about the efficacy of treatment interventions, highlighting the importance of rigorous prospective trials. Many treatments commonly used in the past are now known to be ineffective, including bed rest and lumbar traction.

Clinicians should reassure and educate patients that improvement is very likely and instruct them in self-care. Satisfaction and the likelihood of follow-up increase when patients are educated about prognosis, evidence-based treatments, appropriate activity modifications, and strategies to prevent future exacerbations. Counseling patients about the risks of overtreatment is another important part of the discussion. Patients who report that they did not receive an adequate explanation for their symptoms are likely to request further diagnostic tests.

In general, bed rest should be avoided for relief of severe symptoms or limited to a day or two at most. Several randomized trials suggest that bed rest does not hasten the pace of recovery. In general, early resumption of normal daily physical activity should be encouraged, avoiding only strenuous manual labor. Advantages of early ambulation for ALBP also include maintenance of cardiovascular conditioning; improved bone, cartilage, and muscle strength; and increased endorphin levels. Specific back exercises or early vigorous exercise have not shown benefits for acute back pain. Empiric use of heating pads or blankets is sometimes helpful.

NSAIDs and Acetaminophen Evidence-based guidelines recommend over-the-counter medicines such as NSAIDs and acetaminophen as first-line options for treatment of ALBP. In otherwise healthy patients, a trial of NSAIDs can be followed by acetaminophen for time-limited periods. In theory, the anti-inflammatory effects of NSAIDs might provide an advantage over acetaminophen to suppress inflammation that accompanies many causes of ALBP, but in practice there is no clinical evidence to support the superiority of NSAIDs. The risk of renal and gastrointestinal toxicity with NSAIDs is increased in patients with preexisting medical comorbidities (e.g., renal insufficiency, cirrhosis, prior gastrointestinal hemorrhage, use of anticoagulants or glucocorticoids, heart failure). Some patients elect to take acetaminophen and an NSAID together in hopes of a more rapid benefit.

Muscle Relaxants Skeletal muscle relaxants, such as cyclobenzaprine or methocarbamol, may be useful, but sedation is a common side effect. Limiting the use of muscle relaxants to nighttime only may be an option for patients with back pain that interferes with sleep.

Opioids There is no good evidence to support the use of opioid analgesics or tramadol as first-line therapy for ALBP. Their use is best reserved for patients who cannot tolerate acetaminophen or NSAIDs and for those with severe refractory pain. Also, the duration of opioid treatment for ALBP should be strictly limited to 3–7 days. As with muscle relaxants, these drugs are often sedating, so it may be useful to prescribe them at nighttime only. Side effects of short-term opioid use include nausea, constipation, and pruritus; risks of long-term opioid use include hypersensitivity to pain, hypogonadism, and dependency. Falls, fractures, driving accidents, and fecal impaction are other risks. The clinical efficacy of opioids for chronic pain beyond 16 weeks of use is unproven.

Mounting evidence of morbidity from long-term opioid therapy (including overdose, dependency, addiction, falls, fractures, accident risk, and sexual dysfunction) has prompted efforts to reduce its use for chronic pain, including back pain **(Chap. 13)**. When used, safety may be improved with automated notices for high doses, early refills, prescriptions from multiple pharmacies, overlapping opioid and benzodiazepine prescriptions, and in the United States by state-based prescription drug monitoring programs (PDMPs). A recent study indicated that most patients with opioid use disorder presenting to emergency departments had no prescriptions recorded in the PDMP, reflecting other methods used to obtain opioids. Greater access to alternative treatments for chronic pain, such as tailored exercise programs and cognitive behavioral therapy (CBT), may also reduce opioid prescribing.

Other Approaches There is no evidence to support use of oral or injected glucocorticoids, antiepileptics, antidepressants, or therapies for neuropathic pain such as gabapentin or herbal therapies. Commonly used nonpharmacologic treatments for ALBP are also of unproven benefit, including spinal manipulation, physical therapy, massage, acupuncture, laser therapy, therapeutic ultrasound, corsets, transcutaneous electrical nerve stimulation (TENS), special mattresses, or lumbar traction. Although important for chronic pain, use of back exercises for ALBP are generally not supported by clinical evidence. There is no convincing evidence regarding the value of ice or heat applications for ABLP; however, many patients report temporary symptomatic relief from ice or frozen gel packs just before sleep, and heat may produce a short-term reduction in pain after the first week. Patients often report improved satisfaction with the care that they receive when they actively participate in the selection of symptomatic approaches.

CHRONIC LOW BACK PAIN WITHOUT RADICULOPATHY

Back pain is considered chronic when the symptoms last >12 weeks; it accounts for 50% of total back pain costs. Risk factors include obesity, female gender, older age, prior history of back pain, restricted spinal mobility, pain radiating into a leg, high levels of psychological distress, poor self-rated health, minimal physical activity, smoking, job dissatisfaction, and widespread pain. In general, the same treatments that are recommended for ALBP can be useful for patients with CLBP. In this setting, however, the benefit of opioid therapy or muscle relaxants is less clear. In general, improved activity tolerance is the primary goal, while pain relief is secondary.

Some observers have raised concerns that CLBP may often be overtreated. For CLBP without radiculopathy, multiple guidelines explicitly recommend against use of SSRIs, any type of injection, TENS, lumbar supports, traction, radiofrequency facet joint denervation, intradiskal electrothermal therapy, or intradiskal radiofrequency thermocoagulation. On the other hand, exercise therapy and treatment of depression appear to be useful and underused.

Exercise Programs Evidence supports the use of exercise therapy to alleviate pain symptoms and improve function. Exercise can be one of the mainstays of treatment for CLBP. Effective regimens have generally included a combination of core-strengthening exercises, stretching, and gradually increasing aerobic exercise. A program of supervised exercise can improve compliance. Supervised intensive

physical exercise or "work hardening" regimens have been effective in returning some patients to work, improving walking distance, and reducing pain. In addition, some forms of yoga have been evaluated in randomized trials and may be helpful for patients who are interested.

Intensive multidisciplinary rehabilitation programs can include daily or frequent physical therapy, exercise, CBT, a workplace evaluation, and other interventions. For patients who have not responded to other approaches, such programs appear to offer some benefit. Systematic reviews, however, suggest that the evidence and benefits are limited.

Nonopioid Medications Medications for CLBP may include short courses of NSAIDs or acetaminophen. Duloxetine is approved for the treatment of CLBP (60 mg daily) and may also treat coincident depression. Tricyclic antidepressants can provide modest pain relief for some patients without evidence of depression. Depression is common among patients with chronic pain and should be appropriately treated.

Cognitive Behavioral Therapy CBT is based on evidence that psychological and social factors, as well as somatic pathology, are important in the genesis of chronic pain and disability; CBT focuses on efforts to identify and modify patients' thinking about their condition. In one randomized trial, CBT reduced disability and pain in patients with CLBP. Such behavioral treatments appear to provide benefits similar in magnitude to exercise therapy.

Complementary Medicine Back pain is the most frequent reason for seeking complementary and alternative treatments. Spinal manipulation or massage therapy may provide short-term relief, but long-term benefit is unproven. Biofeedback has not been studied rigorously. There is no convincing evidence that either TENS, laser therapy, or ultrasound are effective in treating CLBP. Rigorous trials of acupuncture suggest that true acupuncture is not superior to sham acupuncture, but that both may offer an advantage over routine care. Whether this is due entirely to placebo effects provided even by sham acupuncture is uncertain.

Injections and Other Interventions Various injections, including epidural glucocorticoid injections, facet joint injections, and trigger point injections, have been used for treating CLBP. However, in the absence of radiculopathy, there is no clear evidence that these approaches are sustainably effective.

Injection studies are sometimes used diagnostically to help determine the anatomic source of back pain. Pain relief following a glucocorticoid and anesthetic injection into a facet or medial branch block are used as evidence that the facet joint is the pain source; however, the possibility that the response was a placebo effect or due to systemic absorption of the glucocorticoids is difficult to exclude.

Another category of intervention for CLBP is electrothermal and radiofrequency therapy. Intradiskal therapy has been proposed using energy to thermocoagulate and destroy nerves in the intervertebral disk, using specially designed catheters or electrodes. Current evidence does not support the use of discography to identify a specific disk as the pain source, or the use of intradiskal electrothermal or radiofrequency therapy for CLBP.

Radiofrequency denervation is sometimes used to destroy nerves that are thought to mediate pain, and this technique has been used for facet joint pain (with the target nerve being the medial branch of the primary dorsal ramus), for back pain thought to arise from the intervertebral disk (ramus communicans), and radicular back pain (dorsal root ganglia). These interventional therapies have not been studied in sufficient detail to draw firm conclusions regarding their value for CLBP.

Surgery Surgical intervention for CLBP without radiculopathy has been evaluated in a number of randomized trials. The case for fusion surgery for CLBP without radiculopathy is weak. While some studies have shown modest benefit, there has been no benefit when compared to an active medical treatment arm, often including highly structured, rigorous rehabilitation combined with CBT. The use of bone matrix protein (BMP) instead of iliac crest graft for the fusion was shown to increase hospital costs and length of stay but not improve clinical outcomes.

Guidelines suggest that referral for an opinion on spinal fusion can be considered for patients who have completed an optimal nonsurgical treatment program (including combined physical and psychological treatment) and who have persistent severe back pain for which they would consider surgery. The high cost, wide geographic variations, and rapidly increasing rates of spinal fusion surgery have prompted scrutiny regarding the lack of standardization of appropriate indications. Some insurance carriers have begun to limit coverage for the most controversial indications, such as LBP without radiculopathy.

Lumbar disk replacement with prosthetic disks is US Food and Drug Administration–approved for uncomplicated patients needing single-level surgery at the L3-S1 levels. The disks are generally designed as metal plates with a polyethylene cushion sandwiched in between. The trials that led to approval of these devices were not blinded. When compared to spinal fusion, the artificial disks were "not inferior." Long-term follow-up is needed to determine device failure rates over time. Serious complications are somewhat more likely with the artificial disk. This treatment remains controversial for CLBP.

LOW BACK PAIN WITH RADICULOPATHY

A common cause of back pain with radiculopathy is a herniated disk affecting the nerve root and producing back pain with radiation down the leg. The term *sciatica* is used when the leg pain radiates posteriorly in a sciatic or L5/S1 distribution. The prognosis for acute low back and leg pain with radiculopathy due to disk herniation is generally favorable, with most patients showing substantial improvement over months. Serial imaging studies suggest spontaneous regression of the herniated portion of the disk in two-thirds of patients over 6 months. Nonetheless, several important treatment options provide symptomatic relief while the healing process unfolds.

Resumption of normal activity is recommended. Randomized trial evidence suggests that bed rest is ineffective for treating sciatica as well as back pain alone. Acetaminophen and NSAIDs are useful for pain relief, although severe pain may require short courses (3–7 days) of opioid analgesics. Opioids are superior for acute pain relief in the emergency department.

Epidural glucocorticoid injections have a role in providing symptom relief for acute lumbar radiculopathy due to a herniated disk, but do not reduce the use of subsequent surgical intervention. A brief course of high-dose oral glucocorticoids (methylprednisolone dose pack) for 3 days followed by a rapid taper over 4 more days can be helpful for some patients with acute disk-related radiculopathy, although this specific regimen has not been studied rigorously.

Diagnostic nerve root blocks have been advocated to determine if pain originates from a specific nerve root. However, improvement may result even when the nerve root is not responsible for the pain; this may occur as a placebo effect, from a pain-generating lesion located distally along the peripheral nerve, or from effects of systemic absorption.

Urgent surgery is recommended for patients who have evidence of CES or spinal cord compression, generally manifesting as combinations of bowel or bladder dysfunction, diminished sensation in a saddle distribution, a sensory level on the trunk, and bilateral leg weakness or spasticity. Surgical intervention is also indicated for patients with progressive motor weakness due to nerve root injury demonstrated on clinical examination or EMG.

Surgery is also an important option for patients who have disabling radicular pain despite optimal conservative treatment. Because patients with a herniated disk and sciatica generally experience rapid improvement over weeks, most experts do not recommend considering surgery unless the patient has failed to respond to a minimum of 6–8 weeks of nonsurgical management. For patients who have not improved, randomized trials show that surgery results in more rapid pain relief than nonsurgical treatment. However, after

Occasional cases of carpal tunnel syndrome produce pain and paresthesias extending into the forearm, arm, and shoulder resembling a C5 or C6 root lesion. Lesions of the radial or ulnar nerve can also mimic radiculopathy, at C7 or C8, respectively. EMG and NCSs can accurately localize lesions to the nerve roots, brachial plexus, or peripheral nerves.

For further discussion of peripheral nerve disorders, see Chap. 446.

SHOULDER

Pain arising from the shoulder can on occasion mimic pain from the spine. If symptoms and signs of radiculopathy are absent, then the differential diagnosis includes mechanical shoulder pain (bicipital tendonitis, frozen shoulder, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, or rotator cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast tumor). Mechanical pain is often worse at night, associated with local shoulder tenderness and aggravated by passive abduction, internal rotation, or extension of the arm. Demonstrating normal passive full range of motion of the arm at the shoulder without worsening the usual pain can help exclude mechanical shoulder pathology as a cause of neck region pain. Pain from shoulder disease may radiate into the arm or hand, but focal neurologic signs (sensory, motor, or reflex changes) are absent.

GLOBAL CONSIDERATIONS

Many of the considerations described above for LBP also apply to neck pain. The Global Burden of Diseases Study 2019 reported that neck pain ranked second only to back pain as a cause of total years lived with disability (YLD). In general, neck pain rankings were also higher in developed regions of the world.

TREATMENT

Neck Pain Without Radiculopathy

The evidence regarding treatment for neck pain is less comprehensive than that for LBP, but the approach is remarkably similar in many respects. As with LBP, spontaneous improvement is the norm for acute neck pain. The usual goals of therapy are to promote a rapid return to normal function and provide pain relief while healing proceeds.

Acute neck pain is often treated with NSAIDs, acetaminophen, cold packs, or heat, alone or in combination while awaiting recovery. Patients should be specifically educated regarding the favorable natural history of acute neck pain to avoid unrealistic fear and inappropriate requests for imaging and other tests. For patients kept awake by symptoms, cyclobenzaprine (5–10 mg) at night can help relieve muscle spasm and promote drowsiness. For patients with neck pain unassociated with trauma, supervised exercise with or without mobilization appears to be effective. Exercises often include shoulder rolls and neck stretches. The evidence in support of nonsurgical treatments for whiplash-associated disorders is generally of limited quality and neither supports nor refutes the common treatments used for symptom relief. Gentle mobilization of the cervical spine combined with exercise programs may be beneficial. Evidence is insufficient to recommend the use of cervical traction, TENS, ultrasound, trigger point injections, botulinum toxin injections, tricyclic antidepressants, and SSRIs for acute or chronic neck pain. Some patients obtain modest pain relief using a soft neck collar; there is little risk or cost. Massage can produce temporary pain relief.

For patients with chronic neck pain, supervised exercise programs can provide symptom relief and improve function. Acupuncture provided short-term benefit for some patients when compared to a sham procedure and is an option. Spinal manipulation alone has not been shown to be effective and carries a risk for injury. Surgical treatment for chronic neck pain without radiculopathy or spine instability is not recommended.

Neck Pain With Radiculopathy

The natural history of acute neck pain with radiculopathy due to disk disease is favorable, and many patients will improve without specific therapy. Although there are no randomized trials of NSAIDs for neck pain, a course of NSAIDs, acetaminophen, or both, with or without muscle relaxants, and avoidance of activities that trigger symptoms are reasonable as initial therapy. Gentle supervised exercise and avoidance of inactivity are reasonable as well. A short course of high-dose oral glucocorticoids with a rapid taper, or epidural steroids administered under imaging guidance can be effective for acute or subacute disk-related cervical radicular pain, but have not been subjected to rigorous trials. The risk of injection-related complications is higher in the neck than the low back; vertebral artery dissection, dural puncture, spinal cord injury, and embolism in the vertebral arteries have all been reported. Opioid analgesics can be used in the emergency department and for short courses as an outpatient. Soft cervical collars can be modestly helpful by limiting spontaneous and reflex neck movements that exacerbate pain; hard collars are in general poorly tolerated.

If cervical radiculopathy is due to bony compression from cervical spondylosis with foraminal narrowing, periodic follow-up to assess for progression is indicated and consideration of surgical decompression is reasonable. Surgical treatment can produce rapid pain relief, although it is unclear if long-term functional outcomes are improved over nonsurgical therapy. Indications for cervical disk surgery include a progressive motor deficit due to nerve root compression, functionally limiting pain that fails to respond to conservative management, or spinal cord compression. In other circumstances, clinical improvement over time regardless of therapeutic intervention is common.

Surgical treatments include anterior cervical diskectomy alone, laminectomy with diskectomy, or diskectomy with fusion. The risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to a fusion is ~3% per year and 26% per decade. Although this risk is sometimes portrayed as a late complication of surgery, it may also reflect the natural history of degenerative cervical disk disease.

FURTHER READING

Agency for Healthcare Research and Quality (AHRQ): Noninvasive treatments for low back pain. AHRQ Publication No. 16-EHC004-EF. February 2016, *https://effectivehealthcare.ahrq.gov/ehc/products/553/2178/back-pain-treatment-report-160229.pdf*

Austevoll IM et al: Decompression with or without fusion in degenerative lumbar spondylolisthesis. N Engl J Med 385:526, 2021.

Bailey CS et al: Surgery versus conservative care for persistent sciatica lasting 4 to 12 months. N Engl J Med 19;382:1093, 2020.

Cieza A et al: Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:2006, 2021.

Engstrom JW: Physical and Neurologic Examination. In Steinmetz et al (eds). *Benzel's Spine Surgery*, 5th ed. Philadelphia, Elsevier, 2021.

Goldberg H et al: Oral steroids for acute radiculopathy due to a herniated lumbar disk. JAMA 313:1915, 2015.

Hawk K et al: Past-year prescription drug monitoring program opioid prescriptions and self-reported opioid use in an emergency department population with opioid use disorder. Acad Emerg Med 25:508, 2018.

Jarvik JG et al: Association of early imaging for back pain with clinical outcomes in older adults. JAMA 313:1143, 2015.

Katz JN, Harris MB: Clinical practice. Lumbar spinal stenosis. N Engl J Med 358:818, 2008.

Theodore N: Degenerative cervical spondylosis. N Engl J Med 383:159, 2020.

Zygourakis CC et al: Geographic and hospital variation in cost of lumbar laminectomy and lumbar fusion for degenerative conditions. Neurosurgery 81:331, 2017.

units per day, may benefit some patients with smell and taste complaints during or following chemotherapy.

A number of medications have reportedly been used with success in ameliorating olfactory symptoms, although strong scientific evidence for efficacy is generally lacking. A report that theophylline improved smell function was uncontrolled and failed to account for the fact that some meaningful improvement occurs without treatment; indeed, the percentage of responders was about the same (~50%) as that noted by others to show spontaneous improvement over a similar time period. Antiepileptics and some antidepressants (e.g., amitriptyline) have been used to treat dysosmias and smell distortions, particularly following head trauma. Ironically, amitriptyline is also frequently on the list of medications that can ultimately distort smell and taste function, possibly from its anticholinergic effects. One study suggested that the centrally acting acetylcholinesterase inhibitor donepezil in AD resulted in improvements on smell identification measures that correlated with overall clinician-based impressions of change in dementia severity scores.

Alternative therapies, such as acupuncture, meditation, cognitive-behavioral therapy, and yoga, can help patients manage uncomfortable experiences associated with chemosensory disturbance and oral pain syndromes and to cope with the psychosocial stressors surrounding the impairment. Additionally, modification of diet and eating habits is also important. By accentuating the other sensory experiences of a meal, such as food texture, aroma, temperature, and color, one can optimize the overall eating experience for a patient. In some cases, a flavor enhancer like monosodium glutamate (MSG) can be added to foods to increase palatability and encourage intake.

Proper oral and nasal hygiene and routine dental care are extremely important ways for patients to protect themselves from disorders of the mouth and nose that can ultimately result in chemosensory disturbance. Patients should be warned not to overcompensate for their taste loss by adding excessive amounts of sugar or salt. Smoking cessation and the discontinuance of oral tobacco use are essential in the management of any patient with smell and/or taste disturbance and should be repeatedly emphasized.

A major and often overlooked element of therapy comes from chemosensory testing itself. Confirmation or lack of conformation of loss is beneficial to patients who come to believe, in light of unsupportive family members and medical providers, that they may be "crazy." In cases where the loss is minor, patients can be informed of the likelihood of a more positive prognosis. Importantly, quantitative testing places the patient's problem into overall perspective. Thus, it is often therapeutic for an older person to know that, while his or her smell function is not what it used to be, it still falls above the average of his or her peer group. Without testing, many such patients are simply told that they are getting old and nothing can be done for them, leading in some cases to depression and decreased self-esteem.

FURTHER READING

Devanand DP et al: Olfactory identification deficits are associated with increased mortality in a multiethnic urban community. Ann Neurol 78:401, 2015.

Doty RL: Olfaction in Parkinson's disease and related disorders. Neurobiol Dis 46:527, 2012.

Doty RL et al: Taste function in early stage treated and untreated Parkinson's disease. J Neurol 262:547, 2015.

Doty RL et al: Systemic diseases and disorders. Handbook Clin Neurol 164:361, 2019.

Doty RL et al: Treatments for smell and taste disorders: A critical review. Handbook Clin Neurol 164:455, 2019.

Fornazieri MA et al: Adherence and efficacy of olfactory training as a treatment for persistent olfactory loss. Am J Rhinol Allergy 34:238, 2020.

Hawkes CH, Doty RL: *Smell and Taste Disorders*. Cambridge, Cambridge University Press, 2018.

Liu G et al: Prevalence and risk factors of taste and smell impairment in a nationwide sample of the US population: A cross-sectional study. BMJ Open 6:e013246, 2016.

London B et al: Predictors of prognosis in patients with olfactory disturbance. Ann Neurol 63:159, 2008.

Moein ST et al: Smell dysfunction: A biomarker for COVID-19. Int Forum Allergy Rhinol 10:944, 2020.

Perricone C et al: Smell and autoimmunity: A comprehensive review. Clin Rev Allergy Immunol 45:87, 2013.

34 Disorders of Hearing

Anil K. Lalwani

Hearing loss can present at any age and is one of the most common sensory disorders in humans. Nearly 10% of the adult population has some hearing loss, and one-third of individuals age >65 years have a hearing loss of sufficient magnitude to require a hearing aid.

PHYSIOLOGY OF HEARING

The function of the external and middle ear is to amplify sound to facilitate conversion of the mechanical energy of the sound wave into an electrical signal by the inner-ear hair cells, a process called mechanotransduction **(Fig. 34-1)**. Sound waves enter the external auditory canal and set the tympanic membrane (eardrum) in motion, which in turn moves the malleus, incus, and stapes of the middle ear. Movement of the footplate of the stapes causes pressure changes in the fluid-filled inner ear, eliciting a traveling wave in the basilar membrane of the cochlea. The tympanic membrane and the ossicular chain in the middle ear serve as an impedance-matching mechanism, improving the efficiency of energy transfer from air to the fluid-filled inner ear. In its absence, nearly 99.9% of the acoustical energy would be reflected and thus not heard. Instead, the eardrum and the ossicles boost the sound energy nearly 200-fold by the time it reaches the inner ear.

Within the cochlea of the inner ear, there are two types of hair cells that aid in hearing: inner and outer. The inner and outer hair cells of the organ of Corti have different innervation patterns, but both are mechanoreceptors; they detect the mechanical energy of the acoustic signal and aid its conversion to an electrical signal that travels by the auditory nerve. The afferent innervation relates principally to the inner hair cells while the efferent innervation relates principally to the outer hair cells. The outer hair cells outnumber the inner hair cells by nearly 6:1 (20,000 vs 3500). The motility of the outer hair cells alters the micromechanics of the inner hair cells, creating a cochlear amplifier, which explains the exquisite sensitivity and frequency selectivity of the cochlea.

Stereocilia of the hair cells of the organ of Corti, which rests on the basilar membrane, are in contact with the tectorial membrane and are deformed by the traveling wave. The deformation stretches tiny filamentous connections (tip links) between stereocilia, leading to opening of ion channels, influx of potassium, and hair cell depolarization and subsequent neurotransmission. A point of maximal displacement of the basilar membrane is determined by the frequency of the stimulating tone. High-frequency tones cause maximal displacement of the basilar membrane near the base of the cochlea, whereas for low-frequency sounds, the point of maximal displacement is toward the apex of the cochlea.

Beginning in the cochlea, the frequency specificity is maintained at each point of the central auditory pathway: dorsal and ventral cochlear nuclei, trapezoid body, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body, and auditory cortex. At low frequencies, individual auditory nerve fibers can respond more or less synchronously with the stimulating tone. At higher frequencies, phase-locking occurs so that neurons alternate in response to particular phases of the cycle of the sound wave. Intensity is encoded by the

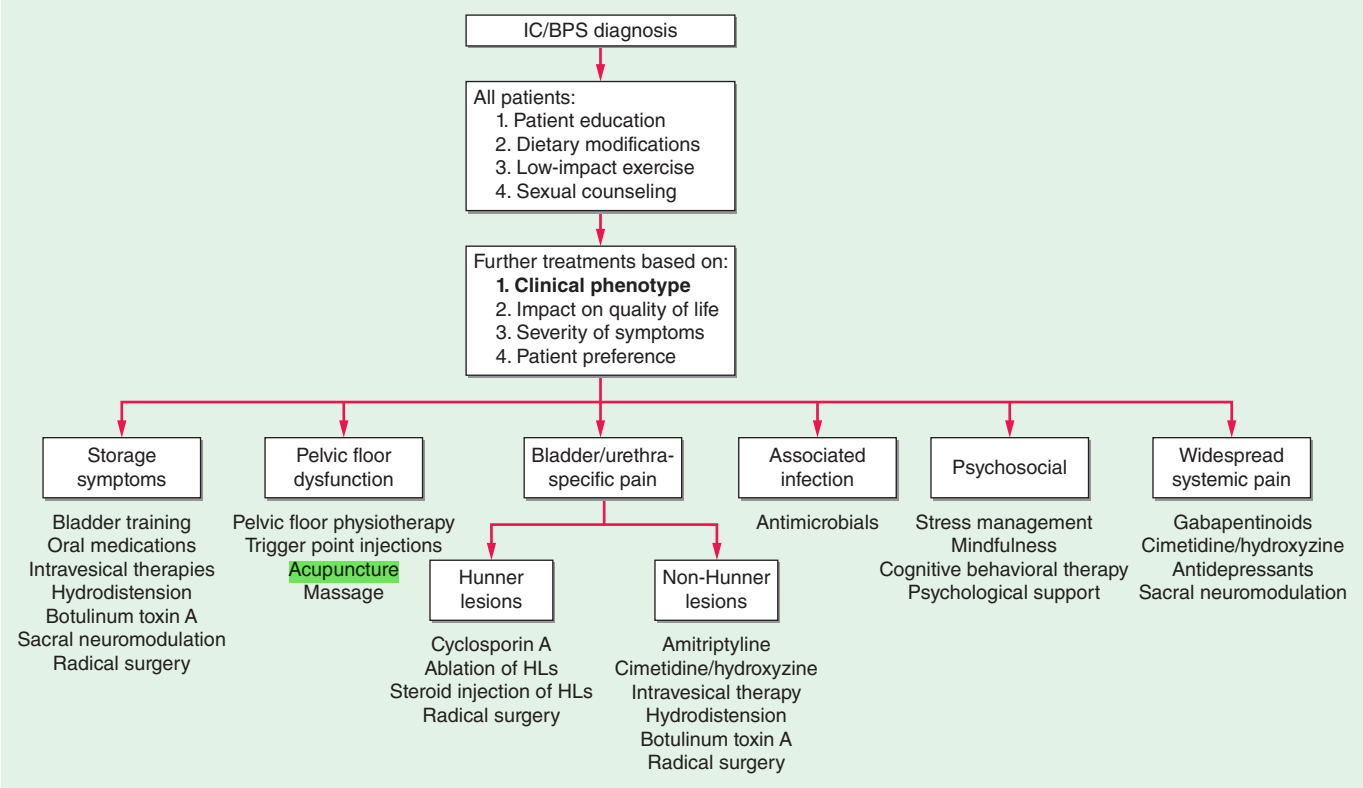

FIGURE 51-1 Proposed management paradigm for the treatment of interstitial cystitis (IC)/bladder pain syndrome (BPS). HLs, Hunner lesions.

CONSERVATIVE MEASURES

Conservative measures should be implemented for all patients with a diagnosis of IC/BPS. These therapies tend to be simple and inexpensive to introduce, pose little risk of significant side effects, and can be intensified or abandoned on the basis of the patient's response.

Patient Education Patient education and empowerment are paramount in this chronic pain disorder. Patients have often seen multiple practitioners prior to their diagnosis of IC/BPS. Acknowledging their suffering while educating them about their disease can go a long way in terms of relieving stress and anxiety related to an unknown and poorly understood problem. This acknowledgement also helps to develop a therapeutic patient–provider relationship. Setting realistic expectations and understanding that cure is not the goal constitute an important first step. Several resources are available for patients to explore at their own leisure.

Dietary Modifications Although limited evidence supports the role of dietary modifications, it has long been recognized that certain foods can trigger flares in IC/BPS patients and that simple dietary modifications can result in meaningful improvements in symptoms. Common dietary triggers include acidic and spicy foods and/or drinks, caffeinated or alcoholic beverages, artificial sweeteners, and/or gluten products; this list is by no means exhaustive, and dietary modifications should be made on an individual basis.

Pelvic Floor Physiotherapy Involvement of the pelvic floor in the pain syndrome can be ascertained on physical examination. Randomized studies have shown that, for patients who are found to have dysfunctional pelvic floors—muscle spasm, trigger points, or tenderness—contributing to their pain syndrome, pelvic floor physiotherapy may be beneficial. The musculoskeletal anatomy of the pelvic floor is complex; finding a provider with training specifically on the pelvic floor can be difficult but is crucial. Because accessing this resource may be financially burdensome for the patient, working together to find a way to obtain this helpful adjunctive therapy is important.

Psychological Interventions Mental health and psychosocial factors have long been identified as significantly prevalent in the IC/BPS population and can impact disease and quality-of-life outcomes. There is some indication that, in IC/BPS and other related chronic pain conditions, mindfulness and cognitive behavioral therapy may improve outcomes. Challenges in accessing these therapies are a major barrier, and there is a general lack of consensus on which specific interventions are best suited to individual patients.

MEDICAL THERAPIES

Only two medications are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of IC/BPS: pentosan polysulfate sodium (PPS) given orally and dimethyl sulfoxide (DMSO) given intravesically. However, a collection of medications, administered orally or intravesically, are commonly used (albeit off-label) for this purpose.

Oral Therapies • **PPS** The only FDA-approved oral medication for IC/BPS has recently come under scrutiny because of reports regarding its association with vision-threatening maculopathy. Although causation has yet to be established, given its marginal benefit in the treatment of IC/BPS, the authors recommend against the long-term use of this medication. For patients currently taking PPS, the risks and benefits of treatment must be weighed. Consideration of a trial of weaning off the medication may be in the best interest of the patient. Any patients experiencing vision-related complaints while taking PPS should undergo immediate ophthalmologic assessment.

ANTIBIOTICS IC/BPS is not an infectious condition, and thus, antibiotics should have no role in treatment. Furthermore, the overwhelming majority of IC/BPS patients will have received at least one course, if not several courses, of antibiotics at some point in the course of their disease. Nevertheless, it is not unreasonable to administer a single course of antibiotics (after obtaining a sample for urine culture and sensitivity testing) if the patient has never previously received such therapy.

AMITRIPTYLINE Amitriptyline's pharmacologic activity is attributable primarily to its anticholinergic properties, its serotonin and norepinephrine uptake–inhibiting activity, and its sedative effects, which may include an antihistaminic pathway. Amitriptyline has been used to treat IC/BPS and other chronic pain syndromes. Studies support

Predictive Factors The two most important predictive factors in breast cancer are ER and HER2 expression, and they should be performed on all primary or metastatic cancer biopsy specimens (Table 79-1). Adjuvant endocrine therapy reduces the risk of recurrence by one-half or more in patients with ER-rich cancers, whereas no detectable benefit is noted in patients with ER-poor or -negative cancers. ER is expressed as the percentage of positive cells within the cancer after IHC staining. Endocrine therapy is recommended for any patient with ≥10% positive cells, but not for those whose cancers only have 0–1% staining. The evidence supporting benefit in cases with 1–9% expression is weak, but given the potential benefit and relatively low toxicities of endocrine therapy, it is recommended for such patients with a low threshold for discontinuation if side effects are intolerable.

The HER2 protein is the target for anti-HER2-directed therapies. Adjuvant trastuzumab therapy reduces the risk of distant recurrence and death in patients with HER2-positive breast cancer by one-third or more but has no discernable effect on HER2-negative cancers. HER2 status is determined using either IHC staining for protein overexpression or fluorescent in situ hybridization (FISH) for gene amplification. IHC staining of 3+ (on a scale of 0–3+) is considered positive, whereas 0–1+ is considered negative. For cases with 2+ staining, reflex FISH analysis is recommended. FISH can either be used as the initial evaluation or for additional evaluation in IHC 2+ cases. *HER2* is considered amplified if the ratio of HER2 to centromere signal on chromosome 17 is ≥2.0. FISH is unnecessary if IHC is 3+ or 0–1+, nor is there reason for IHC testing if FISH is ≥2.0

No reliable predictive factors exist for chemotherapy in general or for specific types of chemotherapies. It has been hypothesized that chemotherapy may be more active in ER-negative and/or HER2-positive cancers. Luminal B cancers may be more chemotherapy sensitive, whereas luminal A cancers are perceived to be relatively chemotherapy resistant. At present, none of the tests for intrinsic subtype should be used to determine not to give chemotherapy to patients with poor anatomic *prognosis*, such as those with T4 or multiple positive nodes, based on *prediction* of resistance. Attempts to identify reliable predictive factors for individual classes of chemotherapeutic agents (such as anthracyclines, alkylating agents, or taxanes) have been unsuccessful. The platin salts (carboplatin, cisplatin) may have higher activity in patients with triple-negative breast cancer and perhaps in patients with HER2-positive disease. The PARP inhibitors may be more active in patients whose tumors have defects in homologous recombination DNA repair, a group that includes those with *BRCA* mutations.

Adjuvant Regimens • **Endocrine Therapy** Adjuvant endocrine therapy is indicated for nearly all patients with a diagnosis of ER-positive breast cancer and never for those with ER-negative disease. Two adjuvant endocrine therapy strategies are proven: the SERM tamoxifen or estrogen ablation. In addition to being effective in preventing new cancers and reducing the risk of locoregional recurrences in patients with DCIS, tamoxifen reduces the risk of distant recurrence and death due to invasive breast cancer by ~40% over the decade following diagnosis. It is equally effective in pre- and postmenopausal women, although it may be slightly less effective in very young (<40 years) patients. Because tamoxifen is a SERM, it has mixed ER antagonism (in the breast and brain) and agonism (in the bone, liver, and uterus). Therefore, it is active against breast cancer in the prevention, adjuvant, and metastatic settings.

Side effects of tamoxifen are predictable based on ER antagonism, including frequent hot flashes as well as vaginal discomfort/sexual dysfunction and myalgias and arthralgias. The agonistic effect results in reduction of osteopenia/osteoporosis, especially in postmenopausal women, but it increases thrombosis risk and endometrial cancers due to this effect in the liver and uterus, respectively.

Estrogen depletion can be achieved surgically in premenopausal women by oophorectomy or ovarian suppression with a gonadotropin-releasing hormone (GnRH) superagonist, such as goserelin or leuprolide, which invoke a tachyphylactic response, or a GnRH antagonist, such as triptorelin. However, women with nonfunctioning ovaries, whether induced or by natural menopause, still produce small amounts of estrogen by adrenal synthesis of estrogen precursors (testosterone, dehydroepiandrosterone [DHEA]). These are converted to estradiol and estrone by aromatase activity in peripheral fat and possibly cancer cells. In postmenopausal women, circulating estrogen can be reduced to nearly imperceptible levels with the use of oral AIs: anastrozole, letrozole, and exemestane. The three AIs are not significantly different in activity or toxicity. All are slightly more effective than tamoxifen.

Toxicities of the AIs are predictable based on very low estrogen levels. These include hot flashes, musculoskeletal symptoms, and atrophic vaginitis/sexual dysfunction. They also induce or worsen osteoporosis and fractures, although this effect can be abrogated with bone-modifying agents, such as bisphosphonates or rank ligand antagonists (denosumab).

For both tamoxifen and the AIs, musculoskeletal symptoms mimicking osteoarthritis and arthralgias can be treated with physical therapy and nonsteroidal anti-inflammatory drugs. After a brief period of washout after discontinuation, switching from one AI to another relieves this symptom in approximately a third of patients. These symptoms can also be reduced with either acupuncture or the antidepressant duloxetine. If AIs cannot be tolerated, tamoxifen is a reasonable therapy, assuming no contraindications, such as a past history of thrombosis or high risk of cerebrovascular disease. Hot flashes from either class of drugs are alleviated in approximately one-half of patients with use of one of several different antidepressant drugs.

For premenopausal women, optimal endocrine therapy depends on prognosis and patient choice. Complete estrogen depletion is slightly more effective than tamoxifen alone, but it may also be associated with more bothersome side effects, such as hot flashes, vaginal dryness, and sexual dysfunction. Complete estrogen depletion, consisting of either oophorectomy or chemical suppression of gonadotropins coupled with an AI, is indicated for women with worse prognosis, in particular node positivity. For those with more favorable prognosis, tamoxifen alone or with ovarian suppression is adequate and produces better quality of life. The AIs should not be administered to women with functioning, or dormant, ovaries, since the negative hypothalamic-pituitary feedback can result in a rebound overproduction of ovarian estrogens.

The duration of adjuvant endocrine treatment is unclear. Formerly, the standard recommendation was at least 5 years of therapy, which clearly reduces the risk of recurrence during that time and for a few years after discontinuation. However, the annual risk of distant recurrence during the subsequent 15 years is 0.5–3%, depending on the initial T and N status. Extended adjuvant endocrine therapy with either tamoxifen or an AI for at least 5 more years continues to reduce this late risk of relapse. The decision of whether to continue adjuvant endocrine therapy or not after 5 years must therefore take into consideration initial risk (T, N, grade), current side effects and potential cumulative toxicities, and the patient's perception of the relative and absolute benefits and risks.

Chemotherapy Multiple-agent adjuvant chemotherapy is more effective than single-agent chemotherapy. Although chemotherapeutic agents are usually delivered in combination, sequential single-agent chemotherapy is as effective, and may be slightly less toxic, although it requires longer total duration to deliver. Administration of four to six cycles of chemotherapy appears to be optimal; one cycle is less effective than six, but more than six cycles have generally increased toxicity without further efficacy. Importantly, although chemotherapy is combined with anti-HER2 therapy in patients with HER2-positive cancers, concurrent endocrine therapy, in particular tamoxifen, is antagonistic with chemotherapy.

can be used in patients with concomitant allergic rhinitis. Montelukast, in particular, is frequently used in children with mild asthma due to concerns of ICS-related growth suppression. Montelukast use may decrease due to safety warnings regarding depression with this compound. Leukotriene modifiers are effective in preventing exercise-induced bronchoconstriction without the tachyphylactic effects that occur with regular use of LABAs. Leukotriene modifiers are particularly effective in aspirin-exacerbated respiratory disease, which is characterized by significant leukotriene overproduction. They have also shown modest effect as add-on therapy in patients poorly controlled on high-dose ICS/LABA.

CysLT$_1$ Antagonists Montelukast and zafirlukast are administered orally once or twice daily, respectively. The onset of effect is rapid (hours), with the majority of chronic effectiveness seen within 1 month.

5-Lipoxygenase Inhibition Zileuton in its extended form is administered orally twice a day.

Safety Montelukast is well tolerated, but an association with suicidal ideation has now resulted in a warning label from the U.S. Food and Drug Administration. Zileuton increases liver function tests (transaminases) in 3% of patients. Intermittent monitoring is suggested. It inhibits CYP1A2, and appropriate dose adjustments of concomitant medications may be necessary.

Cromolyn Sodium Cromolyn sodium is an inhaled agent believed to stabilize mast cells. It is only available by nebulization and must be administered two to four times a day. It is mildly to modestly effective and appears to be helpful for exercise-induced bronchospasm. It is used primarily in pediatrics in those concerned about ICS side effects.

Anti-IgE Omalizumab, a monoclonal antibody to the Fc portion of the IgE molecule, prevents the binding of IgE to mast cells and basophils. Reduction in free IgE that can bind to effector cells blocks antigen-related signaling, which is responsible for production or release of many of the mediators and cytokines critical to asthma pathobiology. In addition, through feedback mechanisms, reduction in IgE production occurs as well. Anti-IgE has been shown to increase interferon production in rhinovirus infections, decrease viral-induced asthma exacerbations, and reduce duration and peak viral shedding. This effect is believed to be due to IgE's ability to reduce interferon γ production in response to viral infections.

Use In asthma, anti-IgE has been tested in patients with a circulating IgE ≥30 IU/mL and a positive skin test or RAST to a perennial allergen. It is generally used in patients not responsive to moderate- to high-dose ICS/LABA. It reduces exacerbations by 25–50% and can reduce asthma symptoms but has minimal effect on lung function. Anti-IgE is dosed based on body weight and circulating IgE and is administered subcutaneously every 2–4 weeks depending on the calculated dose. In the United States, the maximum dose is 300 mg every 2 weeks, which generally restricts the drug to those with a body weight ≤150 kg. Most effects are generally seen in 3–6 months. Retrospective studies have suggested that patients with an exhaled nitric oxide approximately ≥20 ppb or circulating eosinophils ≥260/μL have the greatest response as ascertained by reduction in exacerbations. FeNO is slightly reduced by treatment, but circulating IgE, as measured by available clinical tests, is not affected since these tests measure total circulating IgE, not free IgE.

Safety The incidence of side effects is low. Anaphylaxis has been reported in 0.2% of patients receiving the drug.

IL-5–Active Drugs Mepolizumab and reslizumab are monoclonal antibodies that bind to IL-5, and benralizumab binds to the IL-5 receptor. They rapidly (within a day) reduce circulating eosinophils.

Use In patients symptomatic on moderate- to high-dose ICS/LABA, generally with two or more exacerbations that require OCS per year and with an eosinophil count of ≥300/μL, IL-5–active drugs reduce exacerbations by about half or more. FEV$_1$ and symptoms improve moderately as well. In patients who are not on chronic OCSs, these drugs are less effective in those with eosinophil counts <300/μL. They are also effective in reducing the need for chronic OCSs regardless of circulating eosinophil count (presumably due to the fact that many of those patients have type 2 inflammation but their circulating eosinophils have been suppressed by the systemic OCS). FeNO and IgE are relatively unaffected by these drugs. Most clinical effects are usually seen within 3–6 months.

Safety These drugs are associated with minimal side effects. Mepolizumab and benralizumab are approved for home administration.

Anti–IL-4/13 The IL-4 and IL-13 receptors are heterodimers that share a common subunit, IL-4 receptor α. Dupilumab binds to this subunit and, thus, blocks signaling through both receptors.

Use In addition to effectiveness in the phenotype of patients who respond to anti–IL-5 therapies, poorly controlled patients on moderate- to high-dose ICS/LABA with an FeNO of 20–25 ppb also appear to respond to dupilumab even if their peripheral eosinophils are not elevated. Dupilumab reduces exacerbations by ≥50%, decreases symptoms, and may produce more of an effect on FEV$_1$ than anti–IL-5 drugs. It gradually reduces FeNO and IgE levels. Paradoxically, circulating eosinophil counts may initially temporarily increase. Most effects are seen by 3–6 months of therapy.

Safety Side effects are minimal but cases of serious systemic eosinophilia associated with the reduction of oral corticosteroids have been noted. This drug is also approved for home administration and is also approved for atopic dermatitis.

Bronchial Thermoplasty, Alternative Therapies, and Therapies Under Development • **Bronchial Thermoplasty** This procedure involves radiofrequency ablation of the airway smooth muscle in the major airways administered through a series of three bronchoscopies for patients with severe asthma. There is some evidence that it may reduce exacerbations in very select patients. The procedure may be accompanied by significant morbidity, and most guidelines do not recommend it other than in the context of clinical trials or registries.

Alternative Therapies Alternative therapies such as acupuncture and yoga have not been shown to improve asthma in controlled trials. Studies with placebo have demonstrated that there may be a significant response to placebo.

Therapies in Development Trials are underway targeting pathways and receptors shown in Fig. 287-3. Those in more advanced stages of development include therapies targeting TSLP, IL-33, and CRTH$_2$. Studies targeting IL-17 and TNF-α have not shown efficacy, but it is unclear if they were appropriately targeted. Whether these interventions might prove useful for particular endotypes of asthma is unclear. Proof-of-concept studies targeting mast cells via inhibition of tyrosine kinase have suggested efficacy in severe asthma.

APPROACH TO THE PATIENT

Asthma

U.S. (National Asthma Education and Prevention Program [NAEPP]) and World Health Organization (Global Initiative for Asthma [GINA]) guidelines advise a symptomatic approach to asthma treatment assuming that appropriate measures have been taken to address asthma triggers, exposures, and comorbidities enumerated in Tables 287-2 and 287-3. Additionally, adherence and inhaler techniques need to be addressed. Poor adherence or poor inhaler technique has been identified as the cause of poor asthma control in up to 50% of patients referred for poorly controlled asthma.

The stepwise approach to intensifying and reducing asthma therapy is outlined in **Table 287-5**. It involves "stepping" therapy up or down based on assessment of whether asthma is controlled by

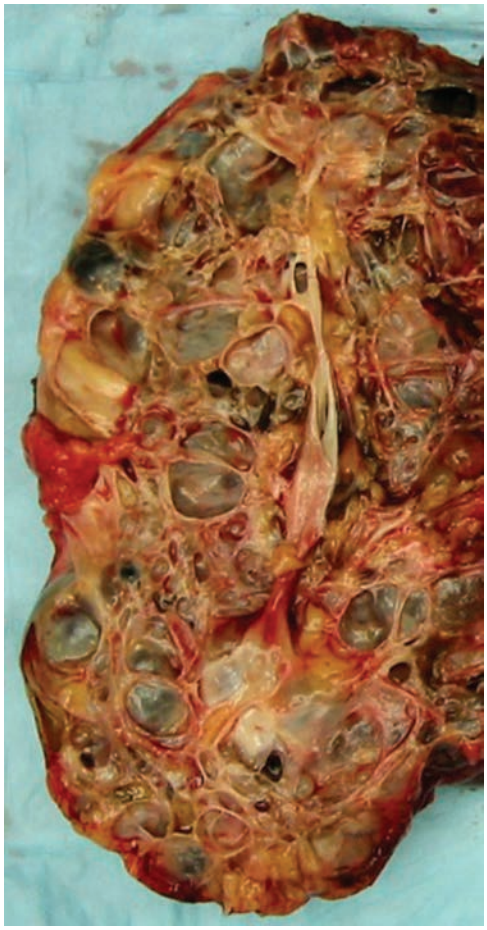

FIGURE 315-2 Photograph showing a kidney from a patient with autosomal dominant polycystic kidney disease. The kidney has been cut open to expose the parenchyma and internal aspects of cysts.

TREATMENT

Autosomal Dominant Polycystic Kidney Disease

No specific treatment to prevent cyst growth or the decline of renal function has been approved by the U.S. Food and Drug Administration. Blood pressure control to a target of 140/90 mmHg is recommended according to the guidelines from the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VIII report) for reducing cardiovascular complications in ADPKD and renal disease progression. More rigorous blood pressure control does not equal greater clinical benefits. Maintaining a target systolic blood pressure to 110 mmHg in patients with moderate or advanced disease may increase the risk of renal disease progression by reducing renal blood flow. Lipid-soluble antibiotics against common gram-negative enteric organisms include trimethoprim-sulfamethoxazole, quinolones, and chloramphenicol, and are preferred for cyst infection because most renal cysts are not connected to glomerular filtration and antibiotics that are capable of penetrating the cyst walls are likely to be more effective. Treatment often requires 4–6 weeks. The treatment of kidney stones in ADPKD includes standard measures such as analgesics for pain relief, and hydration to ensure adequate urine flow. Management of chronic flank, back, or abdominal pain due to renal enlargement may include both pharmacologic (nonnarcotic and narcotic analgesics) and nonpharmacologic (transcutaneous electrical nerve stimulation, acupuncture, and biofeedback). Occasionally surgical decompression of cysts may be necessary. More than half of ADPKD patients eventually require peritoneal dialysis, hemodialysis, or kidney transplantation. Peritoneal dialysis may not be suitable for some patients with massively enlarged polycystic kidneys due to the small intraabdominal space for efficient peritoneal exchange of fluid and solutes and increased chance of abdominal hernia and back pain. Patients with very large polycystic kidneys and recurrent renal cyst infection may require pretransplant nephrectomy or bilateral nephrectomy to accommodate the allograft and reduce the pain.

Specific treatment strategies for ADPKD have focused on slowing renal disease progression and lowering cardiovascular risk. For the latter, the main approach is to control blood pressure by inhibiting the renin-angiotensin-aldosterone system. The HALT PKD trial was set to evaluate the impact of intensive blockade of the renin-angiotensin-aldosterone system and levels of blood pressure control on progressive renal disease. This trial found that rigorous blood pressure control could slow cyst growth. Most approaches target the slowing of renal disease progression by inhibiting cell proliferation and fluid secretion. Several clinical trials have been conducted targeting cell proliferation: sirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR) pathway; OPC31260 and tolvaptan, which inhibits cyclic adenosine monophosphate (cAMP) pathways by antagonizing the activation of vasopressin V2 receptor (V2R) in collecting ducts and reduces cell proliferation by decreasing renal cAMP levels; and somatostatin analogues, which reduce cAMP levels by binding to several G-protein coupled receptors. The TAMPO and ALADIN trials showed that V2R antagonists and somatostatin analogues (octreotide-LAR groups) respectively slowed the decline of renal function. Some side effects, such as liver function impairment, polydipsia, and diarrhea, have been observed for tolvaptan and cholecystitis for octreotide-LAR. A recent report also showed that tolvaptan reduces renal pain. DIPAK, a small multicenter European study, showed that nerve block may be used to relieve pain in ADPKD patients suffering with refractory chronic pain. A combination of different growth inhibitors may enhance efficacy and reduce side effects. Notably, treatments may vary depending on the patient population. For example, the FDA has indicated tolvaptan to be only for patients at risk of rapidly progressing disease. Combining genotypic and imaging information may predict kidney growth rates and help in selecting this patient population.

Additional preclinical studies in animal models include the use of inhibitors to nonreceptor tyrosine kinase Src, B-raf, cyclin-dependent kinase (CDK), transcription factors STAT3 and STAT6 (pyrimethamine and leflunomide), purinergic receptors, hepatocyte growth factor receptor, glucosylceramide, agonists to peroxisome proliferator-activated receptor-gamma (PPARγ) receptors (thiazolidodinediones), and targeting microRNAs. Reprogramming the metabolic pathway through studies of transcription regulator super enhancer as well as dietary control including time-restricted feeding, have been shown in murine models to reduce cyst area, kidney fibrosis, inflammation, and injury. Branched chain amino acids appear to enhance cyst development in a mouse model.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Genetic Considerations ARPKD is a significant hereditary renal disease in childhood, with an estimated prevalence of 1 in 20,000 live births. A carrier frequency of up to 1:70 has been reported. Mutations in a single gene, *PKHD1*, are responsible for all the clinical presentations of ARPKD. *PKHD1*, localized on human chromosome region 6p21.1–6p12.2, is one of the largest genes in the genome, occupies ~450 kb of DNA, and contains at least 86 exons. It produces multiple alternatively spliced transcripts. The largest transcript encodes fibrocystin/polyductin (FPC), which is a large receptor-like integral membrane protein of 4074 amino acids. FPC has a

find it difficult to apply tape, and skin irritation from the tape is common, and like realigning braces, patellar braces may slip.

Although their effect on malalignment is questionable, neoprene sleeves pulled up to cover the knee lessen pain and are easy to use and popular among patients. The explanation for their therapeutic effect on pain is unclear.

In patients with knee OA, acupuncture produces modest pain relief compared to placebo needles and may be an adjunctive treatment, though placebo effect is likely high. In patients with refractory joint pain from OA, radiofrequency ablation of the nerves innervating the joint has been shown to provide prolonged pain relief, although long-term safety is unknown.

PHARMACOTHERAPY

Although approaches involving physical modalities constitute its mainstay, pharmacotherapy serves an important adjunctive role in OA treatment for symptom management. Available drugs are administered using oral, topical, and intraarticular routes. To date, there are no available drugs that alter the disease process itself.

Acetaminophen, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and Cyclooxygenase-2 (COX-2) Inhibitors NSAIDs are the most popular drugs to treat osteoarthritic pain. They can be administered either topically or orally. In clinical trials, oral NSAIDs produce ~30% greater improvement in pain than high-dose acetaminophen. Occasional patients treated with NSAIDs experience dramatic pain relief, whereas others experience little improvement. Initially, NSAIDs should be administered topically or taken orally on an "as-needed" basis because side effects are less frequent with low intermittent doses. If occasional medication use is insufficiently effective, then daily treatment may be indicated, with an anti-inflammatory dose selected (Table 371-1). Patients should be reminded to take low-dose aspirin and ibuprofen or naproxen at different times to eliminate a drug interaction.

NSAIDs taken orally have substantial and frequent side effects, the most common of which is upper gastrointestinal (GI) toxicity, including dyspepsia, nausea, bloating, GI bleeding, and ulcer disease. Thirty to forty percent of patients experience upper GI side effects so severe as to require discontinuation of medication. To minimize the risk of nonsteroidal-related GI side effects, patients should take NSAIDs after food; if risk is high, patients should take a gastroprotective agent, such as a proton pump inhibitor. Certain oral agents are safer to the stomach than others, including nonacetylated salicylates and nabumetone. Major NSAID-related GI side effects can occur in patients who do not complain of upper GI symptoms. In one study of patients hospitalized for GI bleeding, 81% had no premonitory symptoms.

Because of the increased rates of cardiovascular events associated with conventional NSAIDs such as diclofenac, many of these drugs are not appropriate long-term treatment choices for older persons with OA, especially those at high risk of heart disease or stroke. The American Heart Association has identified COX-2 inhibitors as putting patients at high risk, although low doses of celecoxib (≤200 mg/d) are not associated with an elevation of risk. The only conventional NSAIDs that appear safe from a cardiovascular perspective are naproxen and low-dose celecoxib, but they do have GI toxicity.

There are other common side effects of NSAIDs, including the tendency to develop edema because of prostaglandin inhibition of afferent blood supply to glomeruli in the kidneys and, for similar reasons, a predilection toward reversible renal insufficiency. Blood pressure may increase modestly in some NSAID-treated patients. Oral NSAIDs should not be used in patients with stage IV or V renal disease and should be used with caution in those with stage III disease.

NSAIDs can be placed into a gel or topical solution with another chemical modality that enhances penetration of the skin barrier creating a topical NSAID. When absorbed through the skin, plasma concentrations are an order of magnitude lower than with the same amount of drug administered orally or parenterally. However, when these drugs are administered topically in proximity to a superficial joint (knees, hands, but not hips), the drug can be found in joint tissues such as the synovium and cartilage. Trial results have varied but generally have found that topical NSAIDs are slightly less efficacious than oral agents, but have far fewer GI and systemic side effects. Unfortunately, topical NSAIDs often cause local skin irritation where the medication is applied, inducing redness, burning, or itching (see Table 371-1).

TABLE 371-1 Pharmacologic Treatment for Osteoarthritis

TREATMENT	DOSAGE	COMMENTS
Oral NSAIDs and COX-2 inhibitors		Take with food. Increased risk of myocardial infarction and stroke for some NSAIDs. High rates of gastrointestinal side effects, including ulcers and bleeding, occur. Patients at high risk for gastrointestinal side effects should also take either a proton pump inhibitor or misoprostol.[a] There is an increase in gastrointestinal side effects or bleeding when taken with acetylsalicylic acid. Can also cause edema and renal insufficiency.
Naproxen	375–500 mg bid	
Salsalate	1500 mg bid	
Ibuprofen	600–800 mg 3–4 times a day	
Celecoxib	100–200 mg qd	
Topical NSAIDs		Rub onto joint. Few systemic side effects. Skin irritation common.
Diclofenac Na 1% gel	4 g qid (for knees, hands)	
Acetaminophen	Up to 1 g tid	Of limited efficacy and only conditionally recommended
Opiates	Various	Common side effects include dizziness, sedation, nausea or vomiting, dry mouth, constipation, urinary retention, and pruritus. Addiction risk. Less efficacious than oral NSAIDs
Capsaicin	0.025–0.075% cream 3–4 times a day	Can irritate mucous membranes.
Intraarticular injections		
Steroids		
Hyaluronans	Varies from 3 to 5 weekly injections depending on preparation	Mild to moderate pain at injection site. Controversy exists regarding efficacy.

[a]Patients at high risk include those with previous gastrointestinal events, persons ≥60 years, and persons taking glucocorticoids. Trials have shown the efficacy of proton pump inhibitors and misoprostol in the prevention of ulcers and bleeding. Misoprostol is associated with a high rate of diarrhea and cramping; therefore, proton pump inhibitors are more widely used to reduce NSAID-related gastrointestinal symptoms.

Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: From DT Felson: Osteoarthritis of the Knee. N Engl J Med 354:841, 2006. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The treatment effect of acetaminophen (paracetamol) in OA is small and not considered clinically meaningful (Table 371-1). However, for a minority of patients, it is adequate to control symptoms, in which case more toxic drugs such as NSAIDs can be avoided.

Intraarticular Injections: Glucocorticoids and Hyaluronic Acid Because synovial inflammation is likely to be a major cause of pain in patients with OA, local anti-inflammatory treatments administered intraarticularly may be effective in ameliorating pain, for up to 3 months. Glucocorticoid injections provide such efficacy, but response is variable. While some patients having little relief of pain, most experience pain relief lasting up to several months. Synovitis, a major cause of joint pain in OA, may abate after an injection, and this correlates with the reduction in knee pain severity. Glucocorticoid injections are useful to get patients over acute flares of pain. Repeated injections may cause minor amounts of cartilage loss with probably unimportant clinical consequences.

Hyaluronic acid injections can be given for treatment of symptoms in knee and hip OA, but most evidence suggests no efficacy versus placebo (Table 371-1).

GENETICS AND PHYSIOLOGY

As in most complex diseases, it is likely that a number of genes contribute to vulnerability to the development of FM. To date, these genes appear to be in pathways controlling pain and stress responses. Some of the genetic underpinnings of FM are shared across other chronic pain conditions. Genes associated with metabolism, transport, and receptors of serotonin and other monoamines have been implicated in FM and overlapping conditions. Genes associated with other pathways involved in pain transmission have also been described as vulnerability factors for FM. Taken together, the pathways in which polymorphisms have been identified in FM patients further implicate central factors in mediation of the physiology that leads to the clinical manifestations of FM.

Psychophysical testing of patients with FM has demonstrated altered sensory afferent pain processing and impaired descending noxious inhibitory control leading to hyperalgesia and allodynia. Functional MRI and other research imaging procedures clearly demonstrate activation of the brain regions involved in the experience of pain in response to stimuli that are innocuous in study participants without FM. Pain perception in FM patients is influenced by the emotional and cognitive dimensions, such as catastrophizing and perceptions of control, providing a solid basis for recommendations for cognitive and behavioral treatment strategies.

Studies have indicated that some patients meeting criteria for FM may have a small fiber neuropathy. Other studies have identified alterations in expressed gene or metabolic signatures in peripheral blood. These early studies raise the possibility that confirmatory diagnostic testing could be developed in the future to assist in the diagnosis of FM.

APPROACH TO THE PATIENT

Fibromyalgia

FM is common and has an extraordinary impact on the patient's function and health-related quality of life. Optimal management requires prompt diagnosis and assessment of pain, function, and psychosocial context. Physicians and other health professionals can be helpful in managing some of the symptoms and impact of FM. Developing a partnership with patients is essential for improving the outcome of FM, with a goal of understanding the factors involved, implementing a treatment strategy, and choosing appropriate nonpharmacologic and pharmacologic treatments.

TREATMENT

Fibromyalgia

NONPHARMACOLOGIC TREATMENT

Patients with chronic pain, fatigue, and other neuropsychological symptoms require a framework for understanding the symptoms that have such an important impact on their function and quality of life. Explaining the genetics, triggers, and physiology of FM can be an important adjunct in relieving associated anxiety and in reducing the overall cost of health care resources. In addition, patients must be educated regarding expectations for treatment. The physician should focus on improved function and quality of life rather than elimination of pain. Illness behaviors, such as frequent physician visits, should be discouraged and behaviors that focus on improved function strongly encouraged.

Treatment strategies should include physical conditioning, with encouragement to begin at low levels of aerobic exercise and to proceed with slow but consistent advancement. Physical activity and exercise are consistently found to be the most helpful strategies.

TABLE 373-3 Pharmacologic Agents Effective for Treatment of Fibromyalgia

Muscle relaxant
Cyclobenzaprine
Antidepressants: balanced serotonin–norepinephrine reuptake inhibitors
Amitryptiline[a]
Duloxetine[b,c]
Milnacipran[b,c]
Anticonvulsants: ligand of the alpha-2-delta subunit of voltage-gated calcium channels
Pregabalin[b]
Analgesic
Tramadol

[a]RA Moore et al: Cochrane Database Syst Rev 12:CD008242, 2012. [b]Approved by the U.S. Food and Drug Administration. [c]W Hauser et al: Cochrane Database Syst Rev 1: CD010292, 2013.

Source: GJ Macfarlane et al: EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 76:318, 2017.

Patients who have been physically inactive may do best in supervised or water-based programs at the start. Strength training may be recommended after patients reach their aerobic goals. Transcutaneous electric nerve stimulation (TENS) reduces movement-evoked pain and fatigue. Meditative movement therapies, such as qigong, yoga, or Tai Chi, may also be helpful. Other defined physical therapies such as acupuncture or hydrotherapy may also be considered. Exercise programs are helpful in reducing tenderness and enhancing self-efficacy. Cognitive-behavioral strategies to improve sleep hygiene and reduce illness behaviors can also be helpful in management.

PHARMACOLOGIC APPROACHES

It is essential for the clinician to treat any comorbid triggering condition and to clearly delineate for the patient the treatment goals for each medication. For example, glucocorticoids or nonsteroidal anti-inflammatory drugs may be useful for management of inflammatory triggers but are not effective against FM-related symptoms. At present, the treatment approaches that have proved most successful in FM patients target afferent or descending pain pathways. **Table 373-3** lists the drugs with demonstrated effectiveness. It should be emphasized that strong opioid analgesics are to be avoided in patients with FM. These agents have no demonstrated efficacy in FM and are associated with adverse effects that can worsen both symptoms and function. Tramadol, an opioid with mild serotonin-noradrenaline reuptake inhibitor activity, has been studied in this population with indication of efficacy. Use of single agents to treat multiple symptom domains is strongly encouraged. For example, if a patient's symptom complex is dominated by pain and sleep disturbance, use of an agent that exerts both analgesic and sleep-promoting effects is desirable. These agents include cyclobenzaprine, sedating antidepressants such as amitriptyline, and alpha-2-delta ligands such as gabapentin and pregabalin. For patients whose pain is associated with fatigue, anxiety, or depression, drugs that have both analgesic and antidepressant/anxiolytic effects, such as duloxetine or milnacipran, may be the best first choice.

FURTHER READING

Clauw DJ: Fibromyalgia: A clinical review. JAMA 311:1547, 2014.

Macfarlane GJ et al: EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 76:318, 2017.

Wolf F et al: 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 46:319, 2016.

includes 250 mg IM ceftriaxone and a 14-day course of oral doxycycline 100 mg twice daily. If the presentation is acute with high fever, nausea, vomiting, severe abdominal pain, or presence of tubo-ovarian abscess, inpatient therapy is recommended **(Chap. 136)**. Conservative management is an important consideration for *ovarian cysts*, if torsion is not suspected, to avoid unnecessary surgery and associated risks of reduced fertility due to cystectomy or adhesions. If surgery is performed, it is preferable to perform a cystectomy, removing the cyst wall and leaving the remaining ovary, in a reproductive-age woman. Combined hormonal contraceptives are recommended in women with a history of recurrent ovarian cyst formation. Surgical treatment may be required for *ectopic pregnancies* when the patient presents with acute pain, is hemodynamically unstable, or has signs of intraperitoneal bleeding. The choice of salpingectomy versus salpingostomy is based on patient's presentation, desire for future child bearing, and prior pelvic infections. Clinically stable women presenting with unruptured ectopic pregnancies may be appropriate for treatment with methotrexate, which is effective in ~90% of cases when multiple doses are used. Threatened abortion is managed conservatively even in the presence of a subchorionic hemorrhage. The treatment of endometritis is similar to PID. Pain from a degenerating fibroid, if visualized on pelvic sonography, can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs).

CHRONIC PELVIC PAIN

Chronic pelvic pain is a complex condition resulting from gynecologic, urologic, or gastrointestinal organs and contributes to significant frustration and burden of disease. Common gynecologic conditions contributing to chronic pain are endometriosis, fibroids, adenomyosis, and adnexal pathology. Estimated prevalence rates range from 5 to 20% for cyclic and noncyclic pain. In addition to a detailed history and physical exam, the evaluation of chronic pelvic pain typically includes a pelvic ultrasound. As causes other than those related to the female reproductive system are common, referral should be made to other specialists, as appropriate. Neuromuscular and psychosomatic etiologies should also be considered.

Some women experience discomfort at the time of ovulation (*mittelschmerz* or *ovulation pain*). The pain can be quite intense but is generally of short duration. The mechanism is thought to involve rapid expansion of the dominant follicle, although it also may be caused by peritoneal irritation by follicular fluid released at the time of ovulation.

Dysmenorrhea typically refers to the crampy lower abdominal midline discomfort that begins with the onset of menstrual bleeding and gradually decreases over 12–72 h. It may be associated with nausea, diarrhea, fatigue, and headache and occurs in 60–93% of adolescents, beginning with the establishment of regular ovulatory cycles. Its prevalence decreases after pregnancy and with the use of oral contraceptives. *Primary dysmenorrhea* results, in a majority of cases, from hormone-dependent prostaglandin (PG) pathway mechanisms that cause intense uterine contractions, decreased blood flow, and increased peripheral nerve hypersensitivity, resulting in pain. However, variability in response to cyclooxygenase inhibitors suggests that PG-independent pathways, such as platelet activating factor, may also mediate inflammation. *Secondary dysmenorrhea* is caused by underlying pelvic pathology.

Endometriosis results from the presence of endometrial glands and stroma outside the uterus. These deposits of ectopic endometrium respond to hormonal stimulation and are associated with dysmenorrhea, painful intercourse, painful bowel movements, and tender nodules that may be palpated along the uterosacral ligaments during pelvic exam. The stage/severity of endometriosis does not always correlate with the extent of pain, and pain associated with endometriosis can be cyclic or continuous. Transvaginal pelvic ultrasound is part of the initial workup and may detect an endometrioma within the ovary or, in severe cases, rectovaginal or bladder nodules. The CA125 level may be increased, but it has low negative predictive value. Diagnostic laparoscopy is performed when patients do not respond to empiric treatment. If endometriosis is detected, the severity can be staged and the endometriotic lesions ablated or excised. The prevalence is lower in black and Hispanic women than in Caucasians and Asians.

Large *fibroids* can cause chronic pelvic pain or pressure, and submucosal fibroids may be associated with dysmenorrhea. *Other secondary causes* of dysmenorrhea include adenomyosis, a condition caused by the presence of ectopic endometrial glands and stroma within the myometrium. Chronic PID maybe associated with ongoing pelvic pain and is associated with tuberculosis or actinomycosis. *Pelvic congestion syndrome* is associated with pelvic varicosities with low blood flow, resulting in pelvic venous congestion. However, this is no clear evidence to indicate that this finding is associated with chronic pelvic pain.

TREATMENT

Chronic Pelvic Pain

DYSMENORRHEA

Local application of heat is of some benefit. Exercise, sexual activity, a vegetarian diet, use of vitamins D, B_1, B_6, and E and fish oil, acupuncture, and yoga have all been suggested to be of benefit, but studies are not adequate to provide recommendations. However, NSAIDs are very effective and provide >80% sustained response rates. Ibuprofen, naproxen, ketoprofen, mefanamic acid, and nimesulide are all superior to placebo. For best response, treatment should be initiated prior to the onset of menses and continued for at least 2–3 days. Combined oral contraceptives taken cyclically or continuously effectively reduce symptoms of dysmenorrhea.

ENDOMETRIOSIS

Combined hormonal contraceptives or continuous progestin (either orally or a levonorgestrel IUD) are used for the treatment of endometriosis. Evidence of an endometrioma on ultrasound imaging can be medically managed and does not require surgical removal unless symptomatic. Patients who do not respond to medical management and laparoscopic resection of endometriotic lesions can be offered GnRH agonist suppression with add-back therapy or aromatase inhibitors.

Chronic pain and dysmenorrhea associated with *fibroids* can be managed surgically depending on the number and location of fibroids and associated symptoms. Chronic pain and dysmenorrhea associated with adenomyosis can be managed with combined hormonal treatment, levonorgestrel IUD, or hysterectomy after child bearing is complete.

FURTHER READING

Bloomfield H et al: Screening pelvic examinations in asymptomatic average risk adult women. WA-ESP Project #09-009; 2013.

Bouilly J et al: Identification of multiple gene mutations accounts for the new genetic architecture of ovarian insufficiency. J Clin Endocrinol Metab 101:4541, 2016.

Brunham RC et al: Pelvic inflammatory disease. N Engl J Med 372:2039, 2015.

Fourman LR, Fazeli PK: Neuroendocrine causes of amenorrhea—An update. J Clin Endocrinol Metab 100:812, 2015.

Ju H et al: The prevalence and risk factors of dysmenorrhea. Epidem Rev 36:104, 2014.

Morley LC et al: On behalf of the Royal College of Obstetricians and Gynecologists. Metformin therapy for the management of infertility in women with polycystic ovary syndrome. Scientific Impact Paper No. 13. BJOG 124:e306, 2017.

Oladosu FA et al: Nonsteroidal anti-inflammatory drug resistance in dysmenorrhea: Epidemiology, causes, and treatment. Am J Obstet Gynecol 218:390, 2018.

Teede HJ et al: Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. International PCOS Network. Fertil Steril 110:364, 2018.

Vercellini P et al: Endometriosis: Pathogenesis and treatment. Nat Rev Endocrinol 10:261, 2014.

However, total and free testosterone levels are even lower in men with prostate cancer who have undergone prostatectomy, when compared to noncancer age-matched controls. This age-related androgen deficiency in men with prostate cancer is associated with fatigue, sexual dysfunction, mobility limitation, and decreased physical function. Even with bilateral nerve-sparing procedure, >50% of men develop sexual dysfunction after surgery. Although there is some recovery of sexual function with passage of time, 40–50% of men undergoing radical prostatectomy find their sexual performance to be a moderate to large problem 18 months after surgery. Sexual problems are a source of psychosocial distress in men with localized prostate cancer. The men with locally advanced or metastatic prostate cancer who undergo androgen deprivation therapy (ADT) encounter even more distressing symptoms because of the profound androgen deficiency. In addition to fatigue, sexual dysfunction, and hot flushes, these men are at increased risk for diabetes, metabolic syndrome, coronary heart disease, and frailty.

Testosterone Therapy in Men with a History of Prostate Cancer A history of prostate cancer has historically been considered a contraindication for testosterone therapy. This guidance is based on observations that testosterone promotes the growth of metastatic prostate cancer. Metastatic prostate cancer generally regresses after orchidectomy and ADT. Androgen receptor signaling plays a central role in maintaining growth of normal prostate and prostate cancer. PSA levels are lower in hypogonadal men and increase after testosterone therapy. Prostate volume is lower in hypogonadal men and increases after testosterone therapy to levels seen in age-matched controls.

However, the role of testosterone in prostate cancer is complex. Epidemiologic studies and their meta-analyses have not revealed a consistent relationship between serum testosterone and prostate cancer. Others have reported that low testosterone levels are associated with high-grade cancers. In a landmark randomized trial, testosterone therapy of older men with low testosterone did not affect intraprostatic androgen levels or the expression of androgen-dependent prostatic genes. The suppression of circulating testosterone levels by a GnRH antagonist also does not affect intraprostatic androgen concentrations. Open-label trials and retrospective analyses of testosterone therapy in men with prostate cancer, who have undergone radical prostatectomy and have undetectable PSA levels after radical prostatectomy, have found very low rates of PSA recurrence. Even in men with high-grade prostatic intraepithelial neoplasia (HGPIN)—a group at high risk of developing prostate cancer—testosterone therapy for 1 year did not increase PSA or rates of prostate cancer.

A majority of men diagnosed with prostate cancer today have localized disease that can be potentially cured by radical prostatectomy. The men with organ-confined prostate cancer (pT2, N0, M0) and Gleason score <6 are at a very low risk of disease recurrence after radical prostatectomy with 0.5% biochemical recurrence rate and 0.2% local recurrence rate at >10–15 years. Similarly, preoperative PSA <10 ng/mL is associated with lower risk of disease recurrence than PSA >10 ng/mL. After radical prostatectomy, in the absence of residual cancer, PSA becomes undetectable within a month. An undetectable PSA after radical prostatectomy is a good indicator of biochemical recurrence-free survival at 5 years. Therefore, men with organ-confined prostate cancer (pT2), Gleason score <6, and a preoperative PSA of <10 ng/mL, who have had undetectable PSA levels (<0.1 ng/mL) for >2 years after radical prostatectomy, have very low risk of disease recurrence (<0.5% at 10 years) and may be considered for testosterone therapy on an individualized basis. If testosterone therapy is instituted, it should be associated with careful monitoring of PSA levels and close consultation with a urologist.

MEDICAL COMPLICATIONS OF ADT

In patients with prostate cancer and distant metastases, ADT improves survival. In patients with locally advanced disease, ADT in combination with external beam radiation or as an adjuvant therapy (post-prostatectomy and pelvic lymphadenectomy) also has been shown to improve survival. However, ADT is being increasingly used as primary therapy in men with localized disease and in men encountering biochemical recurrence without clear evidence of survival advantage. The overall use of ADT in men with prostate cancer has increased in the past two decades, and its use in men with localized disease and biochemical recurrence accounts for a substantial fraction of this increase. Since most men with prostate cancer die of conditions other than their primary malignancy, recognition and management of these adverse effects is paramount.

Profound hypogonadism resulting from ADT is associated with sexual dysfunction, vasomotor symptoms, gynecomastia, decreased muscle mass and strength, frailty, increased fat mass, anemia, fatigue, bone loss, loss of body hair, depressive symptoms, and reduced quality of life. Diabetes and cardiovascular disease have recently been added to the list of these complications **(Fig. 399-4)**. Treatment with GnRH agonists in men with prostate cancer is associated with rapid induction of insulin resistance, hyperinsulinemia, and a significant increase in the risk of incident diabetes. Metabolic syndrome is prevalent in >50% of men undergoing long-term ADT when compared to age-matched men with prostate cancer not undergoing ADT (22%) and their age-matched eugonadal counterparts (20%). Some but not all studies have reported an increased risk of cardiovascular events, death due to cardiovascular events, and peripheral vascular disease in men undergoing ADT. Some reports suggest that men receiving ADT are at an increased risk of thromboembolic events and cognitive dysfunction. The rates of acute kidney injury are higher in men currently receiving ADT than in men not receiving ADT; the increased risk appears to be particularly associated with the use of combined regimens of a GnRH agonist plus an antiandrogen. ADT also is associated with substantially increased risk of osteoporosis and bone fractures.

APPROACH TO THE PATIENT

Men Receiving ADT

The benefits of ADT in treating nonmetastatic prostate cancer should be carefully weighed against the risks of ADT-induced adverse events **(Table 399-5)**. If ADT is medically indicated, consider whether intermittent ADT is a feasible option. Men being considered for ADT should undergo assessment of cardiovascular, diabetes, and fracture risk; this assessment may include measurement of blood glucose, plasma lipids, and bone mineral density by dual energy x-ray absorptiometry. Institute measures to prevent bone loss, including physical activity, adequate calcium and vitamin D intake, and pharmacologic therapy in men with a previous minimal trauma fracture and those with 10-year risk of a major osteoporotic fracture >20%, unless contraindicated. Bisphosphonates and denosumab have been shown to reduce fracture risk in men undergoing ADT, and zoledronic acid and denosumab have been approved by the U.S. Food and Drug Administration for the prevention of metastasis-related skeletal-related events in this population. Men with prostate cancer who are receiving ADT should be monitored for weight gain and diabetes. Encourage lifestyle interventions, including physical activity and exercise, and attention to weight, blood pressure, lipid profile, blood glucose, and smoking cessation to reduce the risk of cardiometabolic complications. In randomized trials, medroxyprogesterone, cyproterone acetate, and the serotonin reuptake inhibitor venlafaxine have been shown to be more efficacious than placebo in alleviating hot flushes. The side effects of these medications—increased appetite and weight gain with medroxyprogesterone, gynecomastia with estrogenic compounds, and dry mouth with venlafaxine—should be weighed against their relative efficacy. Acupuncture, soy products, vitamin E, herbal medicines, and transdermal estradiol have been used empirically for the treatment of vasomotor symptoms without clear evidence of efficacy. Gynecomastia can be prevented by the use of an antiestrogen, an aromatase inhibitor, or local radiation therapy; these therapies are effective in alleviating pain and tenderness but are less effective in reducing established gynecomastia. For long-standing gynecomastia that persists after cessation of ADT and is bothersome, mammoplasty is an effective treatment option.

TABLE 450-3 ME/CFS Comorbid Conditions

Chronic overlapping pain conditions: fibromyalgia (FM), chronic migraine, temporomandibular joint disease (TMJ), irritable bowel syndrome (IBS), endometriosis, vulvodynia, urologic chronic pelvic pain syndromes (UCPPS)
Postural orthostatic tachycardia syndrome (POTS)
Allergies
Sjögren's syndrome
Ehlers-Danlos syndrome
Mast-cell activation syndrome (MCAS)
Dysautonomia
Multiple chemical sensitivities

laboratory tests are usually within normal limits, their role is in identifying other illnesses and the specific panel of tests should be adjusted based on the patient's presentation. Typically the tests include complete blood count, erythrocyte sedimentation rate, electrolytes, fasting glucose, renal function tests (blood urea nitrogen, glomerular filtration rate), calcium, phosphate, liver function (bilirubin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transferase, total protein, albumin/globulin ratio), C-reactive protein, thyroid function (thyroid-stimulating hormone, free thyroxine), iron studies to assess both iron overload and iron deficiency (serum iron, transferrin saturation, ferritin), celiac disease screening tests, and urinalysis.

DIFFERENTIAL DIAGNOSIS AND COMORBID CONDITIONS

While the differential diagnosis for fatigue is quite broad, further workups and referrals should be chosen carefully based on the patient's history, symptoms (particularly those that are new, worsening, or unusual), and results of initial laboratory tests. Conditions reported to occur in association with ME/CFS **(Table 450-3)** should be kept in mind during the evaluation and follow-up, as management and treatment modalities for these comorbidities could contribute to an improved quality of life.

MANAGEMENT

While there are no approved drugs to treat or cure ME/CFS, patients benefit from receiving a diagnosis and an individualized plan that addresses the symptoms that are most problematic for the patient. Some symptoms, in particular, disturbed sleep **(Chap. 31)** and pain **(Chap. 13)**, may improve with nonpharmacologic therapies (such as sleep hygiene, massage, acupuncture, hot or cold packs) or medications. Any medications should be started at lower doses than usual and only slowly increased. Patients with ME/CFS have been reported to be more sensitive to medications than the general population, and benefits with fewer toxicities may be achieved at lower doses. Narcotics should be avoided, and referral to sleep centers or other specialists may be required.

Controlled therapeutic trials have not established significant benefit for patients with ME/CFS from acyclovir, fludrocortisone, galantamine, modafinil, and IV immunoglobulin, among other agents. These studies have been limited by small numbers and lack power to investigate benefit in patient subgroups. Preliminary small studies reported the possible effectiveness of the B-cell targeting anti-CD20 monoclonal antibody rituximab in ME/CFS, but a subsequent large, well-designed prospective double-blind study found no benefit. Numerous anecdotes circulate regarding other traditional and nontraditional therapies. It is important to guide patients away from therapeutic modalities that are toxic, expensive, or unreasonable.

Educating the patient and family about PEM can be helpful in avoiding the harmful cycle of overexertion during "good days" followed by relapse that can negate any functional gains. This is often referred to as "push and crash." Recognizing limits and using activity management (pacing) can help limit PEM. It is important to maintain tolerated activity levels to minimize deconditioning. Activity may be advanced very gradually as tolerated.

Counseling may help patients and their families cope with the long-term consequences of living with a chronic illness. Consultation with a physical or occupational therapist may identify energy-saving strategies for activities of daily living as well as needed accommodations, such as a wheelchair for activities that require walking longer distances or prolonged standing.

COURSE AND PROGNOSIS

The illness severity varies from mild or moderate, with patients retaining varying degrees of pre-illness function, to severe, with patients essentially homebound. Most patients experience some improvement and stabilize, although return to their prior level of function is unusual. A continued decline in function should prompt evaluation for other illnesses. Patients should be re-evaluated at scheduled intervals to adjust treatments and detect any intercurrent disease. New or changing symptoms should be worked up to identify any new illnesses. Given the social isolation and loss of hope associated with a debilitating chronic illness, serious depression and an increased risk of suicide is reported for patients with ME/CFS. Clinicians should be prepared to screen for this and refer patients as needed.

FURTHER READING

Bateman L et al: Myalgic encephalomyelitis/chronic fatigue syndrome: Essentials of diagnosis and Management. Mayo Clin Proc 2021. *https://doi.org/10.1016/j.mayocp.2021.07.004*

Centers for Disease Control and Prevention: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Available from *https://www.cdc.gov/me-cfs/index.html*. Accessed March 15, 2021.

Institute of Medicine: *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. Washington, DC: The National Academies Press, 2015.

Komaroff AL: Advances in understanding the pathophysiology of chronic fatigue syndrome. JAMA 322:499, 2019.

Lapp CW: Initiating care of a patient with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Front Pediatr 6:415, 2019.

Rowe PC et al: Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: A primer. Front Pediatr 5: 121, 2017.

Section 5 Psychiatric and Addiction Disorders

451 Biology of Psychiatric Disorders

Robert O. Messing, Eric J. Nestler, Matthew W. State

Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization. They are highly heritable, with genetic risk comprising 20–90% of disease vulnerability. As a result of their prevalence, early onset, and persistence, they contribute substantially to the burden of illness worldwide. All psychiatric disorders are broad heterogeneous syndromes that currently lack well-defined neuropathology and bona fide biologic markers. Therefore, diagnoses continue to be made solely from clinical observations using criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, of the American Psychiatric Association **(see Chap. 452)**.

seen as intractable, even the most effective drugs will not work if physicians fail to prescribe them and if patients fail to take them. Although the dominant forms of investigation in medicine seek cellular or molecular therapeutic targets to modify disease, behavioral sciences have revealed cognitive pathways that operate nearly as predictably as the genetic code. The opportunity for behavioral economics to improve health and health care delivery derives from its recognition of these behavioral pathways and the growing empirical evidence about how to best make use of them.

FURTHER READING

Asch DA et al: Automated hovering in health care—Watching over the 5000 hours. N Engl J Med 367:1, 2012.

Asch DA et al: Asymmetric thinking about return on investment. N Engl J Med 374:606, 2016.

Asch DA et al: Toward facilitated self-service in health care. N Engl J Med 380:1891, 2019.

Connolly T, Butler DU: Regret in economic and psychological theories of choice. J Behav Decis Mak 19:148, 2006.

John LK et al: The effect of cost sharing on an employee weight loss program: A randomized trial. Am J Health Promot 32:170, 2018.

Kahneman D: *Thinking, Fast and Slow*. New York, Farrar, Straus and Giroux, 2011.

Kahneman D, Tversky A: Prospect theory: An analysis of decision under risk. Econometrica 47:263, 1979.

Loewenstein G, Chater, N: Putting nudges into perspective. Behavioural Public Policy 1:26, 2017.

Loewenstein G et al: Asymmetric paternalism to improve health behaviors. JAMA 298:2415, 2007.

Loewenstein G et al: Behavioral economics holds potential to deliver better results for patients, insurers, and employers. Health Aff (Millwood) 32:1244, 2013.

Patel MS et al: Generic medication prescription rates after health system-wide redesign of default options within the electronic health record. JAMA Intern Med 176:847, 2016.

Thaler RH, Sunstein CR: *Nudge: Improving Decisions About Health, Wealth and Happiness*. New York, Penguin Books, 2008.

Volpp KG et al: Financial incentive-based approaches for weight loss: A randomized trial. JAMA 300:2631, 2008.

Volpp KG et al: Assessing value in health care programs. JAMA 307:2153, 2012.

482 Complementary and Integrative Therapies and Practices

Helene M. Langevin

The search for health and improved well-being includes many treatments, practices, and systems of care that may have originated outside conventional medicine but are gradually being folded into mainstream health care. The current health care system is fragmented, often emphasizing the pharmacologic treatment of disease alone, while often neglecting the promotion, support, and, importantly, restoration of health. Though the disease-focused model is dominant in our research and health care ecosystem, there has been a longstanding awareness that many chronic diseases, including pain conditions, can be prevented or better managed by incorporating nonpharmacologic interventions such as nutrition, exercise, and stress management into care, with an emphasis on understanding the person as a whole. Many complementary practices follow this model, and there is preliminary evidence indicating that these approaches lead to improved self-care, a better personal sense of well-being, and a greater commitment to a healthy lifestyle. Integrative health emphasizes not only the integration of complementary and conventional care but also an integrative approach to treatment of the whole person. This includes expanding our understanding of how physiologic systems interact with one another and of the connections between physical, psychological, and social aspects of health. Integrative health also includes striving for a better understanding of "salutogenesis" or pathogenesis in reverse, meaning the process by which health is restored when recovering from an injury, acute illness, or the exacerbation of a chronic disease, or when a "predisease" condition such as prediabetes or prehypertension is reversed through changes in behavior rather than pharmacologic treatment.

DEFINITIONS AND SCOPE

Complementary health therapies and practices include a broad range of practices, interventions, and natural products that are not typically part of conventional medical care **(Table 482-1)**. The term *complementary* refers to the use of these practices together with conventional therapies and is increasingly preferred to the term *alternative*, which denotes usage as a substitute for standard care.

The term *integrative health care* refers to conventional and complementary therapies and practices used together in a coordinated way. Integrative health also emphasizes care of the whole person that aims to improve health in multiple interconnected domains: social, psychological, and physical, including multiple organs and systems.

The use of integrative approaches to health and wellness has grown within care settings across the United States. Researchers are currently exploring the potential benefits of integrative health in a variety of situations, including pain management for military personnel and veterans, relief of symptoms in cancer patients and survivors, and programs to promote healthy behaviors.

Although complementary therapies and practices vary widely, it is useful to classify them by their primary therapeutic input, which may be dietary (e.g., diet, herbs), psychological (e.g., meditation), physical (e.g., massage, acupuncture), or the combination of psychological and physical (e.g., yoga, tai chi). Although some complementary health practices are recommended or provided by a physician or a complementary health care provider such as a chiropractor, acupuncturist, or naturopathic practitioner, many of these practices are undertaken as "self-care." Although some are reimbursed, most are paid for out of pocket.

PATTERNS OF USE

The first large survey of use of complementary health practices was performed by David Eisenberg and associates in 1993. It surprised the medical community by showing that >30% of Americans use complementary health products and practices. Many surveys since that time have extended those conclusions. The National Health Interview Survey (NHIS), a large, national household survey in which thousands of Americans are interviewed about their health- and illness-related experiences, is conducted annually by the National Center for Health Statistics, a component of the Centers for Disease Control and Prevention. This survey, which addressed the use of complementary health practices in 2002, 2007, 2012, and 2017, uses methods that create a nationally representative sample and has a sample size large enough to permit valid estimates about some subgroups. Information was obtained from 34,500 adults and 10,200 children in 2012 and 61,267 adults in 2017.*

In the first three surveys, approximately one-third of adults reported using some form of complementary therapy or health practice. In the 2012 survey, 32.2% of adults and 11.6% of children had used one or more modalities. These surveys yielded the estimate that nonvitamin, nonmineral dietary supplements are used by ~18% of adults and 5% of children. To identify trends in Americans' use of specific practices, the 2017 survey data were compared with a version of the survey fielded

*Information on the use of complementary health approaches was collected from a sample of adults aged 18 and over who participated in the 2012 (n = 34,525) and 2017 (n = 26,742) NHIS of adult alternative medicine or complementary health supplements, respectively.

TABLE 482-1 Glossary of Complementary and Integrative Health Therapies and Practices	
Acupuncture	A family of procedures involving stimulation of defined anatomic points, a component of the major Asian medical traditions; most common application involves penetrating the skin with thin, solid, metallic needles that are manipulated by the hands or by electrical stimulation
Ayurvedic medicine	The major East Indian traditional medicine system; treatment combines products (mainly derived from plants, but may also include animal, metal, and mineral), diet, exercise, and lifestyle
Biofeedback	The use of electronic devices to help people learn to consciously control body functions such as breathing or heart rate
Chiropractic	Chiropractic care involves the adjustment of the spine and joints to influence the body's nervous system and natural defense mechanisms to alleviate pain and improve general health; primarily used to treat back problems, headaches, nerve inflammation, muscle spasms, and other injuries and traumas
Dietary supplement	A product that is intended to supplement the diet, is taken by mouth, contains one or more dietary ingredients (including vitamins, minerals, herbs, amino acids, or certain other substances), and is labeled as being a dietary supplement
Homeopathy	A medical system with origins in Germany that is based on a core belief in the theory of "like cures like"—compounds that produce certain syndromes, if administered in very diluted solutions, will be curative
Hypnosis	The induction of an altered state of consciousness characterized by increased responsiveness to suggestion
Massage	Manual therapies that manipulate muscle and connective tissues to enhance the function of those tissues and promote muscle relaxation and well-being
Meditation	A group of practices, largely based in Eastern spiritual traditions, intended to focus or control attention and obtain greater awareness of the present moment, or mindfulness
Mind and body practices	A large and diverse group of procedures or techniques that are administered or taught by a trained practitioner or teacher; examples include acupuncture, massage therapy, meditation, relaxation techniques, spinal manipulation, tai chi, and yoga
Natural products	A variety of products such as herbs (also known as botanicals), vitamins and minerals, and probiotics, which are widely marketed, readily available to consumers, and often sold as dietary supplements
Naturopathy	A clinical discipline that emphasizes a holistic approach to the patient, herbal medications, diet, and exercise; practitioners have degrees as doctors of naturopathy
Osteopathy	A clinical discipline, now incorporated into mainstream medicine, that historically emphasized spinal manipulative techniques to relieve pain, restore function, and promote overall health
Relaxation techniques	A number of practices such as progressive relaxation, guided imagery, biofeedback, self-hypnosis, and deep breathing exercises, with the goal of producing the body's natural relaxation response, characterized by slower breathing, lower blood pressure, and a feeling of increased well-being
Spinal manipulation, osteopathic manipulation	A technique where practitioners use their hands or a device to apply a controlled thrust (i.e., a force of a specific magnitude or degree in a specific direction) to a joint of the spine
Tai chi	A mind and body practice originating in China that involves slow, gentle movements and sometimes is described as "moving meditation"
Traditional Chinese medicine	A medical system that uses acupuncture, herbal mixtures, massage, exercise, and diet

in 2012. Yoga was the most commonly used complementary health approach among U.S. adults in 2012 (9.5%) and 2017 (14.3%). The use of meditation increased more than threefold from 4.1% in 2012 to 14.2% in 2017. The percentage of children aged 4–17 years who used yoga in the previous 12 months increased significantly from 3.1% in 2012 to 8.4% in 2017. Meditation increased significantly from 0.6% in 2012 to 5.4% in 2017.

Americans are willing to pay for complementary health products and practices; the estimated out-of-pocket expenditure for complementary health practices in 2012 was $30.2 billion ($28.3 billion for adults and $1.9 billion for children), representing 1.1% of total health expenditures and 9.2% of out-of-pocket costs. On visits to complementary practitioners, Americans spent $14.7 billion out of pocket, which is almost 30% of what they spent out of pocket on services by conventional physicians ($49.6 billion). On natural products, such as dietary supplements, Americans spent $12.8 billion out of pocket, which was about one-quarter (24%) of what they spent out of pocket on prescription drugs ($54.1 billion).

According to the NHIS surveys, painful conditions are the most common reasons why American adults use complementary health products and practices. About 40 million American adults experience severe pain in any given year, and they spend >$14 billion out of pocket on complementary therapies to manage their pain. In one analysis of data from the 2012 NHIS survey, >40% of people with a musculoskeletal pain disorder used a complementary health approach. This was significantly higher than use by people without a musculoskeletal pain disorder (24%). Many complementary and integrative health interventions are multimodal in nature and may contribute to pain relief by impacting several pain processes simultaneously and addressing the cognitive, emotional, and physical complexities associated with pain.

Some patients seek out complementary health practitioners because they offer optimism or greater personal attention. For others, therapies and practices perceived as outside the mainstream reflect a "self-help" approach to health and wellness or satisfy a search for "natural" or less invasive alternatives. Since dietary supplements are labeled as "natural," they are often believed, incorrectly, to be inherently healthy.

CATEGORIES OF COMPLEMENTARY AND INTEGRATIVE HEALTH THERAPIES AND PRACTICES BASED ON PRIMARY THERAPEUTIC INPUT

PRIMARY DIETARY INPUT

Natural products, including plant and animal products, have a long and impressive history as sources of medicine and as important resources for biologic research. Whether as herbal supplements or as part of a diet, natural products are frequently consumed as a complex mixture. This complexity is further amplified by potential interactions with endogenous metabolic pathways, including those associated with the microbiome. The result is a collection of natural products and their metabolites that, individually and/or collectively, are associated with a network of biologic activity. Importantly, in addition to direct action on biologic targets, the activity of natural products can be influenced by an individual's health and metagenomic background. Although much remains to be understood about mechanisms of action, results of research on some natural products for a few conditions appear promising.

Pain Recent research to identify new sources of medicine based on natural products has yielded beneficial tools for probing the molecular features of pain pathways. Since the early days of pharmacology, natural products such as the opium poppy and capsaicin have provided

homeopathic products are widely believed to be safe because they are highly dilute, one product, a nasal spray called Zicam, was withdrawn from the market when it was found to produce anosmia, probably because of significant zinc content. In January 2017, the FDA warned consumers about homeopathic teething tablets containing belladonna that pose a serious risk to infants and children.

Regulation of advertising and marketing claims is the purview of the Federal Trade Commission (FTC). The FTC does take legal action against promoters or websites that advertise or sell dietary supplements with false or deceptive statements. Misleading marketing of dietary supplements, homeopathic products, and indeed other complementary health products and practices contributes to the very significant risk that individuals will use them instead of effective conventional modalities. For example, in April 2020, the FTC sent warning letters to several companies allegedly selling unapproved products—some of which included high-dose dietary supplements—that may violate federal law by making deceptive or scientifically unsupported claims about their ability to treat or cure COVID-19.

Inherent Toxicity Although the public may believe that "natural" equates with "safe," it is abundantly clear that natural products can be toxic. Misidentification of medicinal mushrooms has led to liver failure. Contamination of tryptophan supplements caused the eosinophilia-myalgia syndrome. Herbal products containing particular species of *Aristolochia* were associated with genitourinary malignancies and interstitial nephritis. In 2013, dietary supplements containing 1,3-dimethylamylamine (DMAA), often touted as a "natural" stimulant, led to cardiovascular problems, including heart attacks. Among the most controversial dietary supplements is *Ephedra sinica*, or ma huang, a product used in traditional Chinese medicine for short-term treatment of asthma and bronchial congestion. The scientific basis for these indications was revealed when ephedra was shown to contain ephedrine alkaloids, especially ephedrine and pseudoephedrine. With the promulgation of the DSHEA regulations, supplements containing ephedra and herbs rich in caffeine sold widely in the U.S. marketplace because of their claims to promote weight loss and enhance athletic performance. Reports of severe and fatal adverse events associated with use of ephedra-containing products led to an evidence-based review of the data surrounding them, and in 2004, the FDA banned their sale in the United States.

A major current concern with dietary supplements is adulteration with pharmacologically active compounds. Multi-ingredient products marketed for weight loss, bodybuilding, "sexual health," and athletic performance are of particular concern. Recent FDA recalls have involved contamination with steroids, diuretics, stimulants, and phosphodiesterase type 5 inhibitors.

Herb-Drug Interactions A number of natural products have potential impacts on the metabolism of drugs. This effect was illustrated most compellingly with the demonstration in 2000 that consumption of St. John's wort interferes with the bioavailability of the HIV protease inhibitor indinavir. Later studies showed its similar interference with metabolism of topoisomerase inhibitors such as irinotecan, with cyclosporine, and with many other drugs. The breadth of interference stems from the ability of hyperforin in St. John's wort to upregulate expression of the pregnane X receptor, a promiscuous nuclear regulatory factor that promotes the expression of many hepatic oxidative, conjugative, and efflux enzymes involved in drug and food metabolism.

Because of the large number of compounds that alter drug metabolism and the large number of agents some patients are taking, identification of all potential interactions can be a daunting task. Several useful Web resources are available as information sources **(Table 482-2)**. Clearly, attention to this problem is particularly important with drugs with a narrow therapeutic index, such as anticoagulants, antiseizure medications, antibiotics, immunosuppressants, and cancer chemotherapeutic agents. Although there are many examples of substances of natural origin successfully used as pharmaceutical drugs, in general, natural products ingested as food, rather than concentrated extracts, are less likely to cause harm.

TABLE 482-2 Resources for Dietary Supplement–Drug Interactions

National Institutes of Health National Center for Complementary and Integrative Health (NCCIH)
https://www.nccih.nih.gov/health/know-science/how-medications-supplements-interact
The National Institutes of Health NCCIH Know the Science initiative provides information for patients about complex scientific health topics such as drug-supplement interactions.
Medscape
http://www.medscape.com/druginfo/druginterchecker?cid=med
This website is maintained by WebMD and includes a free drug interaction checker tool that provides information on interactions between two or more drugs, herbals, and/or dietary supplements.
Natural Medicines
https://naturalmedicines.therapeuticresearch.com/tools/interaction-checker.aspx
This website provides an interactive natural product–drug interaction checker tool that identifies interactions between drugs and natural products, including herbals and dietary supplements. This service is available by subscription.

PRIMARY PSYCHOLOGICAL AND PHYSICAL INPUT

"Mind and body" practices and disciplines consist of physical procedures or exercises, manual therapies, or mental techniques that are administered or taught by a clinician, trained practitioner, or teacher. Examples include acupuncture, massage therapy, meditation, relaxation techniques, spinal manipulation, and yoga. These practices are being used with increasing frequency in mainstream health care facilities for both patients and health care providers. The evidence base for the effectiveness of mind and body practices is still relatively incomplete, but a few rigorous examples where there is promise of usefulness and safety include acupuncture and tai chi for pain associated with osteoarthritis (OA) of the knee; tai chi for fibromyalgia; mindfulness meditation for anxiety-related symptoms; relaxation techniques for acute stress disorder or posttraumatic stress disorder (PTSD) and headaches and migraine; yoga for fatigue and sleep disturbances, depression and anxiety, and quality of life of breast cancer patients; and acupuncture, massage, yoga, and spinal manipulation for chronic back pain. New research is shedding light on the effects of meditation and acupuncture on central mechanisms of pain processing and perception and the regulation of emotion and attention. Although many unanswered questions remain about these effects, findings are pointing to scientifically plausible mechanisms by which these modalities might yield benefit.

Primary Psychological Input For some mind and body therapies and practices, the primary therapeutic input is predominantly mental. This category includes conventional types of psychotherapy, such as cognitive behavioral therapy (CBT), and complementary practices, such as meditation and mindfulness-based stress reduction (MBSR). Relaxation techniques, including biofeedback-assisted relaxation, also fall into this category. The boundary between conventional and complementary can be blurred, as CBT programs, for example, frequently incorporate elements of MBSR and relaxation techniques. These therapies and practices are being gradually integrated into aspects of conventional care, such as cardiac rehabilitation programs, and are playing an increasingly recognized role in the management of pain, as well as stress and sleep disturbances.

PAIN Mindfulness meditation has been found to significantly reduce pain in experimental and clinical settings and to improve a wide spectrum of clinically relevant cognitive and health outcomes, including for low-back pain and fibromyalgia. It is unclear if the analgesic mechanisms supporting mindfulness meditation are distinct from or parallel to those engaged by placebo and/or slow, rhythmic breathing; however, there is emerging evidence suggesting that mindfulness meditation engages multiple unique neural mechanisms not mediated by endogenous opioids to reduce pain. In addition, findings from a few studies have demonstrated that training patients in the use of self-hypnosis significantly reduced their need for sedatives and

analgesia when undergoing interventional radiologic procedures. The efficacy of biofeedback has been evaluated in numerous studies for tension headaches, with positive results. Several studies have shown that biofeedback decreased the frequency of both pediatric and adult migraines, with some showing an effect lasting over an average follow-up phase of 17 months.

SLEEP DISORDERS The American College of Physicians practice guidelines (2016) strongly recommend the use of CBT for insomnia (also called CBT-I) as the initial treatment for chronic insomnia. Although CBT-I often includes relaxation techniques, it is not clear whether relaxation alone is beneficial.

ANXIETY AND STRESS-RELATED DISORDERS Meditation therapy is commonly used and has been shown to be of small to modest benefit for people with anxiety-related symptoms. There is some evidence that transcendental meditation may have a beneficial effect on anxiety. However, there is a lack of studies with adequate statistical power in patients with clinically diagnosed anxiety disorders, which makes it difficult to draw firm conclusions about its efficacy in this context. Relaxation techniques may be helpful in managing a variety of stress-related health conditions, including anxiety associated with ongoing health problems and in those who are having medical procedures. Some studies also have suggested that hypnosis may be helpful for anxiety and health-related quality of life in people with IBS. Evidence suggests that relaxation techniques may also provide some benefit for symptoms of PTSD and may help reduce occupational stress in health care workers. For some of these conditions, relaxation techniques are used as an adjunct to other forms of treatment.

MENOPAUSAL SYMPTOMS There is some evidence suggesting that hypnosis may help improve certain menopausal symptoms, such as hot flashes.

SUBSTANCE USE DISORDERS There is some evidence to suggest that hypnotherapy may improve smoking cessation, but data are not definitive. Available data suggest that mindfulness-based interventions may help significantly reduce the consumption of several substances including alcohol, cigarettes, opiates, and others compared to control groups; however, many studies have had small sample sizes, methodologic problems, and a lack of consistently replicated findings.

Primary Physical Input For another group of mind and body interventions, the primary therapeutic input is predominantly physical. The physical input can be delivered manually (e.g., massage) or using a device (e.g., acupuncture) or can be generated by the patient (e.g., exercise).

PAIN The role of acupuncture in pain management has been controversial for decades, with critics pointing out its "prescientific" theoretical basis, and indeed, the rationale for the use of specific "acupuncture points" remains to be established. However, recent large-scale meta-analyses have demonstrated acupuncture to be superior to both usual care and sham acupuncture for chronic musculoskeletal pain, headache, and OA, with beneficial treatment effects persisting for up to 12 months. The most recent (2017) American College of Physicians clinical guidelines recommend acupuncture as one of the initial treatment options for patients with acute, subacute, and chronic low-back pain. The role of both osteopathic and chiropractic spinal manipulative therapies (SMTs) in management of low-back pain also has been the subject of a number of carefully performed trials and many systematic reviews. Conclusions are not consistent, but the American College of Physicians guidelines conclude that spinal manipulation has a small effect on improving function and pain compared with control—either a sham manipulation or an inert treatment. Although evidence for spinal manipulation for chronic low-back pain is graded as *low quality*, the recommendation for consideration of nonpharmacologic treatment including spinal manipulation is graded as a *strong recommendation*, reflecting increasing concern with the impact of chronic opioid use for low-back pain. The evidence of benefit of spinal manipulation for neck pain is not as extensive, and continued concern that cervical manipulation may occasionally precipitate vascular injury clouds a contentious debate. Low- to moderate-quality evidence suggests that massage therapy is superior to nonactive therapies in reducing arthritis pain and improving functional outcomes. Massage may provide short-term relief from low-back pain, but the evidence is not of high quality. There is some evidence that massage has a positive effect on migraine, tension headaches, and neck pain.

DEPRESSION Acupuncture may provide a modest reduction in symptoms of depression, particularly when compared with no treatment or a control.

CANCER SYMPTOMS AND TREATMENT SIDE EFFECTS Acupuncture or electroacupuncture may be an appropriate addition to drug treatment for managing treatment-related nausea and vomiting in patients with cancer.

SEASONAL ALLERGIES Acupuncture may relieve symptoms of allergic rhinitis. Clinical practice guidelines from the American Academy of Otolaryngology–Head and Neck Surgery include acupuncture among the options that health care providers may offer to interested patients with allergic rhinitis.

Combined Psychological and Physical Input The primary therapeutic input for other mind and body practices is a combination of physical and psychological. Examples of practices in this category include yoga and tai chi, which combine movement, physical postures, and meditation.

PAIN Yoga and tai chi can be beneficial for patients with fibromyalgia or chronic low-back pain, and yoga compared to nonexercise controls results in small to moderate improvements in back-related function at 3 and 6 months. Some studies have demonstrated that tai chi produces beneficial effects similar to those of standard physical therapy in the treatment of knee OA. Regular yoga training may be helpful in reducing knee arthritis symptoms in patients with OA or RA.

MOTOR FUNCTION Tai chi has been shown to improve overall motor function, including balance and stability in older adults.

GENERAL WELLNESS Yoga may benefit people's general wellness by relieving stress, supporting good health habits, and improving mental/emotional health and sleep. Yoga may also help with quitting smoking, anxiety or depressive symptoms associated with difficult life situations, and quality of life for people with chronic diseases. Tai chi also may also improve quality of life in people with heart disease, cancer, and other chronic illnesses.

MULTIMODAL THERAPIES AND SYSTEMS

Multimodal approaches to health comprise two or more interventions such as conventional medicine, lifestyle changes, physical rehabilitation, psychology, and complementary health practices in various combinations, with an emphasis on whole-person health. Complementary health therapies and practices are often multimodal in nature, both in traditional health systems (e.g., traditional Chinese medicine, naturopathy) and in modern integrative practice. The U.S. Veterans Health Administration uses a multimodal model of pain care that emphasizes nonpharmacologic methods, both conventional (e.g., physical therapy, CBT) and complementary (e.g., yoga, acupuncture), and may also include nutrition consultations. Several medical systems, such as chiropractic, osteopathy, naturopathy, and homeopathy, that arose in the late nineteenth century continue to be practiced today. Osteopathic medicine is mostly integrated into conventional medicine, while homeopathy and naturopathy have remained largely separate from mainstream medicine. Chiropractic care is increasingly available in some conventional care settings. A number of multimodal systems, often called "whole health" systems, such as traditional Chinese medicine, Ayurveda, and homeopathy, use a diagnostic and therapeutic framework that is different from that of conventional medicine, which has posed additional challenges to their rigorous investigation.

NATUROPATHY

Naturopathy, or naturopathic medicine, is a multimodal therapeutic system based on philosophical principles that guide practice.

Naturopaths prescribe conventional and unconventional diagnostic tests and medications, with an emphasis on relatively low doses of drugs, herbal medicines, healthy diet, and exercise.

CHIROPRACTIC

The practice of chiropractic care, founded by David Palmer in 1895, is the most widespread practitioner-based complementary health practice in the United States. Although the scope of practice varies widely, chiropractic practice emphasizes manual therapies for treatment of musculoskeletal complaints.

OSTEOPATHIC MEDICINE

Founded in 1892 by the physician Andrew Taylor Still, osteopathic medicine was originally based on the belief that manipulation of soft tissue and bone can correct a wide range of diseases of the musculoskeletal and other organ systems. Over the ensuing century, the osteopathic profession has welcomed increasing integration with conventional medicine. Today, the postgraduate training, practice, credentialing, and licensure of osteopathic physicians are virtually indistinguishable from those of allopathic physicians. Osteopathic medical schools, however, include training in manual therapies, particularly spinal manipulation, as well as diagnostic methods based on palpation of musculoskeletal tissues that are not part of conventional medical education.

HOMEOPATHY

The theoretical framework of homeopathy is based on two unconventional principles: "like cures like," the notion that a disease can be cured by a substance that produces similar symptoms in healthy people; and the "law of minimum dose," the notion that the lower the dose of the medication, the greater its effectiveness. Although the current lack of biologic underpinning for these principles has seriously limited the rationale for their use, the diagnostic framework of homeopathy could be the source of new insights that could be explored. As discussed previously, the regulatory framework for homeopathic remedies differs from that for dietary supplements. Homeopathic remedies are widely available and commonly recommended by naturopathic physicians, chiropractors, and other licensed and unlicensed practitioners.

RESEARCH CHALLENGES

Classic randomized controlled trial (RCT) designs may not be well suited for research on multimodal complementary interventions and systems such as naturopathy and Ayurvedic medicine. The dynamic relationships among an array of factors that affect health and wellness is inherent to the philosophy of these systems of care and poses methodologic challenges to the effective application of conventional RCT design. Pragmatic comparative effectiveness designs with "usual care" comparators are widely used to study these types of interventions, and trials may need to take into account the individualization of interventions and the underlying theories of these multimodal systems. Thus, a key component of research on multimodal therapeutic systems is the development of validated and reproducible "manualized" treatment protocols allowing for some flexibility and individual patient care. Pragmatic studies that compare multimodal treatments with usual care cannot determine which treatment components are responsible for benefits, but other kinds of translational studies can address this issue.

THERAPEUTIC OUTPUT—SYSTEMS IMPACTED AND CHALLENGES OF MECHANISTIC RESEARCH

Complementary and integrative interventions whose therapeutic input is dietary, psychological, and/or physical may exert their effects, or therapeutic output, through a variety of mechanisms and physiologic systems. For example, peppermint oil may relieve pain associated with IBS by directly relaxing gastrointestinal smooth muscle, probiotics may have effects on the nervous system as well as the gut, and some components of traditional Chinese medicine, as well as omega-3 fatty acids and their derivatives, have immune-mediated anti-inflammatory effects. Multimodal interventions with psychological and/or physical therapeutic input such as meditation and acupuncture can have effects on the nervous system and may also target other body systems affected by the pain condition; for example, tai chi may improve balance and stability by increasing flexibility and core strength, and the stretching involved in yoga may improve low-back pain by reducing connective tissue inflammation. For all types of therapeutic input, biopsychosocial interactions also may be important; for example, participation in an integrative group therapy pain management program may provide tools to help relieve symptoms of anxiety and depression as well as pain.

Deepening the scientific understanding of the connections that exist across domains of human health is important to better understand how conditions interrelate, identify multimodal interventions that address these problems, and increase the support of patients through the full continuum of their health experience, including the return to health. Studies of multimodal interventions often require multidisciplinary expertise and use state-of-the-art techniques in areas such as neuroscience, immunology, pharmacognosy, proteomics, genetics, and epigenomics. Further, there are limited preclinical models for some complementary health interventions (e.g., no relevant model for meditative movement practices such as yoga or tai chi). Objective, validated measurement tools are essential, as are processes and procedures to ensure quality control, whether the intervention is a mind and body practice or a natural product.

PATIENT AND PROVIDER RESOURCES

Physicians regularly face difficult challenges in providing patients with advice and education about complementary health therapies and practices. Of particular concern to all physicians are practices of uncertain safety and practices that raise inappropriate hopes. Cancer therapies, antiaging regimens, weight-loss programs, and products that claim to improve sexual function or athletic performance are frequently targeted for excessive claims and irresponsible marketing. A number of Internet resources provide critical tools for patient education **(Table 482-3)**. Because many complementary health products

TABLE 482-3 Internet Resources on Complementary Health Approaches

The Cochrane Collaboration Complementary Medicine Reviews
This website offers rigorous systematic reviews of mainstream and complementary health interventions using standardized methods. It includes >300 reviews of complementary health practices. Complete reviews require institutional or individual subscription, but summaries are available to the public.
http://www.cochrane.org/evidence
MedlinePlus All Herbs and Supplements, A–Z List
MedlinePlus Complementary and Integrative Medicine
MedlinePlus Dietary Supplements
These National Library of Medicine (NLM) Web pages provide an A–Z database of science-based information on herbal and dietary supplements; basic facts about complementary and integrative health practices; and federal government sources on information about using natural products, dietary supplements, medicinal plants, and other complementary health modalities.
http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html
https://medlineplus.gov/complementaryandintegrativemedicine.html
http://www.nlm.nih.gov/medlineplus/dietarysupplements.html
National Institutes of Health National Center for Complementary and Integrative Health (NCCIH)
This National Institutes of Health NCCIH website contains information for consumers and health care providers on many aspects of complementary and integrative health products and practices. Downloadable information sheets include short summaries of complementary health approaches, uses and risks of herbal therapies, and advice on wise use of dietary supplements.
http://www.nccih.nih.gov
Resources for Health Care Providers: *http://www.nccih.nih.gov/health/providers*
NCCIH Clinical Digest e-Newsletter: *http://www.nccih.nih.gov/health/providers/digest*
Continuing medical education lectures: *http://www.nccih.nih.gov/training/videolectures*

and practices are used as self-care and because many patients research these interventions extensively on the Internet, directing patients to responsible websites can often be very helpful.

The scientific evidence regarding complementary therapies is fragmentary and incomplete. Nonetheless, in some areas, particularly pain management, it is increasingly possible to perform the kind of rigorous systematic reviews of complementary health therapies and practices that are the cornerstone of evidence-based medicine. A particularly valuable resource in this respect is the Cochrane Collaboration, which has performed >300 systematic reviews of complementary health practices. Practitioners will find this a valuable resource to answer patient questions. Practice guidelines, particularly for pain management, are also available from several professional organizations. Links to these resources are provided in Table 482-3.

SUMMARY

The frequent use of complementary and integrative health therapies and practices reflects an active interest among the public in improving health and well-being of the whole person. The current health care system is fragmented, with diseases and comorbid conditions mostly treated separately, sometimes with drugs that interact with one another. An important step in whole-person health care is considering health and disease not as separate states but as a bidirectional continuum and understanding how complementary and integrative therapies and practices, which are often multimodal in nature, consider a patient's long-term recovery and overall health.

Acknowledgment

Drs. Josephine Briggs and Stephen Straus contributed to this chapter in prior editions, and some material from prior edition chapters has been retained here.

FURTHER READING

Black LI et al: Use of complementary health approaches among children aged 4–17 years in the United States: National Health Interview Survey, 2007-2012. National health statistics reports; no 78. Hyattsville, MD, National Center for Health Statistics, 2015.

Eisenberg DM et al: Trends in alternative medicine use in the United States, 1990–1997: Results of a follow-up national survey. JAMA 280:1569, 1998.

Gaston TE et al: "Natural" is not synonymous with "safe": Toxicity of natural products alone and in combination with pharmaceutical agents. Regul Toxicol Pharmacol 113:104642, 2020.

Ijaz N et al: Whole systems research methods in health care: A scoping review. J Altern Complement Med 25:S21, 2019.

Nahin RL et al: Evidence-based evaluation of complementary health approaches for pain management in the United States. Mayo Clin Proc 91:1292, 2016.

Nahin RL et al: Expenditures on complementary health approaches: United States, 2012. Natl Health Stat Rep 95:1, 2016.

Paige NM et al: Association of spinal manipulative therapy with clinical benefit and harm for acute low back pain: Systematic review and meta-analysis. JAMA 317:1451, 2017.

Qaseem A et al: Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. Ann Intern Med 166:514, 2017.

Skelly AC et al: Noninvasive nonpharmacological treatment for chronic pain: A systematic review up-date. Comparative Effectiveness Review No. 227. AHRQ Publication No. 20-EHC009. Rockville, MD, Agency for Healthcare Research and Quality; April 2020.

Vickers AJ et al: Acupuncture for chronic pain: Update of an individual patient data meta-analysis. J Pain 19:455, 2018.

483 The Role of Epigenetics in Disease and Treatment

Brian C. Capell, Shelley L. Berger

The term *epigenetics* was coined by Conrad Waddington in 1942, as he sought to explain how changes in phenotype could occur throughout development independent of any changes to genotype. Appending the prefix *epi-* (Greek, meaning "over, outside of, around") to genetics aptly describes the numerous mechanisms by which gene expression and phenotypes are influenced—and sometimes even inherited through cell division—independent of any changes to the underlying DNA sequence. Today, epigenetics occupies one of the most exciting topics in biology and medicine, offering profound opportunities for discovery, as well as promise for the development of new therapies for disease. Interdisciplinary by nature, the field crosses virtually all areas of science and medicine: chemistry and genetics, development and differentiation, immunology, cancer, aging, and neuroscience.

The continuous introduction of ever more powerful technologies for interrogating the epigenome has led epigenetics to become one of the most innovative fields within the biomedical sciences. Given the vast expanse of the topic and limitations of space, in this chapter, we provide a broad but brief overview of the field and then highlight key areas across the landscape of biomedicine where epigenetics has been revealed to play critical roles in physiology and disease, and importantly, where epigenetics-based therapies have demonstrated success in clinical medicine.

THE BIOCHEMICAL BASES OF EPIGENETICS

Fundamental to epigenetic regulation is the intricate organization into chromatin of each cell's genome **(Chap. 466)**. The fundamental unit of the packaging into chromatin is the nucleosome, consisting of 147 base pairs of DNA wrapped around an octamer of 8 histone proteins (two copies of each of the four core histone proteins: H2A, H2B, H3, and H4), and nucleosome assembly into a regular repeating spaced array along the DNA polymer. The presence of nucleosomes and level of compaction of this basic chromatin array determine the accessibility of the DNA strand to transcription factors, to DNA repair machinery, and to other DNA-binding entities. Thus, compaction has a profound influence on gene expression levels and on local DNA mutation rates. Open regions of chromatin (euchromatin) tend to be transcriptionally active, whereas compacted chromatin (heterochromatin) tends to be transcriptionally repressed. Higher order three-dimensional chromatin architecture such as folding and looping further contribute to epigenetic gene regulation and cellular phenotypes.

Histones include the four core histones, which are the most abundant and most frequently found throughout the genome, and the variant histones of H2A, H2B, and H3. The individual protein structures of both core and variant histones include amino- and carboxyl-terminal "tails," which are extended and unstructured, and highly conserved globular domains. The x-ray crystal structure of the nucleosome particle has illuminated the dynamic alterations of chromatin by an astonishing range of regulatory mechanisms, summarized below.

The three main processes that regulate chromatin compaction, and thus access to the DNA template, include direct methylation modifications (and oxidized derivatives of methylation) of the DNA strand itself, posttranslational modifications of histones, and remodeling of nucleosomes to alter their location and composition with variant histones **(Fig. 483-1)**. The major modification of DNA is cytosine methylation of CpG dinucleotides (5-mC), associated with gene repression and catalyzed by the DNMT1, DNMT3A, and DNMT3B enzymes. DNMT3A and 3B catalyze the addition of methyl groups on unmethylated DNA de novo at CpG dinucleotides that are typically located throughout transcribed genes and in intergenic regions, but lacking at promoters, while DNMT1 is critical for the maintenance of the