COURSE #98703 — 15 CONTACT HOURS/CREDITS RELEASE DATE: 09/01/22 EXPIRATION DATE: 08/31/25

Chronic Pain Syndromes: Current Concepts and Treatment Strategies

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, physician assistants, and allied care providers in the primary care setting who may identify and treat patients with chronic pain syndromes.

Accreditations & Approvals

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A complete Works Cited list begins on page 73.

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Course Objective

Chronic pain imposes a distressing sensory and emotional experience on the patient and potentially leads to life-altering negative outcomes. The purpose of this course is to provide clinicians with the information necessary to identify and appropriately manage chronic pain syndromes in accordance with evidence-based guidelines.

Learning Objectives

Upon completion of this course, you should be able to:

1. Recall the epidemiology, contributing factors, and personal/societal cost of chronic pain syndromes.
2. Outline the pathophysiology of visceral and referred pain and therapeutic implications.
3. Describe the management of pain associated with cancer.
4. Describe the presentation and evidence-based management of low back pain.
5. Apply evidence-based strategies for the management of whiplash-associated disorders.
6. Illustrate approaches to the treatment of arthritis-associated pain.
7. Analyze the diagnosis and treatment of gout and gout-related pain.
8. Discuss the diagnosis and management of headaches of various types.
9. Describe key points in the pathophysiology and treatment of endometriosis.
10. Evaluate options available for the management of pain associated with sickle cell disease.
11. Identify postherpetic neuralgia and available treatment modalities.
12. Assess patients' post-amputation pain and identify treatment options.
13. Review key points in the diagnosis and treatment of diabetic neuropathy.
14. Outline the criteria for the diagnosis and management of complex regional pain syndrome.
15. Identify appropriate strategies for the management of fibromyalgia pain.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1]. This definition acknowledges that pain is influenced by emotion, cognition, memory, interpersonal and social context, and other factors and has helped replace previous conceptions of pain as a strictly physiologic phenomenon [1; 2]. Pain itself cannot be palpated, observed, or imaged, and laboratory tests cannot confirm or refute patient complaints of pain. Imaging abnormalities, such as disk protrusion or degeneration, poorly correlate with pain complaint, and chronic severe pain can exist in the absence of identifiable pathology [2; 3]. In the absence of compelling evidence to the contrary, the best clinical approach in most settings is to believe the patient is experiencing what he or she is reporting, even in the absence of a clear pathologic explanation [1]. The National Institutes of Health states that patient self-report is the most reliable measure of pain quality and intensity [4; 5]. The risk imposed by patient malingering on physician assessment or diagnostic error is more than offset by the benefits that come with the projection of compassion, acceptance, and concern.

This course intends to provide clinicians with an understanding of neurobiologic mechanisms that underlie common chronic pain syndromes and the latest recommendations on pain management. Consistent among treatment guidelines for a wide range of chronic pain syndromes are recommendations for using a mechanistic-based treatment approach. This strategy matches the analgesic mechanism of action with the likely underlying pain pathophysiology, combining pharmacologic, psychological, physical rehabilitation, and interventional treatment approaches into a single, multi-modal approach that addresses the sensory, emotional, cognitive, interpersonal, and social contributions to causation and maintenance of pain [2]. The pace of neuroscience discovery and translation into patient care has led to rapid obsolescence of some practice guidelines. Every effort has been made to provide the most updated information on pain and its management for this course. One caveat involves the widespread endorsement of interdisciplinary pain programs for chronic pain. There were roughly 1,000 of these programs in the late 1990s, but insurance industry reimbursement refusal and hospital elimination due to insufficient profits has led to the virtual absence of interdisciplinary pain programs in the United States outside the Veterans Affairs healthcare system [6; 7].

It is worth noting that current knowledge of pain pathophysiology is far from complete, and this has hindered development of more effective analgesics. Clinical trial outcomes are compromised by patient selection based on categories of pain associated with a specific diagnosis, injury, or anatomic location. Reliance on categories of pain, even when using the dichotomy of nociceptive versus neuropathic pain, oversimplifies pain pathophysiology and neglects key distinguishing features. The pain medicine field is moving away from pain categories in favor of identification of pain phenotypes. Pain phenotyping incorporates detailed descriptions of pain (e.g., burning, stabbing, pricking, shooting), specific clinical signs, and other information, such as results from quantitative sensory testing. Although pain phenotyping is a relatively new area of research, the hope is that it will enable researchers and clinicians to better identify and target the underlying neural mechanisms of pain [6].

While the best available evidence is used in this course, there are clinical situations in which the evidence is limited in its quality or applicability. Randomized controlled trials (RCTs) evaluate average treatment response, usually in large numbers of highly selected, homogeneous patient groups. Thus, pain therapy should be tailored to the individual patient's background and presentation as well as the published evidence [8; 9].

BACKGROUND

In accordance with Section 4305 of the 2010 Patient Protection and Affordable Care Act, the Institute of Medicine (IOM) was tasked with evaluating the state of the science regarding pain research, care, and education in the United States and with making recommendations that would serve as a blueprint for transforming the way pain is understood, assessed, treated, and prevented. The 2011 IOM report concluded that the present state of pain treatment is inadequate and cited shortcomings in pain clinician knowledge as a major contributing factor [2].

Effective pain management requires treatment selection guided by an understanding of the pathophysiologic mechanisms of pain as well as the overt causation. Until recently, the subjective perception of pain was thought to originate from spinal transmission and brain signaling of sensory input from a single neuron and pathway. Analgesic intervention focused on pain intensity and not pain mechanism, epitomized by the highly influential 1996 World Health Organization publication that recommended a "pain ladder" approach to cancer pain treatment [4; 10]. Now, however, there is recognition that pain is a more complex, heterogeneous entity and that multiple mechanisms contribute to the onset and maintenance of different pain types. Each pain mechanism is susceptible to the expression of neuronal alteration in function, structure, or chemical profile, a phenomenon referred to as neural plasticity [11]. Causation and maintenance of pain does not arise solely from painful sensory input. The emotional status, psychological response, and social circumstance of the patient fundamentally influence pain intensity and chronicity and the level of impaired functioning [12].

Another newer, clinically relevant aspect of pain management is the recognition that different mechanisms are usually at play with regard to acute and chronic pain syndromes. Previously, chronic pain has been conceptualized as merely the continuation of acute pain beyond a chosen temporal cut-off point, a notion now considered overly simplistic and obsolete. The transition from acute to chronic pain is now understood to involve a shift in pathogenic mechanisms from that associated with early-phase tissue injury and healing to a later period of abnormal, maladaptive sensory processing and neuronal plasticity that develops within peripheral and central pain pathways [2; 13; 14]. There are, however, acute pain disorders that persist for extended periods without a shift in the underlying mechanism [15].

Historically, the initial approach to diagnosis and management of pain emphasized the identification of disease, lesion, or anatomic site of the pain, without reference to the underlying neural mechanisms or the application of this to treatment considerations [16]. Evidence now strongly supports combining the conventional etiology-based approach with a mechanism-based approach that classifies pain syndromes by the type of maladaptive nervous system alteration that has developed in reaction to the original insult. This approach provides a comprehensive dual therapeutic focus that targets the pathologic sustaining mechanism of the pain as well as the original disease, lesion, or tissue injury that has been the traditional focus of pain management [16; 17]. Such an approach is believed to optimize pain diagnosis and treatment by avoiding the limitations associated with the traditional etiology-based approach [2; 14; 18; 19; 20; 21].

Most pain syndromes involve multiple, often overlapping, neurobiologic mechanisms determined by the stage of the disease process. Current concepts of pain classify these into four main categories: nociceptive, inflammatory, neuropathic, and centralized [22].

Nociceptive pain is a physiologic response to tissue injury, the perception that arises from intense stimulation of specialized peripheral sensory neurons (nociceptors) that respond only to noxious (pain) stimuli. Nociceptive pain is subgrouped by location of involved tissues into somatic pain (muscle or connective tissue) and visceral pain (visceral structures) [23]. Nociceptive pain is considered adaptive during tissue healing but maladaptive and pathologic when it persists after healing has occurred.

Inflammatory pain occurs in response to tissue injury or infection that activates peripheral nociceptors and initiates the immune response. While the resultant production and recruitment of pro-inflammatory mediators to the injury site may serve to perpetuate discomfort, it also facilitates tissue repair; thus, this is considered an adaptive pain mechanism.

Neuropathic pain originates from peripheral or central nervous system (CNS) injury. Unlike nociceptive and inflammatory pain, the mechanism of neuropathic pain has no adaptive function and is strictly pathologic [14; 24]. Acute pain from somatosensory damage is termed "acute neural injury." The term "neuropathic pain" implies pain that persists beyond the period of expected or actual tissue healing, and the underlying mechanism involves a maladaptive alteration in somatosensory nervous system function [20].

Centralized pain results from heightened nociceptive sensitivity in the absence of detectable peripheral stimulus and with negligible peripheral inflammatory pathology. The mechanism is poorly understood and is regarded as strictly pathologic as it lacks any evident adaptive function. Centralized pain disorders include conditions such as fibromyalgia, tension headache, and irritable bowel syndrome [14; 23; 25].

The persistence of acute nociceptive, inflammatory, or neural injury pain beyond tissue healing or repair reflects ongoing nociceptive activity that has become dissociated from peripheral nociceptive input to become maladaptive. Regardless of whether acute pain originates from tissue injury, tissue infection, or peripheral nerve injury, a similar process occurs by which nociceptive, inflammatory, and neuropathic pain signals are relayed from tissue injury site to the brain. This highly intense or prolonged pain signaling can lead to profound alteration in neuronal pathways that are further "upstream" from the peripheral tissue pain origin. Among these are increased ascending pathway signaling to the brain, reduced descending inhibitory signaling, expansion of pain receptive field, and induction of spontaneous and widespread pain. The resulting peripheral and central pathway hypersensitivity represents a state of abnormal nervous system function, amplified CNS sensory signaling, and abnormally low threshold pain response. The pain is no longer a symptom of peripheral insult, but a disease state of the nervous system [20]. This transition from acute to chronic pain occurs in discrete pathophysiologic steps involving multiple signaling pathways [26].

VISCERAL AND REFERRED PAIN

Visceral pain refers to pain originating from an internal organ or structure, such as the chest, abdomen, or pelvis. It often involves a temporal evolution and can be insidious and difficult to pinpoint in the early stages. The vague, diffuse, and poorly defined sensation of visceral pain is the result of low density in viscera sensory innervation and extensive divergence of visceral input within the CNS. Visceral pain is usually perceived in the midline at the level of the lower sternum or upper abdomen, independent of the actual site of origin [27].

The sources of visceral pain are multiple and the character and intensity, as described by the patient, are variable (e.g., dull ache, gnawing, cramping, burning) depending on whether the source is a solid organ, hollow viscus, or retroperitoneal structure. Visceral pain is often accompanied by autonomic symptoms and signs such as pallor, sweating, nausea, vomiting, diarrhea, tachycardia, fever, and hypotension. Sensing something new and serious, patients commonly exhibit anxiety, fear, anguish, or despondency [27; 28].

The intensity of visceral pain may not correlate well with the severity of the underlying pathology. An example is the angina patient presenting with intense chest discomfort from myocardial ischemia (without necrosis), in contrast to the patient with "silent" myocardial infarction (muscle necrosis), who has little or no pain whatsoever. The experienced clinician bears in mind this common disconnect between symptom intensity and disease severity [27].

Noncardiac chest pain (NCCP) is the term applied in reference to patients who present with chest discomfort of such character and severity as to raise concern for cardiac angina, yet after a thorough and at times invasive evaluation do not meet the diagnostic criteria for cardiac ischemia. The chest pain of true angina, often severe and alarming, is typically brought on by exertion and described as a squeezing, tightness, or pressure in the anterior chest with radiation to the neck, jaw, or left arm [29]. In general, NCCP is common and of multiple causes, some of which have features that overlap with angina. This is among the most common problems prompting a visit to the emergency department.

Chest pain is the second leading reason for emergency department visits annually in the United States with approximately 53% of adult visits seeking care for chest pain each year [30]. In one review, the most common diagnoses were musculoskeletal chest pain (20.4%), reflux esophagitis (13.4%), costochondritis (13.1%), stable angina pectoris (10.3%), and unstable angina or possible myocardial infarction (1.5%) [31]. NCCP is frequently observed in the healthcare setting, with as many as 30% of patients undergoing coronary angiography for chest pain showing normal coronary arteries. The prevalence of NCCP is distributed evenly between men and women, but it is over-represented in patients with a diagnosis of gastroesophageal reflux disease [30].

According to the American College of Gastroenterology, in patients who have chest pain without heartburn and who have had adequate evaluation to exclude heart disease, objective testing for GERD (endoscopy and/or reflux monitoring) is recommended.

(https://journals.lww.com/ajg/fulltext/2022/01000/acg_clinical_guideline_for_the_diagnosis_and.14.aspx. Last accessed August 19, 2022.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, low level of evidence

Functional abdominal pain syndrome (FAPS) refers to chronic, recurrent abdominal pain not attributable to a structural, organic, or metabolic disorder. Moreover, the discomfort of FAPS is not provoked, aggravated, or relieved by usual activities and physiologic functions such as exercise, eating, defecation, and menstruation. Although classified similarly, FAPS is separate and distinct from functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS), which has demonstrable intestinal dysmotility and predictable triggers [32]. It is estimated that 0.5% to 2% of the population in North America suffers from FAPS, a frequency much lower than that for IBS (10% to 20%). The female to male ratio is 3:2 [32].

During the years 2004 and 2009 in the United States, the most common diagnoses among patients admitted to a hospital for abdominal pain and associated gastrointestinal (GI) symptoms were cholecystitis/cholelithiasis, pancreatitis, appendicitis, and diverticulitis [33]. As abdominal pain is also the cardinal symptom in patients with common

dyspepsia, FAPS, and FGID, and the prevalence of these disorders in the adult population is estimated to be 15% to 25%, one can see that abdominal pain is an important clinical issue. The management of the patient with chronic abdominal pain syndrome can be difficult for primary care and subspecialist alike [33].

The patient with FAPS can be especially challenging because, in response to chronic pain and the uncertainty of diagnosis, these patients often exhibit ingrained maladaptive behaviors that frustrate management and must be addressed as well. These include pain symptom reporting disproportionate to clinical and laboratory findings; failure to recognize psychosocial stressors as contributory factors; discontinuity of care reflected in multiple visits to emergency departments and physicians' offices; demand for (repeated) diagnostic imaging and/or exploratory surgery to establish an organic cause; and insistence on immediate relief, often coupled with opioid drug dependence, rather than a willingness to embrace a long-term, symptom-management strategy that may require psychotherapy and a commitment to preventive self-care [32].

PATHOPHYSIOLOGY

The etiology of organic visceral pain is diverse and can include [28]:

- Inflammation
- Infection
- Disruption of normal mechanical processes (e.g., GI dysmotility)
- Neoplasm
- Alteration in visceral afferent sensory nerves
- Ischemia

Although very common, recognition of chronic visceral pain as a distinct pain syndrome is fairly new. This is because the pathophysiologic mechanisms of somatic pain nociception had been assumed to apply to visceral pain mechanisms. Evidence indicates important differences between the two [31].

Peripheral sensory (afferent) nerve fibers sense and transmit pain stimuli to the dorsal root ganglia of the spinal column, where the signal is then transmitted up the spinal column to the somatosensory cortex of the brain. Visceral afferent fibers project in the same nerves that carry autonomic (sympathetic and parasympathetic) efferent nerve fibers to all visceral organs, a feature that is termed "dual innervations." These afferent cell bodies reside in sensory ganglia (dorsal root), project to separate regions of the spinal cord/brainstem and encode both innocuous and noxious stimuli detected in the corresponding viscera. Because primary visceral pain afferents usually project along autonomic nerve fibers, autonomic symptoms such as nausea/vomiting, hypotension, bradycardia, and sweating often accompany visceral pain [34].

Some visceral afferents innervate more than one visceral organ, contributing to the frequent comorbidity of visceral pain disorders. Separate afferents from multiple visceral organs can converge on a single dorsal horn neuron. This can cause poor localization and discrimination of the visceral pain source and may explain referred pain when separate locations account for differences in the origin and perception of pain [35]. Visceral afferent fibers also converge on the same dorsal horn neurons as somatic afferent fibers, resulting in referred pain to the cutaneous area innervated at that level [35].

Signal transduction at the primary afferent terminal is dependent on the activation of receptors in the afferent fiber membrane. Multiple ionotropic and metabotropic receptors contribute to visceral nociceptive processing, with some representing potential therapeutic targets in functional or chronic visceral pain syndromes [35]. Visceral hypersensitivity, characterized by heightened perception of visceral stimuli, has been demonstrated in some visceral pain forms. Mechanisms responsible for hypersensitivity include sensitization of peripheral afferent nerves (peripheral sensitization) and sensitization of spinal dorsal horn neurons (central sensitization) [34].

THERAPEUTIC IMPLICATIONS

Visceral pain should be treated promptly and adequately to minimize the risk of long-term sensitization, referred hyperalgesia, and trophic changes [27]. Very few medications have received U.S. Food and Drug Administration (FDA) approval specifically for visceral pain syndromes. One example is pentosan polysulfate sodium, approved for the treatment of pelvic/bladder pain from interstitial cystitis [31; 36].

Effective therapies for acute visceral pain of unknown etiology include corticosteroids, intraspinal local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Opioids, used alone or in combination with the other modalities, may represent the best therapeutic option [37].

NSAIDs are ineffective for acute exacerbations of chronic functional abdominal visceral pain because peripheral sensitization and visceral nociceptor hyperalgesia are the pain mechanisms rather than acute inflammation. Opioids, tricyclic antidepressants (TCAs), and probiotics represent available agents with demonstrated efficacy. Newly approved and investigational agents with efficacy include peripherally acting serotonergic agents such as the 5-HT3 antagonist alosetron, the 5-HT4 agonist tegaserod, and the kappa-opioid receptor agonist asimadoline [38].

For NCCP, several efficacious approaches have been identified through RCTs [39; 40]:

- Acid suppression: Proton pump inhibitors or histamine H2-receptor antagonists
- Smooth muscle relaxants: Use of nitrates, phosphodiesterase-5 inhibitors, anticholinergic drugs, and calcium channel blockers is supported, although the overall evidence quality is low
- TCAs: Imipramine 50 mg effective in the long-term reduction of chest pain episodes
- Selective serotonin reuptake inhibitors (SSRIs): Sertraline
- Serotonin-norepinephrine reuptake inhibitors (SNRIs): Venlafaxine

Pancreatitis and other organic causes of acute abdominal pain can produce severe pain, and early administration of opioids and possibly other analgesics is recommended in these cases [39].

POSTSURGICAL PAIN

In the United States, more than 11.8 million surgeries were performed in 2019, a rate of 36.1 per 1,000 population [41]. A 2011 report indicated that 80% of surgical patients experience postoperative pain, and adequate pain relief is reported by less than 50% [2]. Of these patients, 88% report moderate, severe, or extreme pain; 10% to 50% develop chronic pain (depending on surgery type), and 2% to 10% report severe, chronic postoperative pain [2]. The estimated prevalence rates for chronic (more than three months) postoperative pain include 43% for mastectomy, 39% for cardiac surgery via sternotomy, and 30% for inguinal hernia repair [42]. Incidence rates for chronic pain one year after surgery are 10% to 15% for modified radical mastectomy and 61% to 70% for thoracotomy [43]. A random sample of 250 surgical patients found that 80% reported acute postoperative pain; of these, 86% experienced moderate-to-severe pain, and more patients reported pain after hospital discharge than before discharge [44]. Risk factors for chronic postsurgical pain include female sex, psychosocial issues, intensity of preoperative pain, type of surgical trauma, nerve damage, severity of acute postoperative pain and inflammatory responses, insufficient perioperative analgesia, type of disease, younger age, surgery duration longer than three hours, and radiation therapy [26; 44].

Postsurgical pain is an expected, inevitable byproduct of surgical tissue damage or insertion of drains and tubes. However, it may also originate from unpleasant emotional and mental experiences surrounding surgery [45]. Postsurgical pain can be nociceptive, neuropathic, inflammatory, or a combination of pain types. Pain intensity can range from mild to extreme, and pain is associated with autonomic, endocrine-metabolic, physiologic, and behavioral

responses [46]. Patients with postsurgical pain often experience sensory abnormalities and localized stimulus-evoked pain, suggesting a contribution from both abnormal sensory nerve function and ongoing nociception to the continuing pain [26].

PATHOPHYSIOLOGY

Surgical incision induces the release of inflammatory mediators by the damaged tissue, triggering an inflammatory cascade. The inflammatory response in the damaged tissue reduces sensory threshold and increases nociceptor response to subsequent sensory input, resulting in peripheral sensitization. In many patients during the course of normal wound healing, peripheral sensitization and facilitation of synaptic transmission to the CNS reverts back to normal intrinsic nociceptor activity, and postsurgical pain diminishes and then resolves. However, a variety of factors, such as a prolonged inflammatory state or chronic nerve stretching, can perpetuate peripheral sensitization and facilitation to induce pathophysiologic alteration in nociceptors. Such factors include gene expression, receptor translocation to the cell membrane, prolonged inflammatory and glial cell activation, and spinal inhibition and facilitation. Chronic pain pathophysiology via peripheral and central sensitization becomes established with the development of these structural changes [26; 43].

Postsurgical pain encompasses inflammatory and neuropathic processes. Because multiple ligand- and voltage-gated ion channels activate diverse intracellular cascades, pain control is optimized with a multimodal treatment strategy. Severity and persistence of pain is also influenced by the specific involved tissue, underlying genetics, and patient psychological status. Intra-operative nerve damage results from procedures such as thoracotomy and mastectomy, elevating risk of chronic neuropathic pain [26].

TREATMENT

Following breast, thoracic, and hernia repair surgery, subsequent chronic pain is strongly predicted by postoperative pain severity. Severe and persistent preoperative pain is also significantly associated with chronic pain development. Thus, aggressive pain management in the peri- and postoperative period is necessary to alleviate needless patient suffering and minimize the risk of chronic pain [26; 43]. The best approach involves multiple analgesic agents that target different pain mechanisms in order to address pain comprehensively, minimize side effects, and achieve additive analgesic effects [29]. Most postoperative patients experience Aδ and C fiber pain, which accounts for the superiority in pain control with opioid analgesics and NSAIDs [47].

The following recommendations for postsurgical pain are from guidelines published by the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists Committee on Regional Anesthesia; the European Association of Urology; and the American Society of Anesthesiologists Task Force on Acute Pain Management [45; 46; 48]. Note that very few recommendations were made for specific analgesic agents.

Preoperative Recommendations

- Adjust or continue medications to avert abstinence syndrome and treat pre-existent pain.
- Initiate therapy for postoperative pain management.
- Educate patient and family regarding their roles in achieving comfort, reporting pain, and proper use of recommended analgesic methods.
- Dispel erroneous beliefs regarding inflated risks of adverse effects and patient addiction.
- Use patient education to address behavioral approaches for pain and anxiety control.

Perioperative Recommendations

- Use epidural or intrathecal opioids, systemic opioid patient-controlled analgesia, and regional techniques instead of intramuscular opioids given "as needed," based on risks and benefits in each patient.
- Administration of local anesthetic at the incisions reduces postoperative pain.
- Only use therapies within one's expertise that can be delivered safely.
- Be vigilant with continuous infusion modalities for drug accumulation.

Multimodal Pain Management Recommendations

- Individualize postoperative multimodal therapy for the particular patient, operation, and circumstance.
- Select analgesic options on the basis of advantages, disadvantages, contraindications, and patient preference.
- Unless contraindicated, administer around-the-clock NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, or acetaminophen.
- Consider regional blockade with local anesthetics instead of opioids.
- Patient-controlled epidural analgesia provides superior analgesia, fewer complications, and improved patient satisfaction compared to systemic delivery, and is recommended.
- Dosing should be calculated to optimize efficacy and minimize adverse event risk.
- Tailor medication selection, dose, route, and duration to each patient.

Guidelines by the Australian and New Zealand College of Anaesthetists emphasize the utility of protective analgesia, an approach that uses pre- and postsurgical analgesia to reduce risk of sensitization [49]. Efficacy in reducing chronic postsurgical pain has been found with combinations of gabapentin, opioids, clonidine, NSAIDs, and the *N*-methyl-D-aspartate (NMDA) antagonists ketamine and dextromethorphan, with greatest benefit coming from low-dose IV ketamine added to epidural analgesia.

A systematic review of perioperative gabapentin or pregabalin evaluated efficacy in preventing chronic (two or more months) postsurgical pain. Eleven RCTs involving 930 patients were analyzed. All three pregabalin trials found a very large reduction in chronic postsurgical pain (pooled odds ratio [OR]: 0.09; P=0.007), while six of eight gabapentin trials demonstrated a moderate-to-large reduction in chronic pain development (pooled OR: 0.52; P=0.04) [50].

CANCER PAIN

Pain is perhaps the most feared of symptoms by patients with cancer. Unrelieved pain denies comfort and seriously degrades quality of life, while effective pain control is associated with improved survival outcomes [23].

Estimates of cancer pain indicate a 50% to 70% prevalence rate among patients actively receiving cancer treatment and a 60% to 90% rate in patients with advanced-stage cancer. Among patients with advanced malignancy, pain causation can be attributed to tissue infiltration by tumor in about 66% of cases and to the adverse effects of therapy in 25% [51]. Overall, more than 50% of patients with cancer experience severe, uncontrolled pain during the course of their illness. Therefore, pain management is a primary challenge for the patient with cancer and the treating oncologist.

Cancer pain syndromes are classified as acute or chronic (***Table 1***). Acute pain is commonly precipitated by structural and vascular complications directly attributable to tumor growth (e.g., obstruction, hemorrhage, fracture) or by the side effects and toxicities of chemotherapy and irradiation. With chronicity, the source of pain tends to become more complex and multifactorial as patients develop distant metastases and advanced disease, especially if subject to multiple procedures and therapies [52]. In order to provide effective pain control to patients with cancer, it is essential to identify the specific origin, because pain of different underlying mechanism preferentially responds to specific therapies.

COMMON CANCER PAIN SYNDROMES	
Tumor-Related Pain	**Treatment-Related Pain**
Acute pain	
Vertebral collapse and other pathologic fractures Acute obstruction of hollow viscus Headache from intracranial hypertension Hemorrhage into tumor	Chemotherapy • Painful oropharyngeal mucositis • Painful peripheral neuropathy • Bone/muscle pain from colony-stimulating factors or chemotherapies Radiation therapy • Painful oropharyngeal mucositis • Radiation enteritis and proctocolitis • Early-onset brachial plexopathy • Painful dermatitis • Hormone therapy • Bone pain flare • Arthralgia, myalgia
Nociceptive pain syndromes (chronic pain)	
Bone and joint/soft tissue pain syndromes • Multifocal or generalized pain (focal metastases or marrow expansion) • Base of skull metastases • Vertebral syndromes • Pain syndromes of bony pelvis or hip • Tumor invasion of joint or soft tissue Paraneoplastic pain syndromes (e.g., hypertrophic osteoarthropathy) Tumor-related gynecomastia	Painful osteonecrosis • Radiation- or corticosteroid-induced necrosis of femoral or humeral head • Osteoradionecrosis of other bones Painful lymphedema Painful gynecomastia Chronic abdominal pain • Due to intraperitoneal chemotherapy • Due to radiation therapy Radiation-induced chronic pelvic pain
Visceral involvement of neoplasm (chronic pain)	
Hepatic distension syndrome Rostral retroperitoneal syndrome Chronic intestinal obstruction Peritoneal carcinomatosis Malignant pelvic and perineal pain Chronic ureteral obstruction	—
Neuropathic pain syndromes (chronic pain)	
Painful peripheral mononeuropathies Painful polyneuropathies Plexopathy • Cervical • Brachial • Lumbosacral • Sacral	Postsurgical neuropathic pain syndromes • Postmastectomy syndrome • Post-thoracotomy syndrome • Postradical neck dissection syndrome • Postnephrectomy syndrome • Stump pain/phantom limb pain Postradiotherapy pain syndromes • Radiation fibrosis of cervical, brachial, or lumbosacral plexus • Radiation-induced neoplasm • Radiation myelopathy Postchemotherapy pain syndromes
Bisphosphonate-related pain (chronic pain)	
—	Bone pain Osteonecrosis

Source: [52] *Table 1*

The pathophysiology includes nociceptive (visceral and somatic), neuropathic, affective, behavioral, and cognitive mechanisms [23]. Somatic pain in skin, muscle, or bone is usually described as an aching, stabbing, throbbing, or pressure-like pain sensation. Visceral pain originating from internal organs or viscera is experienced as a gnawing, cramping, aching, or sharp pain. Patient description of neuropathic pain from nerve damage is described as burning, tingling, shooting, electric/shocking, or numbness. The damaged nerve structure can induce aching pain or dysesthesia anywhere in the innervated dermatomal region, and motor, sensory, or autonomic dysfunction in the innervated region may or may not be present [23].

Cancer pain does not originate solely from physiologic sources but also from the interaction of nociceptive aspects of pain with personality, mood, behavior, and social relations. Spiritual distress, frequently overlooked by clinicians, includes existential questions, the search for meaning and purpose, anger at "fate," and possibly specific issues regarding faith. Social pain relates to patient status within their community or society, financial concerns, and family and caregiver impact of the pain. Fear, anxiety, and depression contribute to and are caused by the cancer pain and its personal and interpersonal impact [53].

As noted, the "gold standard" of pain assessment is patient self-report, although intimate others often serve as proxies when cognitive or language factors impede patient-provider communication [52]. Pain severity at initial assessment is highly predictive of subsequent pain management complexity, including greater pharmacologic and multidimensional treatment requirements and timeframe for achieving stable pain control. Patient assessment should investigate the subjective quality, location, aggravating and relieving factors, cognitive reaction and cognitive impairment related to the current pain experience, patient goals related to pain control, and changes in pattern, intensity, or severity [52]. All relevant quality-of-life aspects, including physical, psychological, social, spiritual, and familial domains, should be investigated.

PATHOPHYSIOLOGY

Tumor-generated pain is determined by histologic type, location of the primary neoplasm, and location of metastases [54]. Pathogenic mechanisms that underlie some forms of cancer pain are discussed in this section.

Local and systemic inflammatory response stimulates release of pro-inflammatory mediators that facilitate pain transmission and increase pain intensity [54]. Tumor infiltration of sensitive tissues may entrap or injure nerves, producing visceral pain or neuropathic pain, respectively. Tumor activation of the immune response and local release of endothelin, prostaglandins, and tumor necrosis factor-alpha (TNF-α) results in excitation of peripheral nociceptive primary afferents. Tissue acidosis and proteolytic enzymes released by tumor cells may damage sensory and sympathetic nerve fibers, leading to neuropathic pain [54]. Central sensitization, induced by the ongoing bombardment of nociceptive and inflammatory pain signaling, contributes to the maintenance of chronic pain.

Metastatic cancer to bone causes pain through injury or infiltration of sensory neurons that innervate bone marrow. Bone infiltration also impairs normal bone turnover by disrupting the mechanisms that regulate osteoclast and osteoblast balance and activity. Mechanical bone strength becomes degraded with advanced disease and bone becomes vulnerable to osteolysis, pathologic fracture, and microfractures. Mechanical distortion can occur in the periosteum, potentially causing severe pain [54].

Different mechanisms underlie chemotherapy-induced neuropathy as well. Some chemotherapy drugs induce cytokine release by disrupting tubulin function, which can damage or destroy sensory neurons and sensitize primary nociceptive afferents. Radiation therapy that produces tissue fibrosis may result in nerve compression or microvascular obstruction, promoting central sensitization [54].

TREATMENT

Patients with cancer who experience pain receive care from a multidisciplinary team comprised of different specialist physicians (e.g., oncology, chronic pain, orthopedics), nurses, medical social workers, physiotherapists, pharmacists, psychologists, and chaplains. In addition, the physiologic aspect of cancer pain should not be treated in isolation, ignoring other contributing factors. One option for cancer pain is palliative care, an interdisciplinary therapeutic approach that emphasizes reducing suffering and maintaining quality of life, with a focus on the patient and family as the unit of care [55].

As discussed, cancer survival is linked to symptom control and pain management is linked to quality-of-life improvement; thus, pain management is essential to maximize patient outcomes. All patients should be assessed for pain at every contact, and if pain is present, pain management strategies should be implemented with the goals of improved comfort and function [23; 52]. It is useful to have patients rate severity in reference to a pain scale, where 0 represents no pain and 10 is the worst pain imaginable. Thus, the level of pain intensity may be rated as mild (1–3), moderate (4–6), or severe (7–10). The level of pain intensity, effectiveness of analgesia, and experienced side effects should be reassessed at regular intervals [52].

In general, opioids are the primary therapy for cancer pain, and adjuvant analgesics are meant to complement opioid management. The appropriate opioid dose is that required to achieve pain relief throughout the dosing interval without unmanageable adverse effects [23]. Most patients require complex pharmacologic strategies to optimize pain control, minimize opioid side effects, and target specific pain mechanisms using adjuvant analgesics. Ongoing cancer pain requires fixed-schedule dosing, preferably with extended-release opioids for background analgesia, coupled with supplemental, short-acting opioids to control breakthrough pain as needed. Rapid-onset oral transmucosal fentanyl is effective for breakthrough pain in opioid-tolerant patients. When indicated, methadone should be initiated by physicians with experience and expertise in its use. The term "opioid-irrelevant pain" describes the contribution to pain by factors not amenable to analgesics, such as psychosocial concerns [56].

Opioid-Naïve Patients

Patients are considered opioid tolerant after receiving ≥ 60 mg oral morphine (or equianalgesic dose of another opioid) daily for one week or longer. Patients not meeting this threshold are considered opioid naïve. Principles for treating pain in opioid-naïve patients include [23]:

- Anticipation and treatment of analgesic side effects, including beginning a bowel regimen to control constipation when initiating opioids
- Consideration of adjuvant analgesics for specific pain syndromes
- Provision of psychosocial support and patient/family/caregiver education
- Optimization of integrative interventions
- NSAIDs or acetaminophen, as appropriate

For opioid-naïve patients with mild pain, a trial of NSAIDs or acetaminophen is indicated before titrating a short-acting opioid (e.g., hydrocodone or codeine). If pain is moderate, the National Comprehensive Cancer Network recommends using oral morphine (5–15 mg) as the first-line short-acting opioid [23].

The initial treatment for opioid-naïve patients with severe pain is rapid titration of a short-acting opioid, specifically IV 2–5 mg morphine or equivalent. If the patient is morphine intolerant, IV hydromorphone, oxymorphone, or fentanyl should be substituted. Patients are reassessed every 15 minutes after an IV dose or every 60 minutes after an oral dose. If the pain is unchanged or worse, the dose may be increased by 50% to 100%. If the pain decreases to level 4–6, repeat the same opioid dose and reassess again after 60 minutes for oral or 15 minutes for IV dose. If the pain score decreases to 0–3, the current opioid dose is then continued as needed for the initial 24 hours. Insufficient relief of moderate-to-severe pain at reassessment after two to three opioid cycles should result in a change in route or a change in strategy [23].

ADJUVANT ANALGESICS FOR CANCER-RELATED PAIN	
Type of Pain	**Recommended Adjuvant Analgesic**
Neuropathic pain	Antidepressants (first-line: amitriptyline, imipramine, nortriptyline, desipramine; second-line: duloxetine, venlafaxine) Anticonvulsants (first-line: gabapentin, pregabalin) Topical agents (lidocaine patch 5%, diclofenac gel 1%, or diclofenac patch 180 mg) Corticosteroids (if neural structures or bones are involved)
Nerve compression or inflammation	Trial of NSAIDs or corticosteroids
Bone pain without oncologic emergency	NSAIDs Bisphosphonates or other bone-modifying agents For diffuse bone pain: hormone therapy or chemotherapy, corticosteroids, and/or systemic radioisotopes For local bone pain: local radiation therapy, nerve block, vertebroplasty, or kyphoplasty
Painful lesions likely to respond to antineoplastic therapies	Trial of radiation, hormones, or chemotherapy
NSAIDs = nonsteroidal anti-inflammatory drugs.	
Source: [23]	*Table 2*

Opioid-Tolerant Patients

For opioid-tolerant patients with breakthrough pain level ≥4 or pain level <4 with inadequate pain control and function, the rescue dose may be increased by 10% to 20% of the total opioid amount given in the previous 24 hours. Then, assess every 15 minutes after IV dose or 60 minutes after oral dose. If the pain remains unchanged or worsens, administer 50% to 100% of the previous opioid rescue dose [23]. If the pain decreases to a level of 4–6 after the rescue dose, repeat the same opioid dose and reassess after 60 minutes for oral or 15 minutes for IV dose. If the pain score decreases to 0–3, the current opioid dose should be continued as needed for the ensuing 24 hours. If the pain level is unchanged (moderate-to-severe pain) after two to three opioid cycles, change the route or change the overall strategy [23].

A 2013 meta-analysis compared rapid-onset oral fentanyl preparations against oral morphine in onset and effectiveness of breakthrough cancer pain. The results strongly indicated more rapid and superior pain control with fentanyl and suggest buccal tablet, sublingual, or oral transmucosal fentanyl products be considered in place of standard oral morphine therapy for these patients [57].

Subsequent Management of Pain

Subsequent treatment is based on continued patient pain rating score. It is important to remember that all pain levels require regular-dose and rescue-dose opioids, and the approach will depend on the type of pain experienced (***Table 2***). For persistent moderate pain, continue opioid and adjuvant analgesic titration and consider specific pain syndrome problems and pain specialist consultation. For example, antidepressants and anticonvulsants are first-line adjuvant analgesics for cancer-related neuropathic pain and can improve pain control with partial response to opioids. If persistent pain is severe, also re-evaluate the diagnosis, opioid titration, and adjuvant selection and consider specialist consult.

Complementary approaches may be useful adjuncts to pharmacotherapy. A systematic review was performed of RCTs comparing drug therapy plus acupuncture with drug therapy alone in the treatment of cancer pain. A significant difference was found in pain reduction when acupuncture was combined with pharmacotherapy [58]. Acupuncture typically provides pain relief 15 to 40 minutes after stimulation. Relief seems to be related to the release of endorphins and a susceptibility to hypnosis [59]. The efficacy of acupuncture for relieving pain has not been proven, as study samples have been small. However, acupuncture has been found to be of some benefit for cancer-related pain when the therapy is given in conjunction with analgesic therapy [58].

Massage, which can be broadly defined as stroking, compression, or percussion, has led to significant and immediate improvement in pain in the hospice setting [60]. Both massage and vibration are primarily effective for muscle spasms related to tension or nerve injury, and massage can be carried out with simultaneous application of heat or cold. Massage may be harmful for patients with coagulation abnormalities or thrombophlebitis [59].

Focused relaxation and breathing can help decrease pain by easing muscle tension. Progressive muscle relaxation, in which patients follow a sequence of tensing and relaxing muscle groups, enables patients to feel more in control, provides distraction from pain, and may lessen the level of ambient discomfort [59]. This technique should be avoided if the muscle tensing will be too painful.

Other nonpharmacologic interventions reportedly helpful for some patients but lacking a strong evidence base include manipulative and body-based methods (such as application of cold or heat and positioning), yoga, distraction, and music or art therapy. The application of cold and heat are particularly useful for localized pain and have been found to be effective for cancer-related pain caused by bone metastases or nerve involvement, as well as for prevention of breakthrough incident pain [59]. Alternating application of heat and cold can be soothing for some patients, and it is often combined with other nonpharmacologic interventions.

Cold therapy can be applied through wraps, gel packs, ice bags, and menthol. It provides relief for pain related to skeletal muscle spasms induced by nerve injury and inflamed joints. Cold application should not be used for patients with peripheral vascular disease. Heat can be applied as dry (e.g., heating pad) or moist (e.g., hot wrap, tub of water) and should be applied for no more than 20 minutes at a time, to avoid burning the skin. Heat should not be applied to areas of decreased sensation or with inadequate vascular supply or for patients with bleeding disorders.

Changing the patient's position in the bed or chair may help relieve pain and also helps minimize complications such as pressure ulcers, contractures, and frozen joints. Members of the healthcare team as well as family members and other informal caregivers can help reposition the patient for comfort and also perform range-of-motion exercises. Physical and occupational therapists can recommend materials, such as cushions, pillows, mattresses, splints, or support devices.

Hatha yoga is the branch of yoga most often used in the medical context, and it has been shown to provide pain relief for patients who have osteoarthritis and carpal tunnel syndrome but it has not been adequately studied in patients with cancer-related pain. Yoga may help relieve pain indirectly in some patients through its effects on reducing anxiety, increasing strength and flexibility, and enhancing breathing [61]. Yoga also helps patients feel a sense of control.

Methods to provide distraction from pain come in a wide variety of methods, including reciting poetry, meditating with a calm phrase, watching television or movies, playing cards, visiting with friends, or participating in crafts. Music therapy and art therapy are also becoming more widely used as nonpharmacologic options for pain management.

Listening to music has been shown to decrease the intensity of pain and reduce the amount of opioids needed, but the magnitude of the benefit was small and the review was withdrawn [62]. Research suggests that art therapy contributes to a patient's sense of well-being [63]. An art therapist can help with reflection on the implications of the art work. Art therapy is especially helpful for patients who have difficulty expressing feelings with words, for physical or emotional reasons.

Side Effect Management

Opioids are associated with many side effects, the most notable of which is constipation, occurring in nearly 100% of patients. The universality of this side effect mandates that once extended treatment with an opioid begins, prophylactic treatment with laxatives must also be initiated. The recommended first-line treatment is a stimulant laxative with or without a stool softener and/or polyethylene glycol. If inadequate, use metoclopramide and/or a saline enema. Finally, if the constipation is still persistent, methylnaltrexone or naloxegol should be considered. If refractory, consider neuraxial analgesics, neuroablative techniques, or other interventions to decrease pain, alleviate constipation, and/or reduction of opioid dose [23].

Nausea may occur alone or with vomiting, a neuromuscular reflex. Nausea and vomiting can exacerbate pain and contribute to insomnia, fatigue and weakness, and anorexia. It can also limit activities and cause distress for the patient and family. Nausea is the result of stimulation of one of several pathways: the chemoreceptor trigger zone (located in the medulla), the cortex of the brain, the vestibulocochlear nerve, or the GI tract. Prochlorperazine, thiethylperazine, metoclopramide, or haloperidol should be used to address this complication. If nausea and vomiting persist, add therapies that target different mechanisms of action, such as corticosteroids or the 5-HT3 receptor antagonists granisetron or ondansetron. Tolerance to nausea and sedation usually develops within three to seven days. Opioid rotation should be considered if nausea or vomiting remains a problem despite treatment [23].

Other possible side effects include pruritus, sedation, and delirium. Pruritus is generally addressed using diphenhydramine or promethazine, although low-dose naltrexone or nalbuphine may be added in severe or intractable cases. If pruritus continues despite treatment, switch opioids. Sedation may be treated with methylphenidate, dextroamphetamine, modafinil, or caffeine. First-line choices for delirium include haloperidol, olanzapine, or risperidone. Persistent delirium may require a switch to another opioid [23].

PAIN OF SPINAL ORIGIN

LOW BACK PAIN

Of all pain syndromes, low back pain (LBP) in general and chronic LBP (CLBP) in particular are the most common and impose the greatest clinical, social, economic, and public health burden [64]. CLBP is now recognized as a clinical syndrome caused by a variety of pathologies in the lumbar spine and adjacent structures [65].

The current strategy for managing patients with CLBP involves enhancing coping skills, restructuring maladaptive beliefs, and improving functional ability and activity tolerance [66]. In patients with chronic disabling pain, the use of cognitive-behavioral therapy, progressive relaxation, yoga, or meditation combined with progressive activity or exercise therapy produces superior outcomes relative to lumbar spine-targeted approaches such as decompressive laminectomy. While pain reduction can be achieved with surgical approaches, improvement in physical functional status is often unsatisfactory. This is concerning given the strong correlation between physical performance and future disability [67; 68]. Interestingly, CLBP therapies that address well-defined mechanical problems, such as back strengthening exercises for muscular weakness or atrophy, have demonstrated improvement independent of the original specific physiologic or anatomic target [67].

Clinical research in these patients suggests that there are acquired alterations in brain structure and function that may contribute to CLBP and disability [68]. Among these is the observation that central processing of sensory input is altered, demonstrated by abnormal amplitude and spatial topography of cortical somatosensory-evoked potentials in response to painful or non-painful stimuli. Another is that background muscle activation modifies somatosensory-evoked potentials in response to pain stimuli. These findings are thought to reflect changes in the neural interactions between pain perception and motor output that develop with CLBP [69]. Together, these findings suggest that the reduction in pain and disability and enhanced physical function observed with integrative therapy approaches to CLBP are the result of changes at higher neurologic levels [67].

In the United States, the prevalence of CLBP ranges from 15% to 45%, with a point prevalence of 30% [64]. From 1990 to 2016, LBP declined from the third leading cause of disability-adjusted life years to the fifth [70]. However, as the U.S. population ages, the burden of musculoskeletal disorders, including LBP, is expected to increase [70].

Major depressive disorders were the second leading cause of years lived with disability in 2016 [70]. Longitudinal studies have found a significant association between major depression and the development of chronic pain, including CLBP [64].

Among primary care patients with back pain, the prevalence of LBP etiology is [21; 71; 72]:

- Nonspecific LBP: 85%
- Herniated disk: 4%
- Compression fracture: 4%
- Spinal stenosis: 3%
- Cancer: 0.7%
- Ankylosing spondylitis: 0.3%
- Cauda equina syndrome: 0.04%
- Spinal infections: 0.01%

Risk factors for progression to chronic back pain include obesity; smoking; low education, socioeconomic, and job satisfaction levels; psychosocial distress, somatization, depression, and psychiatric or substance abuse history; and genetic factors [64]. Additionally, abnormal serum lipid levels may be positively correlated with LBP and increased risk for CLBP [73; 74; 75]. Severe pain and multiple episodes of recurrent LBP also heighten the risk of progression to chronic LBP. The greatest baseline predictors of persistent disabling LBP include maladaptive pain coping behaviors, non-organic signs, functional impairment, low general health status, and the presence of psychiatric comorbidities [67].

Pathophysiology

The pathophysiology underlying the transition from acute to chronic nonspecific LBP is not yet fully explained, but several likely mechanisms have been identified. These include interaction between inflammatory and neuropathic processes, patient-specific factors, factors related to the precipitating injury or trauma that induce peripheral sensitization, and central sensitization [26].

Muscle tissue shows a high innervation density of nociceptors containing the neuropeptide substance P, calcitonin gene-related peptide (CGRP), and somatostatin, released with nociceptor activation by noxious stimuli. Substance P and CGRP induce local vasodilatation and edema, triggering the release of bradykinin from plasma proteins and increasing the excitability of nociceptor nerve endings. Soft tissue overuse, ischemia, or inflammation elevates tissue concentrations of bradykinin and serotonin (5-HT) to induce the release of arachidonic acid from cell membranes by phospholipase A2. Prostaglandin E2 is released, and a proinflammatory cascade is triggered that results in muscle nociceptor sensitization. Prolonged transmission of nociceptive stimuli to the dorsal horn results in dorsal horn neuron hyperexcitability caused by the release of substance P and glutamate from the spinal terminals of muscle afferents and by the ensuing activation of NMDA channels in dorsal horn neurons. This leads to expansion of the receptive field of the muscle nerve and central sensitization. Transition from

acute to chronic LBP involves structural changes that perpetuate the functional changes. Numerous mechanisms are involved, including cell death, primarily in inhibitory interneurons due to bombardment by intense nociceptive stimuli. Decreasing the population of these neurons promotes chronic disinhibition and continuous generation of pain by nociceptive neurons with or without the presence of noxious stimuli [65; 67; 76].

Most persons with degenerative spine changes such as disk herniation, spinal stenosis, and foraminal stenosis do not have pain. In patients who do have pain with disk herniation and associated radiculopathy, it is thought to be primarily due to chemical inflammation and not merely mechanical compression. Inflammatory mediators play an important role in the pathogenesis of lumbar radicular pain and LBP in lumbar degenerative diseases. The cytokine interferon gamma (IFN-γ) contributes to the biochemical cascade, triggering pain in lumbar radicular pain [77]. Epidural corticosteroid injection is effective in suppressing the functional activity of inflammatory mediators such IFN-γ and phospholipase A2, decreasing pain from inflammation in the epidural space and surrounding nerve roots [65].

Pain resulting from injury or lesion to a peripheral nerve, dorsal root ganglion, or dorsal root arising from trauma, compression, inflammation, or ischemia represents peripheral neuropathic pain. In CLBP with a peripheral neuropathic pain component, mechanisms that alter the structure and function of peripheral nerves and their central terminals include [78]:

- Sensitization of neural connective tissue nociceptors: Impaired intraneural circulation and hypoxia in response to nerve injury may elicit an inflammatory response within neural connective tissues, resulting in nociceptor sensitization and an increase in nociceptive drive.
- Ectopic excitability: Upregulation of ion channels at nerve injury sites may induce abnormal impulse generating sites, which fire spontaneously and independently of a peripheral stimulus. These sites may cause hyper-reactivity of injured nerves to thermal, mechanical, or chemical stimuli.
- Cross-excitation: Electrically or chemically mediated excitation between adjacent injured and uninjured neurons may amplify nociceptive signaling.
- Structural changes: Axonal sprouting of non-nociceptive Aβ fibers may occur into dorsal horn laminae that receive nociceptive inputs to enhance onward nociceptive signaling in ascending tracts.
- Neuro-immune interactions: Nerve injury may activate peripheral and CNS immune cells, such as microglia in the dorsal horn, which stimulates the release of additional chemical modulators that may contribute to the development and persistence of peripheral neuropathic pain.

Clinical Presentation

The onset of LBP is described as discomfort in the vicinity of the low back ranging from a dull ache to a sudden, sharp, shooting or stabbing pain and may include limited flexibility and/or range of motion or inability to stand straight [79]. Although the symptoms of back pain can originate anywhere from the thoracic spine to the sacrum and coccyx, most cases originate in the lumbar spine, as this is the site of support for upper body weight [79].

With LBP, the clinical presentation varies according to etiology. In general, radicular pain suggests nerve root involvement, while axial pain suggests disk degeneration, facet arthropathy, sacroiliac (SI) joint arthropathy, or myofascial pathology of the spine.

Nonspecific LBP

Up to 85% of LBP in patients presenting to the primary care setting is nonspecific, meaning that it lacks a clear origin and is not caused by specific local or systemic disease or spinal abnormality [1]. Nonspecific LBP is a diagnosis of exclusion made after ruling out serious causes of the back pain. Although pain can originate from ligaments, facet joints, muscle, fascia, nerve roots, the vertebral periosteum, or outer portions of the disk, the effective management of nonspecific LBP does not require a precise anatomic diagnosis [66]. The pain is usually unilateral and may radiate to the buttocks or posterior thigh but not past the knee. This can lead to incorrect diagnosis of radiculopathy or disk herniation. However, true radicular symptoms radiate below the knee in a dermatomal distribution and can involve sensory loss, weakness, or reflex changes. Painful spasm may be present, and pain may be worsened by movement, while lying flat decreases the pain. Complaints of numbness, weakness, or bowel or bladder dysfunction are absent [80]. Degenerative changes revealed by lumbar imaging should usually be considered nonspecific, because they poorly correlate with symptom severity [21; 81].

Lumbosacral Radiculopathy

Lumbosacral radiculopathy is a clinical diagnosis of nerve root irritation and compression, resulting in a symptom distribution of the affected lumbar or sacral nerve root such as numbness, weakness, or paresthesia. Sciatica is the most common symptom of lumbar radiculopathy and refers to pain that radiates down the leg below the knee in the distribution of the sciatic nerve to indicate nerve root compromise from mechanical pressure or inflammation [21].

Causes of lumbar radiculopathy include disk herniation, arthritic degeneration, cord compression, spinal stenosis, tumor, and infection. With herniated disk, the pain is described as a deep, aching, axial midline pain concurrent with radicular pain. Discogenic pain results from a tear in the outer disk layer (annulus fibrosis) that causes the inner gelatinous material (nucleus pulposus) to prolapse, inflame, and compress a nerve root [80]. The resulting pain from pressure and nerve irritation improves with the resolution of local inflammation, and the disk protrusion may spontaneously remit with time. Although disk herniation and radiculopathy are often viewed as causally linked, herniation is often asymptomatic and only occasionally the cause of sciatica [80].

Lumbar Spinal Stenosis

Lumbar spinal stenosis refers to the frequently age-related narrowing of the spinal canal that may result in bony constriction of the cauda equina and the emerging nerve roots [21]. Spinal stenosis can produce pain in the low back that radiates down the back of both legs, often worsened with standing or walking. To make the pain more bearable, patients often walk a short distance with a hunched back, and then sit down for relief. The pain will then dissipate after several minutes. Congenital lumbar canal stenosis is a predisposing factor. Patients show less tenderness over the lumbar spine than those with acute lumbar disk herniation, and the straight leg-raising test may be normal [65].

Most persons 60 years of age and older exhibit varying degrees of spinal stenosis from disk herniation, osteophytes, or degenerative spondylolisthesis. Fortunately, clinical pain manifests in less than 30% and, just as with degenerative disk disease, there is poor correlation between symptom severity and extent of spinal canal stenosis revealed by magnetic resonance imaging (MRI) [80].

Myofascial Pain

Myofascial pain of the low back or neck is common, especially following trauma or repetitive motion injury. This is thought to result from strain or sprain to the muscles and ligaments. Myofascial pain is described as a deep, aching, poorly localized discomfort made worse by activity. It can be limited to discomfort in the paraspinal muscles or may extend to the buttocks and upper thigh areas [82].

Epidural Compression Syndrome

Epidural compression syndrome is an umbrella term that encompasses spinal cord compression, cauda equina syndrome, and conus medullaris syndrome. While these conditions differ in the level of neurologic deficit at presentation, they are otherwise similar in symptoms, evaluation, and management. Massive herniation of a midline disk, typically at the L4 to L5 disk level, is the most common cause of epidural compression syndrome. Tumor, epidural abscess, spinal canal hematoma, or lumbar spine spondylosis represent other causes [80].

In these patients, neurologic status at diagnosis is the greatest predictor of ultimate neurologic outcome and underscores the importance of early accurate diagnosis. The dominant symptom is back pain with accelerating pain severity. Pain from epidural spinal cord compression is made worse with recumbent positioning, and unilateral or bilateral radiculopathy may develop over time. For many patients, leg pain or neurologic symptoms are more dominant than back pain. Also common at diagnosis is symmetrical lower extremity weakness that may have progressed to gait disturbance or paralysis. Decreased lower extremity reflexes are associated with cauda equina syndrome [80].

Lumbar Facet Joint Syndrome

Lumbar facet joint syndrome is seen in as many as 35% of patients with LBP and is frequently associated with arthritis or lumbar facet joint injury [65]. Dominant symptoms include unilateral LBP that may radiate down the back or front of the thigh and morning stiffness with isolated facet arthropathy [83]. Tenderness is usually found over the lumbar paraspinal muscles and facet joints. Back pain is worsened with back extension and lateral rotation to the side of the pain, and the leg-raising test is negative. MRI and computed tomography (CT) findings of facet joint arthropathy do not correlate with clinical findings [65].

Sacroiliac Joint Syndrome

SI joint syndrome typically manifests as localized pain in the lower back or upper buttock area that overlies the SI joint. Pain is intensified by attempts to walk upstairs, and while pain may be referred to the posterior thigh, extension below the knee is unusual [79]. Tenderness over the SI joint is often found in physical examination, and pain is aggravated by the Patrick test or single-leg standing [65]. The onset of SI joint pain is usually gradual (over months to years), and although etiology is often elusive, trauma, infection, and tumor represent infrequent yet known causes of SI joint pain [79].

Spinal Cord Injury

Spinal cord injury (SCI) occurs in 17,810 persons every year in the United States (78% of new cases are men), and an estimated 294,000 patients are living with SCI [84]. Less than 1% of persons with SCI experience complete neurologic recovery by the time of hospital discharge [84]. One study found that, among patients with SCI, 86% report that pain persists six months after discharge and 27% report that pain is severe enough to interfere with most daily activities [85]. SCI pain may develop at or below the level of spinal injury and does not correlate well with the magnitude or location of the lesion nor the presence of myofascial pain syndrome. However, injury from gunshot is associated with more severe pain [65].

Neuropathic, musculoskeletal, and/or visceral pain can contribute to SCI pain. Central neuropathic pain can develop weeks to months following injury and is described as a burning, sharp, or shooting pain at or below the level of injury in areas with partial or complete loss of sensation to touch. Segmental pain around the trauma site often develops within the first couple of months post-injury and can manifest as allodynia (pain induced by light touch) and hyperalgesia, potentially resulting in severe pain if nerve root entrapment is involved [65].

Muscle spasm below the level of SCI and arthritis in disused joints may contribute to pain, described as dull or aching pain intensified with movement and relieved by rest. Constipation and urinary retention secondary to sphincter dysfunction reflects visceral involvement, in which case patients often complain of cramping, burning, and near-constant discomfort [65].

Failed Back Surgery Syndrome

More than 900,000 spinal surgeries are performed annually in the United States, primarily for lumbar and cervical disk herniation [86]. Of these, failed back surgery occurs in 13% to 35% of cases, with up to 74% continuing to experience pain following surgery [87]. The level of pain is widely variable and may occur with neurologic deficits. Contributors to pain and the clinical features of failed back surgery syndrome include recurrent disk herniation, epidural abscess, scar tissue formation around nerve roots, facet joint syndrome, and muscle spasm [65]. Patients with this syndrome should be questioned to identify new or persistent problems needing further evaluation. A frequent source of late-onset back pain following previous fusion surgery involves wear and tear to the facet joints and disks directly above and below the fused segment(s). Patients with persistent radicular pain, usually from chronic nerve injury, greatly benefit from treatment that addresses the neuropathic pain [65].

Assessment

Most patients with acute low back pain have ligamentous or muscle strain syndrome, follow a benign course, and show significant improvement within two to three weeks. The challenge for clinicians is to recognize early the possibility of serious disease, such as spinal metastatic cancer or vertebral and epidural space infection, and then to identify those with herniated disk, radiculopathy, or spinal stenosis.

The proper assessment of the patient with back pain requires vigilance and careful attention for factors and warning signs suggestive of serious or life-threatening disorders. A thorough history and physical examination should be performed on all patients, during which the patient is assessed for the presence of warning signs or "red flags." Red flags represent alarm symptoms or signs that warrant prompt, specific diagnostic testing, urgent treatment, or referral to a specialist. Among these are weight loss, prior history of cancer, nocturnal or rest pain, age older than 50 years, recent trauma, fever and chills, history of injection drug use, chronic corticosteroid therapy, difficulty urinating, bowel or bladder incontinence, and neurologic deficits such as saddle anesthesia, perianal or perineal sensory loss, or motor weakness in the extremities [67; 80]. As an example, there is a common association between spontaneous vertebral fracture and any combination of age older than 70 years, female gender, recent trauma, and prolonged corticosteroid use. There is also a moderate to highly significant predictive value for age older than 50 years, history of prior cancer, unexplained weight loss, and failure of conservative therapy in identifying spinal malignancy [67].

Patients should also be assessed for "yellow flags," or risk factors for poor prognosis and chronicity [66; 67]. Areas to explore include maladaptive beliefs, attitudes, and behaviors regarding the back pain and recovery, such as passivity or reluctance to self-manage, dependency on the provider to "cure," fear avoidance beliefs, and beliefs that harm will come from activity and discomfort. Other areas include depression, anxiety, maladaptive coping response to stress, social withdrawal or isolation, and lack of social support. Adverse economic and work environment circumstances, such as job dissatisfaction, excessive and inflexible physical workplace demands, high levels of work-related stress, poor workplace social support, and adversarial or dysfunctional workplace relationships should also be noted [66].

Early detection and intervention (if indicated) for problematic motivational, emotional, or social dysfunction are important because these factors influence the selection and effectiveness of therapeutic interventions.

In the absence of red flags, use of imaging and diagnostic tests for acute LBP is discouraged, as imaging findings rarely change clinical management [81]. Overuse of lumbar imaging in LBP correlates with, and likely contributes to, the two- to threefold increase in surgical rates for LBP over the last 10 years [86]. Assigning significance to imaging anomalies requires skill at the specialist level to integrate historical, clinical, and imaging findings. Imaging abnormalities are essentially normative by 40 years of age; for instance, 80% of persons 60 years of age and older exhibit a protruding disk, which is symptomatic for only a fraction of patients. Incorrect communication of imaging findings to the patient may lead to patient fixation, contribute to fear-avoidance behaviors, and increase the risk of iatrogenic aggravation of chronic LBP. Guidelines suggest that physicians without advanced training defer imaging tests to qualified specialists [88].

However, imaging and other testing should be performed in patients with new-onset or progressive neurologic deficits and those with suspicion of serious underlying conditions. In patients with persistent pain and symptoms consistent with radiculopathy or spinal stenosis, MRI should be performed only when such patients are candidates for surgery or epidural steroid injection. CT scanning is an alternative option to first-line MRI [89; 90].

The Subgrouping for Targeted Treatment (STarT) Back Screening Tool is a nine-item standardized, validated screening tool that can be used in the initial assessment to identify patients with LBP at risk of progression to chronicity. This tool has been shown to accurately stratify patients to treatment based on risk, increase the efficiency in physical therapy referrals, improve clinical outcomes, and reduce costs [91; 92].

Treatment

Although acute LBP improves in most patients within three to six weeks using conservative therapy, up to 33% of patients with LBP report pain of moderate or greater severity at one-year follow-up and 20% report ongoing pain severe enough to limit activity [21]. With chronicity, LBP may become disabling and impose a severe emotional and functional burden. The management goals for chronic LBP are to minimize pain and disability, improve functional status, and facilitate restoration of normal activity, while limiting the use of marginally effective or inappropriate medication [21; 81].

Many pharmacologic therapies and minimally invasive or invasive procedures have been utilized in a strategy designed simply to relieve pain—with variable results. However, there is little evidence these focused pain approaches are comparable or superior to interventions that focus primarily on restoration of function instead of pain relief. This contradicts the biomedical model in medicine that emphasizes escalation of costly and invasive therapies to achieve "pain cure" in patients lacking response to lower-intensity approaches [64; 88]. It is now recognized that treatment for conditions such as CLBP persisting in the absence of a unique underlying pathologic lesion must address potential contributory factors such as affective disorders, maladaptive beliefs and coping skills, and interpersonal and occupational dysfunction. Dysregulated cortical, pre-frontal, and higher neural level mechanisms associated with CLBP are being identified and may represent therapeutic targets in functional restoration-based approaches. As with other chronic pain syndromes, greater understanding of pain pathway alterations will better inform therapy selection.

Virtually universal among practice guidelines for CLBP is the emphasis on a multidisciplinary, multimodal approach that includes exercise and activity, cognitive restructuring of maladaptive attitudes and coping skills, a behavioral component addressing fear avoidance, physiotherapy and manual therapy, and analgesics as indicated [18; 21; 81; 88; 93; 94; 95]. This is often best accomplished by consultation or referral to an established pain treatment center. Multidisciplinary functional restoration programs, which are intensive (>100 hours) biopsychosocial interventions whereby physical rehabilitation is combined with cognitive-behavioral therapy and delivered by an interdisciplinary team, embody this recommendation. Moderate-to-strong evidence supports their efficacy in CLBP. They have been found effective in reducing pain and improving physical function, work readiness, and return to work. Weaker outcomes are found in programs that are less intensive or lacking a behavioral component. Patients who do not improve with less intensive therapy options and have high levels of pain, distress, and disability should be considered for multidisciplinary functional restoration programs [66].

The following treatment recommendations are based on practice guidelines by the American Pain Society, the American Society of Anesthesiologists, the American Society of Regional Anesthesia and Pain Medicine, the American College of Physicians, the National Institute for Health and Clinical Excellence, the American College of Occupational and Environmental Medicine, the Institute for Clinical Systems Improvement, and several published reviews and systematic reviews [18; 64; 65; 88; 93; 94; 95].

Persistent Nonspecific LBP

For persistent nonspecific LBP lasting longer than 12 weeks, patients should be offered education material on self-care developed from evidence-based guidelines and should be informed of the generally favorable outcome and natural time course of recovery [21; 93]. Maintenance of activity is important, and bed rest should be avoided. A structured, tailored exercise program may be established that includes aerobic activity, movement instruction, muscle strengthening, postural control, and stretching [88; 95]. Ice and/or heat should be applied to the painful area, with avoidance of prolonged exposure to extreme cold or heat (to the extent that tissue could be damaged). The pharmacologic approach for patients with persistent nonspecific LBP consists of acetaminophen or NSAIDs as needed [81]. Spinal manipulation, manual therapy, and/or acupuncture should be considered.

For patients unresponsive to less intensive therapy and who display high disability and/or psychological distress levels, referral to a multidisciplinary functional restoration program is indicated [88; 95]. If acetaminophen or over-the-counter NSAIDs are ineffective, use a COX-2 inhibitor [81]. Moderate-quality evidence shows that TCAs are not effective for CLBP compared with placebo [81]. Clinicians should only consider opioids as an option in patients who have failed other therapies and only if the potential benefits outweigh the risk for individual patients [81].

Patients with persistent nonspecific LPB despite optimal care may be considered for spinal fusion [88; 95]. However, appropriate care for any significant psychological distress should be pursued before surgery is considered. In the first three months of LBP onset, the only patients to benefit from surgery are those with severe spinal disease or debilitating symptoms and evidence of specific nerve root compromise on imaging studies [88; 95].

TREATMENT OF CHRONIC LOW BACK PAIN BASED ON UNDERLYING CAUSE OR TYPE	
Pain Type	**Possible Treatment Approaches**
Nonspecific nonradicular	NSAIDs Norepinephrine reuptake inhibitor antidepressants (e.g., amitriptyline, imipramine, nortriptyline, maprotiline, doxepin) Extended-release oral opioids Intensive interdisciplinary rehabilitation with cognitive/behavioral emphasis Capsaicin for temporary flare-ups Transcutaneous electrical nerve stimulation (TENS) Caudal epidural steroid injection in discogenic pain without disk herniation or radiculitis Lumbar transforaminal epidural injections Implantable intrathecal opioid infusion for severe intractable pain
Radiculopathy pain	Alpha-2-delta calcium channel antagonist, sodium-channel antagonist, and membrane-stabilizing anticonvulsants drugs Tricyclic antidepressants (TCAs) Extended-release oral opioids Caudal epidural steroid injection Lumbar interlaminar epidural injection for disk herniation and radiculitis Spinal cord stimulation for persistent radicular pain in patients unresponsive to other therapies, with a trial performed before considering permanent implantation For severe, disabling radiculopathy pain: • Intrathecal opioid injection or infusion • Neuraxial opioid trials should be performed before considering permanent implantation • Percutaneous lumbar discectomy with disk herniation origin • Lumbar discectomy in radiculopathy due to nerve root compression
Spinal stenosis	Gabapentin for severe neurogenic claudication with limited walking distance Caudal epidural steroid injection Decompression surgery for severe intractable pain Implantable intrathecal opioid infusion for severe intractable pain
Vertebral compression fracture	Vertebroplasty Kyphoplasty Percutaneous disk decompression
Facet joint pain	Medial branch blocks Radiofrequency neurolysis of medial branches (Intra-articular facet joint injection is NOT supported by evidence.)
Sacroiliac joint pain	Sacroiliac (SI) joint corticosteroid injections with identifiable cause of SI pain Water-cooled radiofrequency ablation
Degenerative disk disease	Intradiscal electrothermoplasty for young, active patients with early single-level degenerative disk disease with well-maintained disk height
Myofascial pain	Physiotherapy techniques that include stretching, strengthening exercises, massage, and iontophoresis (ion therapy) Trigger point injection of local anesthetic
Failed lumbosacral spine surgery	Caudal epidural steroid injection Percutaneous adhesiolysis Endoscopic adhesiolysis Spinal cord stimulation in the absence of nerve root compression, with a trial performed before considering permanent implantation Implantable intrathecal opioid infusion for severe intractable pain

Table 3 continues on next page.

TREATMENT OF CHRONIC LOW BACK PAIN BASED ON UNDERLYING CAUSE OR TYPE *(Continued)*	
Pain Type	**Possible Treatment Approaches**
Spinal cord injury	Spinal cord stimulation, with a trial performed before considering permanent implantation For associated neuropathic pain: Gabapentin, amitriptyline, nortriptyline, intravenous lidocaine For associated musculoskeletal pain and/or spasticity: Intrathecal baclofen, intrathecal morphine, clonidine For associated visceral pain: Appropriate management of bowel or bladder dysfunction
Cauda equina syndrome	Spinal cord stimulation, with a trial performed before considering permanent implantation
Spondylolisthesis	Lumbar fusion for isthmic or degenerative spondylolisthesis
Source: [18; 64; 65; 88; 94]	*Table 3*

Chronic Low Back Pain

For all pharmacotherapy recommendations for CLBP, clinicians must weigh the potential benefits against potential risks and consider patient comorbidity. Some risks can be mitigated; for example, the use of proton pump inhibitors to prevent GI side effects in patients using NSAIDs [88; 95]. All minimally invasive and invasive interventional therapies are recommended only for symptomatic pain relief, with full discussion of potential benefits, risks, and evidence for each suggested approach. In addition, all patients with chronic back pain, independent of additional therapies, should be involved in multimodality therapy [81; 88; 95].

All patients with CLBP should be provided evidence-based information and encouraged to remain active and to use self-care options [21; 81]. Medications with proven benefits should be used in conjunction with patient education and self-care. For most patients, first-line medication options are acetaminophen or NSAIDs [21; 81]. In patients not improving with self-care, consider multidisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation. When patients with CLBP do not respond to these interventions, further assessment to determine etiology should be considered, with further treatment then based on these findings (***Table 3***).

According to the Institute for Clinical Systems Improvement, clinicians should advise patients with acute and subacute low back pain to stay active and continue activities of daily living within the limits permitted by their symptoms.

(https://www.icsi.org/guideline/low-back-pain. Last accessed August 19, 2022.)

Strength of Recommendation/Level of Evidence: Strong Recommendation/Moderate Quality Evidence

Tapentadol is a newer opioid available for the treatment of chronic moderate-to-severe pain. The mechanism of action involves a novel mu-opioid receptor (partial) agonist combined with norepinephrine reuptake inhibition. Its efficacy for CLBP is demonstrated by the results of a randomized, double-blind trial that compared tapentadol ER (100–250 mg twice daily) against oxycodone CR (20–50 mg twice daily) and placebo in 958 patients with CLBP (baseline pain "severe" in 88.5%) [96]. After 12 weeks maintenance therapy, tapentadol was superior to the other treatment arms by the following measures among responders: patients with ≥30% and ≥50% pain intensity reduction; patients who were "very much improved" or "much improved;" and patients with significant improvement in function and quality of life. No differences were found between oxycodone and placebo in response rate, ≥30% pain reduction, or ≥50% pain reduction.

A meta-analysis of yoga effectiveness for LBP evaluated 10 RCTs enrolling 967 patients with CLBP. Strong evidence was found that practicing yoga is associated with significant improvement in near-term pain relief, back-specific disability, general improvement, and long-term pain control. Moderate evidence supported findings of significant long-term improvement in back-specific disability. The authors concluded that yoga should be recommended for patients with CLBP [97].

WHIPLASH PAIN

Between 210,000 and 987,000 Americans are estimated to sustain a whiplash injury each year, for an annual incidence of 16 to 329 cases per 100,000 population [98; 99]. Although long-held conventional wisdom is that most patients recover within several months of injury, data indicates that 37% experience moderate-to-severe pain at three months and that neck pain remains problematic for 50% of patients one year post-whiplash [100]. Also, 58% of patients initially seen in emergency rooms report symptom persistence 30 months or longer post-injury [101].

A large prospective cohort study found that motor vehicle accident with whiplash injury was the single greatest etiology of chronic neck pain. When insidious age-related onset of degenerative cervical disease (the second highest cause) was removed, motor vehicle accident whiplash accounted for more cases of chronic neck pain than all other etiologies combined. Based on their findings, the authors conservatively estimated that 15.5 million Americans experienced chronic neck pain originating from motor vehicle accident-induced whiplash injury [102].

Whiplash is the result of energy from the accident transferred to the neck through an acceleration-deceleration mechanism. The threshold for cervical muscle injury is 5 miles per hour [103]. Although whiplash injury and pain are primarily caused by motor vehicle accidents, sports injury is the second most common cause. Following the injury, symptoms can appear immediately or delayed over the first 24 hours. Forced extension-flexion trauma to the neck in the absence of direct impact to the head or neck may result in skeletal or soft-tissue injuries that present clinically in a variety of ways: neck pain or stiffness, headache, dizziness, paresthesia, and, on occasion, cognitive impairment such as confusion or memory loss. Also common are visual and auditory disturbances, temporomandibular joint pain, photophobia, and fatigue. Muscle spasm and trigger points involving one or more muscles of the occiput or neck may be present, and persistent sleep or mood disturbances can develop [99]. Varying degrees of psychological distress have been observed following whiplash and may contribute to symptom persistence. There is also increasing awareness that post-traumatic stress symptoms can emerge in some patients [28; 104; 105].

A variety of more complex symptoms and signs is seen in as many as 20% to 30% of affected individuals. These include allodynia and hyperalgesia in the neck region and possibly in remote peripheral sites; cold hyperalgesia (a negative prognostic indicator); spinal cord hyperexcitability demonstrated by heightened flexor withdrawal responses; substantially reduced neck movement; and motor control deficits such as abnormal muscle recruitment in the neck and shoulder girdles. For many patients, these difficulties eventually resolve following recovery from injury; for others, they do not, and over time they contribute to chronic pain and disability. Collectively, the persistent discomfort and other associated syndromes described are referred to as whiplash-associated disorders or WAD [28; 99; 104]. Chronic pain following whiplash injury is aggravated by cervical spine motion, tension, sitting, or reading and by push/pull activities such as vacuuming. Prolonged or repetitive use of the shoulder girdle muscles, such as when carrying items or washing dishes, may induce radiating pain in the upper

extremities [28; 99] High initial levels of pain and/or disability represent the strongest indicator of poor recovery. Low risk factors for developing protracted post-whiplash symptoms include crash impact at the rear of the vehicle, ability to sit instead of lie down in the emergency department, ability to be ambulatory without interruption, delayed neck pain onset, and absence of midline cervical spine tenderness. The greatest gains in recovery occur during the first three months, following which symptom reduction tends to plateau [28].

The diagnosis of WAD does not depend on imaging or other workup but rather the patient's own self-reporting. Imaging is not recommended and is not helpful in the diagnosis or management of WAD, the exception being cases in which fracture or dislocation is suspected. The most widely accepted and utilized whiplash injury classification system has been the Quebec Task Force Classification; however, its usefulness is now in question because of the identification of post-whiplash sensory, motor, and psychological features that were not considered by this system [28; 106].

Some have suggested that active litigation artificially inflates patient reporting of pain and disability severity by incentivizing symptom exaggeration [105]. This assumption has been disproved by several studies showing that elimination of the financial incentive to over-report whiplash symptoms had no effect on the intensity or duration of self-reported neck pain [102; 107].

The most effective management approach to patients with WAD begins with an assessment of both the physical and psychological impairments that underlie the disorder. The goal is to elucidate potential underlying mechanisms as the basis for a successful therapeutic strategy [108].

Pathophysiology

The changes that follow whiplash injury are heterogeneous and complex, and several pathogenic mechanisms are thought to account for the clinical findings. Evidence suggests the contribution of initial structural injury combined with the secondary effects on sensory and motor function [99]. Injuries are most likely to occur in cervical spine structures, especially the zygapophyseal joints. Augmented central pain processing mechanisms are the likely basis of persistent chronic post-injury pain. Muscle strain and associated dysfunction likely account for disturbances in movement and neuromotor control. Kinesthetic deficits, loss of balance, and loss of eye movement control are the result of disturbances in sensorimotor control, which likely contributes to symptoms of dizziness [108]. Cerebrospinal fluid (CSF) leak has also been suggested as a contributing factor [109].

Alteration in peripheral and central pain processing is considered important in the pathogenesis of chronic WAD. CNS hyperexcitability contributes to sensory hypersensitivity (both generalized and expressed in unaffected tissue remote from the injury site). This is initiated by alteration in spinal cord neuron excitability secondary to peripheral nociceptive signaling bombardment. It is sustained by NMDA receptor activation and resultant release of COX-2 in the spinal cord and by glial cell activation. Dysregulation in the balance between descending facilitatory and inhibitory pathways, originating within cortical centers, also contributes to central hyperexcitability [110].

Peripheral sensitization is augmented by the inflammatory response to structural injury, which releases inflammatory mediators such as substance P, prostaglandins, and bradykinin. This amplifies the intensity and prolongs the duration of nociceptive signaling, which in turn alters peripheral nerve fiber characteristics in such a way as to perpetuate primary hyperalgesia [110].

Treatment

The relative lack of published research on treatment efficacy in WADs has resulted in an overall paucity of evidence-based treatment guidelines. Identifying and comparing studies on treatment outcome is further complicated by the absence of uniform patient classification by symptom severity [98]. Nonetheless, a systematic review to evaluate the strength of evidence for various WAD therapies was published in 2010 [98; 100; 101; 111]. The authors evaluated 83 studies, including 40 RCTs, published between 1980 and 2009. Their recommendations, along with those from practice guidelines, systematic reviews, and clinical trials form the basis for the treatment of acute, post-acute, and chronic-phase WAD [88; 108; 110; 112; 113; 114; 115; 116; 117]. The conclusions for most minimally invasive and surgical interventions are based on single published trials and should be viewed with caution given this limited evidence base [111].

Behavioral and Lifestyle Interventions

Patient education that addresses therapeutic barriers, therapy compliance, and prevention of chronicity should be offered in all phases of WAD. Lifestyle and behavioral changes are the first (and often only necessary) treatments for patients with mild-to-moderate whiplash-related pain [99]. Exercise programs are effective in reducing short-term pain intensity in all WAD phases [111]. However, the results of one systematic review found a lack of significant improvements in long-term pain and disability in individuals with WAD who participated in general exercise interventions [118]. Vestibular rehabilitation can be offered for dizziness in chronic-phase WAD. Of greatest benefit in improving pain and function during the acute phase are range of motion, neck and scapular strengthening, and neck stabilization exercises. One study investigated ventral neck muscle interactions in 26 individuals with chronic WAD randomized to neck-specific exercise or a wait list for three months [119]. The researchers used real-time, non-invasive ultrasound measurements and calculations of the deformed area and deformation rate in the neck muscles. After three months, significant improvements were observed in neck muscle interactions and pain intensity in the neck-specific exercise group compared to the wait list group, demonstrating that non-invasive ultrasound may be a useful diagnostic tool for muscle impairment and may be used to evaluate exercise interventions in WAD [119]. Aggressive strengthening programs may worsen symptoms and should be avoided [111].

Encouraging the patient to maintain good range of motion is important. Soft-collar cervical immobilization should be discouraged as active mobilization during acute phase WAD can actually reduce pain intensity [99]. Multimodality therapy programs that include joint mobilization, relaxation therapy, electrotherapies, exercise, and a cognitive-behavioral component that address pain and functional deficits are effective in patients with subacute or chronic WAD who have not improved with simple activity-related approaches [99]. Patients with severe symptoms should be enrolled as soon as is feasible following injury. However, patients with cold hyperalgesia and/or widespread allodynia may not respond to this intervention. Early referral to a pain clinic is advisable for patients at risk of developing chronic symptoms [111]. Patients should also be assessed and monitored for symptoms of anxiety and depression, then treated accordingly.

Pharmacotherapy

Prompt, effective pain control should be achieved early, because high pain levels can interfere with recovery. There is little available guidance on the effectiveness of specific opioid and non-opioid analgesics. Some recommend initiating acetaminophen or NSAIDs for pain and adding codeine if appropriate and necessary [111]. If a patient remains symptomatic despite optimal analgesia, adding a TCA, such as amitriptyline, may be beneficial [99].

Methylprednisolone infusion may improve recovery in moderate-to-severe acute WAD. In addition, intra-articular dextrose and lidocaine injections may reduce pain and disability [111].

Medial branch block of the cervical zygapophyseal joints effectively reduced sensory hypersensitivity in a small group of patients with chronic WAD, but these results need larger-scale prospective replication [111]. Supportive evidence is equivocal for botulinum toxin injections and lacking for intra-articular or selective nerve root block or corticosteroid injections in chronic WAD [111].

Surgical Interventions

Moderate evidence indicates that radiofrequency neurotomy is effective in reducing pain in chronic WAD, although relief is not permanent [111]. Some patients benefit from occipital nerve decompression, carpal tunnel decompression, and cervical discectomy and fusion. In addition, combined surgical fasciectomy and spinal accessory nerve neurolysis is effective in patients with severe, refractory WAD with spinal accessory nerve entrapment and/or chronic compartment syndrome of the trapezius muscle.

Patients with chronic WAD often complain of headache, dizziness, and nausea, symptoms also experienced by patients with CSF leak. Ishikawa et al. explored the relationship between chronic WAD and CSF leak and investigated the efficacy of epidural blood patch in chronic WAD [109]. Of 66 patients (mean duration of WAD: 33 months) imaged with radioisotope cisternography, CSF leak was detected in 37 patients who then received epidural blood patch. Compared with baseline, symptom reduction one week after epidural blood patch was noted in most patients, including improvements in headache (100% vs. 17%), memory loss (94% vs. 28%), dizziness (83% vs. 47%), visual impairment (81% vs. 25%), and nausea (78% vs. 42%). Treatment response remained at six-month follow-up, and work status was also significantly improved at follow-up. The authors concluded that in some cases of chronic WAD, the possibility of CSF leak should be assessed, and that epidural blood patch may be beneficial for patients with positive findings. There are no other published studies confirming these observations.

Alternative Therapies

Massage therapy, chiropractic, physical therapy, and occupational therapy constitute adjunctive modalities that may be of benefit in all phases of WAD [111]. Acupuncture has also been shown to reduce pain in chronic WAD, although evidence of functional improvement is lacking [88; 111; 112]. Pulsed electromagnetic field therapy can decrease pain intensity and increase cervical range of motion in acute WAD. Myofeedback training may be beneficial for some patients with chronic WAD [88; 111; 112; 120].

An RCT of 51 patients with chronic nonspecific neck pain compared a self-help exercise program with Iyengar yoga [121]. Following a nine-week trial of both yoga and neck pain interventions, yoga resulted in significantly greater improvement than home-based exercise for pain, pain intensity, disability, mental health-related quality of life, and neck muscle functional status. Patients randomized to yoga were further evaluated one year after completing the nine-week formal protocol [122]. Statistically significant improvements from baseline were found in pain intensity, neck-related disability, and bodily pain. Sustained yoga practice was the strongest predictor of long-term effectiveness.

Optimal treatment of WAD continues to be a challenge, which may be related to the need for better understanding of the subjective experiences and perceptions of patients living with the condition. In one study, researchers conducted individual telephone interviews with patients with WAD and then analyzed the transcribed audio tapes. Two main themes emerged from the interviews. First, the participants described what it was like to navigate the healthcare system to understand their injury, interpret therapeutic recommendations, and find the right healthcare practitioner to help with the process. Additional navigational complexities were related to compensation and funding systems. Second, participants described a journey of trial and error in establishing self-management strategies to prevent and relieve pain. This included the gradual

realization that they could be faced with an ongoing residual deficit. Early identification of the patient's expectations for recovery and validation of their injury by the healthcare practitioner can aid the recovery process [123].

ARTHRITIC PAIN CONDITIONS

OSTEOARTHRITIS

Osteoarthritis is the most common form of arthritis and is characterized by degeneration of cartilage and its underlying bone within a joint, with resultant bony overgrowth. This process of tissue breakdown eventually leads to pain and joint stiffness [124]. The estimated overall annual prevalence of osteoarthritis in the United States was 32.5 million adults in 2013-2015, an increase from the 1990 estimate of 21 million [125]. Osteoarthritis is the most common cause of disability in adults [126].

Patients often describe the pain from osteoarthritis as deep, aching, and poorly localized. The most commonly afflicted joint sites include the distal and proximal interphalangeal joints and the first metacarpal joint of the hand; the lumbar and cervical spine; and the weight-bearing joints in the knees, hips, and ankles. The joint pain in osteoarthritis is exacerbated by activity, and continued loss of cartilage contributes to worsening pain with disease progression. Patients with severe osteoarthritis may experience pain with little joint motion or during rest [124].

Traditionally, osteoarthritis was thought to affect primarily the articular cartilage of synovial joints; however, pathophysiologic changes also are known to occur in the synovial fluid, as well as in the underlying (subchondral) bone, the overlying joint capsule, and other joint tissues [127]. Nociceptor innervation is found in the intra-articular and periarticular structures of the joint, including the menisci, adipose tissue, synovium, and periosteum; cartilage is aneural [127]. The increase in cytokine release that accompanies joint inflammation and pathologic structural changes characteristic of osteoarthritis results in peripheral sensitization that manifests as primary hyperalgesia, spontaneous pain, and pain with normally innocuous movement. Bone marrow lesions, synovitis, effusions, and possibly meniscal abnormalities represent the specific pathologic features that contribute to pain in osteoarthritis [127].

Joint damage has been the presumed origin of osteoarthritis-associated pain and has represented the target of pain-alleviating therapies. However, evidence strongly suggests alteration in central pain processing contributes to the state of chronic pain [127]. Peripheral mechanisms likely account for early-stage pain, with central mechanisms becoming dominant in later stages [128]. For example, secondary hyperalgesia in osteoarthritis results from CNS alteration. Sensitivity to mechanical stimuli outside the area of injury is enhanced, which heightens the response to peripheral input or central sensitization and manifests clinically as referred or radiating pain with reduced pain thresholds in unaffected joints [128]. Other evidence supporting dysregulation in central pain processing in osteoarthritis includes the lack of correlation between joint pathology and reported pain intensity; diffuse hyperalgesia to mechanical or heat provocation; lower mechanical pain thresholds and greater mechanical and thermal temporal summation relative to controls; augmented CNS pain processing; and efficacious response in patients with knee osteoarthritis to the centrally acting drug duloxetine [129].

Pain sensitivity in osteoarthritis may also be influenced by genetic factors. The catechol-*O*-methyl transferase Val158Met polymorphism has been associated with hip osteoarthritis-related pain. Psychological factors are also likely to contribute to the pain experienced in osteoarthritis. Increased affective and motivational response has been demonstrated in patients with osteoarthritis [130].

Physical examination may reveal localized tenderness and pain on passive motion, especially at the extreme of movement. Soft tissue changes, effusion, or osteophytosis contribute to the joint enlargement common in patients with osteoarthritis. Joint crepitus may be audible or palpable, and the presence of a limp, deformity of the knee, or instability may be observed by inspection of gait [127]. In the absence of specific laboratory abnormalities with diagnostic utility, osteoarthritis is usually diagnosed on the basis of clinical and radiologic findings [127].

Different prevalence rates have been found between cases based on radiographic identification and clinical symptoms with radiographic confirmation. Although symptomatic osteoarthritis is most common in the knee, structural changes indicative of osteoarthritis are most commonly observed in the hands. Women have higher rates of osteoarthritis than men (especially after 50 years of age), and the overall incidence rate increases with age but levels off around 80 years of age [127]. Among persons with osteoarthritis, 39% report they are not able to access the rehabilitative services they need [124]. Risk factors for osteoarthritis include trauma, advancing age, and genetic predisposition [127].

Treatment

Altered central pain processing and central sensitization are involved in osteoarthritis pain. Treatment approaches are beginning to address this CNS origin of pain. Cognitive-behavioral therapy and neuroscience education potentially reduce emotional sensitization and descending pain facilitation, while centrally acting drugs such as duloxetine may increase endogenous analgesia by enhancing descending pathway inhibition [131; 132].

With no currently available cure for osteoarthritis, treatment focuses on symptom relief, functional improvement, and prevention of disease progression through a combination of patient education, physical therapy, weight control, and pharmacotherapy [124; 133]. The 2019 guidelines from the American College of Rheumatology (ACR) represent the practice guidelines with the highest level of scientific rigor and broadest clinical applicability [133]. These guidelines depart from previous ACR recommendations, and from those of other organizations, by abandoning the sequenced order of interventions for patients failing to respond to recommended initial therapies, as this management strategy has not received empirical validation. The selection of interventions and the order in which interventions are used will vary among patients. No specific hierarchy of one option over another is implied other than on the basis of strength of the recommendation [133].

The ACR guidelines for initial management of osteoarthritis are organized according to affected joint (***Table 4***, ***Table 5***, and ***Table 6***).

According to the American Academy of Orthopaedic Surgeons, oral acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

(https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Last accessed August 19, 2022.)

Strength of Recommendation: Strong (Evidence from two or more "high" quality studies with consistent findings for recommending for or against the intervention.)

An important point is that patient failure with conservative therapies may be due to lack of adherence to self-management or medication. Many of these cases can be identified through the patient history [134].

In the treatment of osteoarthritis, no clear advantage based on side effect profile has been shown with any non-opioid oral analgesic. Given the different adverse event profiles of each agent, treatment decisions should be guided by patient factors, such as age, comorbidity, and concomitant medication [135].

HAND OSTEOARTHRITIS, INITIAL MANAGEMENT	
Strength of Recommendation	**Recommended Approaches**
Nonpharmacologic recommendations	
Strong recommendations[a]	Exercise (strongly recommended for all patients with OA, but more evidence for its benefit for knee/hip OA) Patient participation in self-efficacy, self-management programs Hand orthoses for patients with first CMC joint OA
Conditional recommendations[b]	Cognitive-behavioral therapy Hand orthoses for patients with OA in joint of the hand other than first CMC joint Acupuncture Thermal interventions (e.g., moist heat, diathermy, ultrasound, hot/cold pack, paraffin)
No recommendations	Balance training Weight loss Tai chi, yoga
Pharmacologic recommendations	
Strong recommendations[a]	Oral NSAIDs
Conditional recommendations[b]	One or more of the following: • Topical NSAIDs • Intra-articular glucocorticoid injection • Acetaminophen • Duloxetine • Tramadol • Chondroitin sulfate
Strong recommendations against using[a]	Bisphosphonates Glucosamine Hydroxychloroquine Methotrexate Biologics (e.g., tumor necrosis factor inhibitors)
Conditional recommendations against using[b]	Intra-articular therapies
No recommendations	Ultrasound-guided intra-articular glucocorticoid injection Intra-articular botulinum toxin Prolotherapy Platelet-rich plasma Stem cell injection
CMC = carpometacarpal, NSAID = nonsteroidal anti-inflammatory drug, OA = osteoarthritis. [a]Compelling evidence of efficacy with benefits that clearly outweigh harms and burdens [b]Quality of evidence proved low or very low and/or balance of benefits versus harms and burdens was close, requiring shared decision-making between patient and clinician.	
Source: [133]	*Table 4*

KNEE OSTEOARTHRITIS, INITIAL MANAGEMENT	
Strength of Recommendation	**Recommended Approaches**
Nonpharmacologic recommendations	
Strong recommendations[a]	Exercise (current evidence insufficient to recommend specific exercise prescriptions) Weight loss if overweight or obese Self-efficacy/self-management programs Tai chi Use of a cane Tibiofemoral knee braces
Conditional recommendations[b]	Balance training Yoga Cognitive-behavioral therapy Patellofemoral braces Kinesiotaping Acupuncture Thermal interventions Radiofrequency ablation
Strong recommendations against using[a]	Transcutaneous electrical stimulation
Conditional recommendations against using[b]	Modified shoes Lateral/medial wedged insoles Massage therapy Manual therapy with/without exercise Pulsed vibration therapy
No recommendations	Paraffin Iontophoresis
Pharmacologic recommendations	
Strong recommendations[a]	Topical NSAIDs Oral NSAIDs Intra-articular glucocorticoid injection
Conditional recommendations[b]	Topical capsaicin Intra-articular glucocorticoid injection (compared with other injections) Acetaminophen Duloxetine Tramadol
Strong recommendations against using[a]	Bisphosphonates Glucosamine Chondroitin sulfate Hydroxychloroquine Methotrexate Platelet-rich plasma Stem cell injection Biologics

Table 5 continues on next page.

KNEE OSTEOARTHRITIS, INITIAL MANAGEMENT *(Continued)*	
Conditional recommendations against using[b]	Non-tramadol opioids Colchicine Fish oil Vitamin D Intra-articular hyaluronic acid injection Intra-articular botulinum toxin Prolotherapy
No recommendations	Ultrasound-guided intra-articular glucocorticoid injection

NSAID = nonsteroidal anti-inflammatory drug.
[a]Compelling evidence of efficacy with benefits that clearly outweigh harms and burdens
[b]Quality of evidence proved low or very low and/or balance of benefits versus harms and burdens was close, requiring shared decision-making between patient and clinician.

Source: [133] *Table 5*

Regarding chondroitin sulfate and glucosamine, clinical trials have shown comparable but not superior benefits relative to NSAIDs for pain relief and function improvement. With most of the studies performed outside the United States and involving pharmaceutical-grade preparations, the results may not generalize to the United States with over-the-counter preparations [135].

Operative Treatment

Operative treatment for osteoarthritis should be delayed until all possible nonoperative options have been exhausted [136]. In general, the indications for operative treatment are debilitating pain and major limitations in function and activities of daily living [136]. Proper patient selection and adherence to precise surgical procedure are critical to success [137].

In an effort to delay total knee or hip replacement, many have recommended arthroscopic lavage and debridement, but several studies, systematic reviews, and meta-analyses have shown that there is no evidence to support the efficacy of this approach for treatment of osteoarthritis of the knee [137; 138; 139; 140; 141]. In addition, comparisons between the use of intra-articular corticosteroids and joint lavage showed no differences between the two treatments with respect to efficacy or safety [142; 143]. Arthroscopic lavage and debridement may be useful for removing unstable tissues (e.g., loose bodies, meniscal tears, loose cartilage) that are causing mechanical symptoms [136; 138].

The American Academy of Orthopaedic Surgeons (AAOS) updated its guideline on surgical management of knee osteoarthritis in 2015 [144]. This guideline states that moderate evidence supports no difference between unicompartmental knee arthroplasty or valgus-producing proximal tibial osteotomy in outcomes and complications in patients with symptomatic medial compartment osteoarthritis of the knee [144]. The AAOS recommends against performing arthroscopy with debridement or lavage in patients with a primary diagnosis of symptomatic osteoarthritis of the knee [144]. The AAOS notes that arthroscopic partial meniscectomy or removal of loose bodies is an option for patients who have failed physical therapy or other nonsurgical treatments [145]. In addition, the AAOS found that arthroscopic partial meniscectomy can be used in patients with osteoarthritis of the knee with a torn meniscus [144].

HIP OSTEOARTHRITIS, INITIAL MANAGEMENT	
Strength of Recommendation	**Recommended Approaches**
Nonpharmacologic recommendations	
Strong recommendations[a]	Exercise Weight Loss Self-efficacy/self-management programs Tai chi Use of a cane
Conditional recommendations[b]	Balance training Cognitive-behavioral therapy Acupuncture Thermal interventions
Strong recommendations against using[a]	Transcutaneous electrical nerve stimulation
Conditional recommendations against using[b]	Lateral/medial wedged insoles Massage therapy Manual therapy with/without exercise
No recommendations	Modified shoes Radiofrequency ablation Iontophoresis Pulsed vibration therapy
Pharmacologic recommendations	
Strong recommendations[a]	Oral NSAIDs Intra-articular glucocorticoid injection Ultrasound-guided intra-articular glucocorticoid injection
Conditional recommendations[b]	Intra-articular glucocorticoid injection (compared with other injections) Acetaminophen Duloxetine Tramadol
Strong recommendations against using[a]	Bisphosphonates Glucosamine Chondroitin sulfate Hydroxychloroquine Methotrexate Intra-articular hyaluronic acid injection Platelet-rich plasma Stem cell injection Biologics
Conditional recommendations against using[b]	Colchicine Fish oil Vitamin D Intra-articular botulinum toxin Prolotherapy
No recommendations	Topical NSAIDs Topical capsaicin

NSAID = nonsteroidal anti-inflammatory drug.
[a]Compelling evidence of efficacy with benefits that clearly outweigh harms and burdens
[b]Quality of evidence proved low or very low and/or balance of benefits versus harms and burdens was close, requiring shared decision-making between patient and clinician.

Source: [133] *Table 6*

Experts have described satisfactory outcomes after arthroscopic debridement of the elbow [146; 147]. The ideal candidate for the procedure is younger than 60 years of age, is active, and has impingement pain at the extremes of the range of motion but not at the midpoint of the arc of motion or at rest [146; 148]. Compared with open debridement, the arthroscopic procedure is associated with decreased intraoperative bleeding and less postoperative pain. The procedure is technically demanding but is safe when performed by an experienced surgeon familiar with the technique [146].

Debridement (through arthroscopy or arthrotomy) of the ankle has relieved pain, decreased swelling and stiffness, and improved activity levels in more than half of patients [149]. Improvement is most likely when debridement is done to remove osteophytes, smooth unstable chondral surfaces, and remove loose bodies [149].

RHEUMATOID ARTHRITIS

In the United States, rheumatoid arthritis afflicts 1.5 million, or roughly 1% of the adult population, and has a prevalence rate of 0.4% to 1.3% [150]. Women are diagnosed three times more often than men. Risk factors for rheumatoid arthritis in women include a history of exogenous hormone use, irregular menses, not breastfeeding following delivery, and nulliparity [151]. Symptom onset in women is typically between 30 and 60 years of age. While men have a later average onset, sex differences diminish in older age groups [151; 152].

Patients with rheumatoid arthritis have a two-fold higher mortality rate relative to age-matched controls, attributable mainly to cardiovascular disease. Other highly prevalent comorbid conditions in patients with rheumatoid arthritis include infections (most commonly tuberculosis), psychiatric conditions, and lymphoproliferative malignancies such as leukemia and multiple myeloma [153].

Rheumatoid arthritis manifests clinically as pain and swelling in three or more joints, primarily in the hands and feet [152; 154]. Pain is often accompanied by redness, swelling, and warmth, and patients with more severe rheumatoid arthritis may exhibit joint deformities and bony growths called rheumatoid nodules [151; 154].

The clinical hallmark of rheumatoid arthritis is stiffness after prolonged periods of inactivity, particularly when rising in the morning. Another feature is bilateral symptom presentation, producing a mirroring effect. Symptoms not generally associated with osteoarthritis, such as depression, extreme fatigue, weight loss, and fever, may commonly occur with rheumatoid arthritis and are explained by the systemic inflammatory disease basis of the disease [152; 154].

Although the natural history of rheumatoid arthritis shows marked variability among patients, it is believed the disease follows at least three courses [154]:

- Monocyclic: A single episode ending within two to five years of initial diagnosis without recurrence. This outcome may be attributable to early diagnosis and/or aggressive treatment.
- Polycyclic: Characterized by a fluctuating level of disease activity throughout the course of the condition.
- Progressive: The disease progressively increases in its severity and is unremitting.

The pathogenesis of rheumatoid arthritis is not fully understood. However, in genetically susceptible persons, an external trigger such as infection or trauma may precipitate an autoimmune reaction targeting the synovium. This results in synovial hypertrophy, chronic joint inflammation, and possibly extra-articular manifestations such as cartilage deterioration, bone damage, and joint deformity [155; 156].

Major cellular/molecular contributors to rheumatoid arthritis pathophysiology include CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils. Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators has been demonstrated in patients with rheumatoid arthritis [156; 157].

As an important regulator of proinflammatory molecules and stimulator of the secretion of matrix metalloproteinases, TNF plays a central role in rheumatoid arthritis pathobiology. TNF is intimately involved in mediating the activity of numerous compounds inside the joint, including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. TNF directly influences inflammation and the formation of pannus, a mass of tissue that causes localized joint destruction [156; 158].

Abnormal stress response also contributes to rheumatoid arthritis pathophysiology. Patients with rheumatoid arthritis have shown a maladaptive proinflammatory response to experimentally induced pain stimuli, including elevations in C-reactive protein, TNF-α, and the pro-inflammatory cytokine interleukin-6. These findings suggest an important role played by hyperalgesia in shaping the long-term symptomatology of rheumatoid arthritis [156; 159].

Some patients do not experience pain reduction despite treatment with anti-inflammatory disease-modifying antirheumatic drugs (DMARDs). This suggests that inflammation may not be the sole contributor to pain in rheumatoid arthritis, and abnormalities in CNS pain processing and modulation have been found in patients with rheumatoid arthritis. The role of central sensitization as an underlying pathophysiology in patients not experiencing pain reduction with DMARDs is indicated by the symmetrical manifestation of the disease, absence of correlation between disease activity and symptoms, and the generalized hyperalgesia at both articular and nonarticular sites for different kinds of stimuli [114]. Few rheumatologists are familiar with the use of drug therapies that target central pain pathways [128].

Classification

Rheumatoid arthritis is diagnosed clinically but may be classified according to the 2010 ACR and European League Against Rheumatism classification criteria for rheumatoid arthritis (***Table 7***). For classification purposes, a patient has definite rheumatoid arthritis if he or she scores at least 6 points using the established system.

Early diagnosis and DMARD treatment are extremely important for suppression of synovitis and prevention of bone erosion in the joints, as this greatly reduces the risk of permanent disability. The 2010 criteria were developed to improve sensitivity in detecting early-stage rheumatoid arthritis by including tender and swollen joint count, acute phase reactants, anticitrullinated peptide antibodies or rheumatoid factor, and symptom duration. Also, the former criterion requiring six weeks of symptom duration was eliminated. The criteria are intended for use following differential diagnosis of synovitis in patients with at least one swollen joint, and patients showing bone erosion are automatically classified as rheumatoid arthritis [161].

Treatment

Pain is common for many patients with rheumatoid arthritis, even with optimal therapy addressing the pathophysiology. Patients with rheumatoid arthritis report that pain control is their greatest priority. The treatment goals for all patients with rheumatoid arthritis are control of pain and inflammation and ultimately the induction of disease remission or greatly diminished disease activity [158]. Pharmacologic treatments are the backbone of therapy and fall into three general categories: corticosteroids, NSAIDs, and DMARDs, including biologic, conventional synthetic, and targeted synthetic DMARDs [156; 158; 162].NSAIDs and corticosteroids have a short onset of action, while DMARDs can take several weeks or months to demonstrate a clinical effect [163]. In contrast to the 2015 guideline recommendations, the 2021 ACR guideline recommendations for the treatment of rheumatoid arthritis (***Table 8***) considers current disease activity, prior therapies used, and the presence of comorbidities as the factors most relevant to treatment decisions [162].

2010 AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS[a]	
Criteria	**Score**
Joint involvement	
1 large joint[b]	0
2–10 large joints	1
1–3 small joints[c] (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
Serology (at least one test result needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants (at least one test result needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP and abnormal ESR	1
Duration of symptoms	
Less than six weeks	0
Six or more weeks	1

RF = rheumatoid factor; ACPA = anticitrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
[a]Target population: patients who have at least one joint with definite clinical synovitis in whom the synovitis is not better explained by another disease.
[b]Large joints include shoulders, elbows, hips, knees, and ankles.
[c]Small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

Source: [160] *Table 7*

The 2021 ACR treatment guidelines also include recommendations for patients with specific comorbidities, including those with subcutaneous nodules, pulmonary disease, heart failure, hepatitis B infection, nonalcoholic fatty liver disease, and previous serious infection [162].

Corticosteroids (e.g., methylprednisolone, prednisone, prednisolone) are prescribed orally for rheumatoid arthritis to reduce inflammation and subsequent joint pain and swelling through receptor binding at inflammation sites. These agents inhibit movement of inflammatory cells, neutrophil function, and prostaglandin production. However, while they may control symptoms, they do not impact disease progression [158; 163].

Oral DMARDs are heterogeneous agents grouped together on the basis of slow action and ability to improve symptoms, reduce or prevent joint damage, and preserve structure and function in patients with inflammatory disease. They include methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine [158; 163].

2021 ACR GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS	
Patient Population	**Recommendation(s)**
DMARD-naïve patients with moderate-to-high disease activity	Methotrexate monotherapy is strongly recommended over hydroxychloroquine or sulfasalazine; bDMARD or tsDMARD monotherapy; orcombination of methotrexate plus a non-TNF inhibitor bDMARD or tsDMARD. Methotrexate is conditionally recommended over leflunomide, dual or triple csDMARD therapy, and combination of methotrexate plus a TNF inhibitor. Initiation of a csDMARD without short-term (less than three months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids. Initiation of a csDMARD without longer-term (three months or more) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids.
DMARD-naïve patients with low disease activity	Hydroxychloroquine is conditionally recommended over other csDMARDs. Sulfasalazine is conditionally recommended over methotrexate. Methotrexate is conditionally recommended over leflunomide.
csDMARD-treated, methotrexate-naïve patients with moderate-to-high disease activity[a]	Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD
All patients receiving methotrexate	Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate. Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is conditionally recommended over initiation/titration to a weekly dose of <15 mg. A split dose of oral methotrexate over 24 hours or weekly subcutaneous injections, and/or an increased dose of folic/folinic acid, is conditionally recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate. Switching to subcutaneous methotrexate is conditionally recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.
Patients treated with DMARDs who are not at target	A TTT approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs. A TTT approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. A minimal initial treatment goal of low disease activity is conditionally recommended over a goal of remission. Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target. Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target. Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target. Addition of/switching to DMARDs (with or without IA glucocorticoids) is conditionally recommended over use of IA glucocorticoids alone for patients taking DMARDs who are not at target.

Table 8 continues on next page.

2021 ACR GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS *(Continued)*	
Patient Population	**Recommendation(s)**
Patients tapering DMARDs	Continuation of all DMARDs at their current dose is conditionally recommended over a dose reduction of a DMARD. Dose reduction is conditionally recommended over gradual discontinuation of a DMARD. Gradual discontinuation is conditionally recommended over abrupt discontinuation of a DMARD. Gradual discontinuation of sulfasalazine is conditionally recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD. Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of a bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD.
DMARD = disease-modifying antirheumatic drug, bDMARD = biologic DMARD, csDMARD = conventional synthetic DMARD, IA = intra-articular TNF = tumor necrosis factor, tsDMARD = targeted synthetic DMARD, TTT = treat-to-target. [a]Recommendations are the same as for DMARD-naïve patients, except for this population.	
Source: [162]	*Table 8*

Biologic DMARDs are an injectable form of DMARD that differ from oral agents in the selectivity of immune system target. Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab block proinflammatory-mediating cytokines through TNF inhibition [156]. The other biologic DMARDs include anakinra, an interleukin-1 receptor antagonist; abatacept, an immunosuppressant that interferes with T lymphocyte activation; rituximab, which removes circulating B cells; and tocilizumab, an interleukin-6 (IL-6) antagonist [158].

Oral tofacitinib received FDA approval in 2012 for the treatment of rheumatoid arthritis in patients who have failed a trial of methotrexate. Tofacitinib is the first recent nonbiologic, small-molecular treatment for rheumatoid arthritis. Tofacitinib is a Janus kinase (JAK) inhibitor. Inhibition of JAKs reduces production of and modulates the proinflammatory cytokines central to rheumatoid arthritis [156]. Extensive evaluation has shown it superior to placebo, comparable to the anti-TNF agent adalimumab, efficacious in patients not responding to other anti-TNF agents, and superior to methotrexate. As with methotrexate, patients receiving tofacitinib are at risk for myelosuppression and should be monitored for cytopenias [36; 164; 165]. In 2018, the FDA approved a second JAK inhibitor, baricitinib as a second-line treatment for rheumatoid arthritis in patients with moderately-to-severely active disease who have had an inadequate response or intolerance to one or more TNF antagonists [36; 156; 166]. Baricitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs [156]. It should not be used in combination with biologic DMARDs or immunosuppressant agents (e.g., azathioprine, cyclosporine) [156; 166]. Baricitinib is dosed at 2 mg once daily [36]. Another JAK inhibitor, upadacitinib, was approved by the FDA in 2019 for treatment of rheumatoid arthritis in patients with moderately-to-severely active disease who have had an inadequate response or intolerance to one or more TNF blockers [36; 167]. The recommended dose of oral upadacitinib is 15 mg once daily [36; 167].

Sarilumab injection received FDA approval in 2017 for the treatment of rheumatoid arthritis in patients with moderately-to-severely active disease who have had an inadequate response or intolerance to one or more DMARDs [36; 162; 168; 169]. Approval of sarilumab was based on the results two trials [156]. In the first trial, patients treated with sarilumab plus methotrexate had reduced signs and symptoms and improved physical function and demonstrated significantly less radiographic progression of structural damage compared with placebo plus methotrexate [170]. The second trial produced similar results as the first trial [171]. Sarilumab may be use as monotherapy or in combination with methotrexate or other conventional DMARDs. The usual dose is 200 mg subcutaneously once every two weeks [36; 168]. For patients with early rheumatoid arthritis (less than six months in duration) who have never taken a DMARD, oral DMARD monotherapy (preferred agent: methotrexate) is recommended as first-line treatment [162]. Sulfasalazine is similarly effective, and leflunomide may provide comparable results [135; 158; 163]. In methotrexate-naïve patients with early rheumatoid arthritis, symptom response is similar between methotrexate and adalimumab or etanercept, and improvement in functional capacity is similar between methotrexate and adalimumab [163]. Adding prednisone reduces radiographic progression and joint erosion but increases risk of adverse events. Biologic DMARDs are more effective than oral DMARDs in limiting radiographic evidence of progression [135; 158].

In patients with longstanding active disease, biologic DMARDs offer greater likelihood of remission than oral agents and therefore are often the approach used [135; 158; 163]. Combining two biologic DMARDs does not improve disease activity, functional capacity, or symptom response, yet it does increase the risk of serious adverse events. However, if oral DMARDs are used, a combination of two or three agents is more effective than monotherapy [135; 158].

In patients with longstanding active disease requiring a change in therapy, biologic DMARDs are preferred over oral DMARDs [135; 158; 162]. The combination of a biologic DMARD and methotrexate provides greater symptom reduction than either agent alone without increasing the risk of serious adverse events.

Recognition of the substantial burden imposed by persistent rheumatoid arthritis pain prompted the development of recommendations for pharmacologic pain control in rheumatoid arthritis by the 3e (evidence, expertise, exchange) Initiative (***Table 9***). The guideline was initially developed in reference to the broad category of inflammatory arthritis, but most of the evidence in the final report pertains to rheumatoid arthritis [141].

Other pain control options are being studied and may be considered in intractable cases. Nefopam hydrochloride is a benzoxazocine analgesic widely used in Europe for rheumatic disease and moderate-to-severe pain as an opioid alternative [174]. Nefopam blocks voltage-sensitive sodium channel activity in CNS neuron membranes to inhibit presynaptic glutamate release and postsynaptic neuronal excitation following glutamate receptor activation [175]. Following activation of voltage-sensitive calcium channels, nefopam inhibits calcium influx, cyclic guanosine monophosphate formation, and NMDA receptor-dependent neurotoxicity [176]. A published review of neuromodulator therapy in rheumatoid arthritis found two RCTs of nefopam showing significant pain reduction after two weeks [177]. However, this agent remains investigational in the United States.

An RCT of capsaicin found significant pain reduction at one and two weeks, with a 2% dropout from side effects [177]. Capsaicin may be considered as adjunctive therapy in patients with persistent local pain and inadequate response or intolerance to other analgesic approaches [178].

3E INITIATIVE RECOMMENDATIONS FOR PHARMACOLOGIC PAIN MANAGEMENT IN INFLAMMATORY ARTHRITIS
Pain should be measured routinely.
Acetaminophen should be used for persistent pain.
Systemic glucocorticoids are not recommended for routine pain management in the absence of significant inflammation.
Use TCAs and neuromodulators as adjuvant treatment; muscle relaxants and benzodiazepines are not recommended.
Weak opioids may be used for short-term pain treatment when other therapies have failed or are contraindicated; consider long-term use but perform regular review. Strong opioids should only be used in exceptional cases.
With inadequate response to acetaminophen or NSAID, add a drug with a different mechanism; do not combine two or more NSAIDs.
Use NSAIDs at the lowest effective dose.
Use existing guidance regarding the safety of pain medicine during pre-conception, pregnancy, and lactation.
Methotrexate is safe with standard doses of acetaminophen and/or NSAIDs (excluding anti-inflammatory doses of aspirin).
Acetaminophen is the first choice in patients with gastrointestinal comorbidities; non-selective NSAIDs in combination with a PPI, or COX-2 selective inhibitors with or without PPI, may be used with caution. With liver disease, standard precautions with NSAIDs and other analgesics should be applied.
With hypertension, cardiovascular disease, or renal disease, acetaminophen is first choice; use NSAIDs and COX-2 inhibitors with caution.
COX-2 = cyclooxygenase-2, NSAID = nonsteroidal anti-inflammatory drug, PPI = proton-pump inhibitor, TCA = tricyclic antidepressant.
Source: [172; 173] *Table 9*

GOUT

Gout is a metabolic disorder associated with elevated urate levels in the body and is the most common cause of inflammatory arthritis in the United States. Gouty arthritis is characterized by recurring episodes of acute, usually monarticular, arthritis that tend to remit over several days to weeks; however, undiagnosed, untreated patients are at risk for developing a chronic deforming arthritis. An estimated 9.2 million adults in America are affected [179]. Gout is rarely encountered in persons younger than 30 years of age, with the predominant age range being 30 to 60 years. However, onset may occur in men in their early 20s who have a genetic predisposition and lifestyle risk factors. The peak age of onset in women is the sixth to eighth decade of life [179]. The estimated prevalence of gout is 5.9% in men and 2.0% in women [179]. The prevalence and incidence of gout has increased over the past several decades [179; 180].

Gout develops in persons with hereditary or acquired chronic hyperuricemia or in those with marked perturbations in serum urate associated with such factors as alcohol consumption, drug use, eating foods high in purines, overweight/obesity, and myeloproliferative disorders [179; 181]. The normal serum urate is generally considered to be ≤6.8 mg/dL. The majority of patients at the time of an acute flare have demonstrable hyperuricemia (in excess of 7 mg/dL); however, about 20% do not. The presence of hyperuricemia in the absence of symptoms is not diagnostic of gout [179]. In all cases, the hyperuricemia is caused by some dysregulation in the balance between production and excretion of urate. An estimated 80% to 90% of gout cases are due to urate underexcretion and not overproduction [179]. Hyperuricemia can occur without precipitating gout, and in the absence of symptoms, it may not warrant intervention [179; 182].

Uric acid is a final metabolic product of purine nucleotides found in many foods and in human tissue. Intermediary processes of purine metabolism include the initial breakdown of purines to inosine and then to hypoxanthine. Hypoxanthine is metabolized to xanthine, and xanthine to uric acid, with both stages catalyzed by the enzyme xanthine oxidase (the primary site for pharmacologic intervention by allopurinol) [183].

The human body is limited in its capacity to excrete a heavy urate load. In the setting of persistent hyperuricemia, often combined with stress to weight-bearing joints such as the great toe, monosodium urate crystals precipitate within joint synovial fluid, producing an intense inflammatory reaction. With chronicity, adjacent tissues may become saturated with urate, leading to deposits within articular, periarticular, bursal, bone, auricular, and cutaneous sites. These deposits, termed tophi, are detectable on physical exam or by radiographs and are a cardinal pathognomonic feature of gout. The presence of crystals, within joint fluid or in tissue, activates monocytes and macrophages to clear the crystals through phagocytosis. The release of proinflammatory cytokines and chemokines into the immediate area triggers an acute inflammatory reaction and influx of neutrophils into the joint space [184; 185; 186].

The clinical presentation of gout is typically one of arthritis and intense pain, and patients may exhibit inflammation and edema in the afflicted joint. Although the great toe is the most common site, other joints and their surrounding tissue can be affected, including the insteps, ankles, heels, knees, wrists, fingers, and elbows [179]. Gout may be confused with other causes of arthritis as all forms share the cardinal signs of inflammation: pain, redness, warmth, tenderness, and swelling [181; 187]. While gout initially manifests in severe, discrete episodes of pain, the condition may progress to more frequent attacks with shorter asymptomatic periods between attacks [179; 187]. Synovial fluid analysis is the gold standard for diagnosing gout, confirmed by the presence of monosodium urate. Calcium pyrophosphate deposition disease, or "pseudogout," is a similar crystalline arthritis that occurs in patients with underlying osteoarthritis and is identified by the presence in synovial fluid of calcium pyrophosphate dehydrate crystals [179; 181; 186].

Treatment

Gout is perhaps the most easily treated, and preventable, form of arthritis. This is due to widespread understanding of its underlying mechanisms and the availability of effective treatment [181]. It is managed by controlling the current acute attack and preventing future attacks. Medications addressing the underlying pathophysiology include the xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat and the uricosuric agents probenecid, fenofibrate, and losartan [181; 188]. (Note: The use of fenofibrate and losartan for the treatment of gout is off label.)

Updated guidelines for the management of gout were published by the ACR in 2020 [184; 188; 189]. The initial steps include patient education, testing to rule out other causes of hyperuricemia, and evaluation of the disease burden to determine appropriate treatment. All patients with hyperuricemia and established gout should be advised to begin dietary modification. This involves avoiding organ meat high in purine content, high-fructose corn syrup, and excessive alcohol use. Portions of high purine-content seafood, sugar, and salt should be limited. The ideal diet will include low- or non-fat dairy products and vegetables. Other lifestyle modifications can also assist in managing gout, including weight loss in overweight patients, regular exercise, smoking cessation, and adequate hydration [184; 188; 189].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Rheumatology conditionally recommends that patients with gout limit their consumption of purine-rich foods (e.g., meat and seafood), alcohol, and high-fructose corn syrup (particularly in sweetened soft drinks and energy drinks).

(https://www.rheumatology.org/Portals/0/Files/Gout-Guideline-Final-2020.pdf. Last accessed August 19, 2022.)

Certainty of Evidence: Low or very low

The acute pain of gout may be treated with NSAIDs, a COX-2 inhibitor, systemic corticosteroids, or oral colchicine monotherapy in mild-to-moderate disease (≤6 on a 10-point pain scale). Combination therapy (i.e., colchicine and NSAIDs, oral corticosteroids and colchicine, or intra-articular steroids with each of the other options) may be used in cases of severe disease with intense pain and polyarticular presentation. Intramuscular triamcinolone acetonide is recommended in patients unable to take oral medication or likely to be poorly adherent to the multidose oral regimen [188].

An inadequate response to therapy after escalation (<20% pain reduction within 24 hours or <50% pain reduction after ≥24 hours) should prompt reconsideration of the diagnosis. If gout is confirmed, switching to another form of monotherapy or adding a second agent may prove effective [184; 188]. In 2023, the FDA approved canakinumab, for the treatment of gout flares in adults who cannot be treated or do not respond to treatment with NSAIDs, colchicine, or repeated courses of corticosteroids [327]. The agent, a humanized anti-interleukin-1β monoclonal antibody, is administered in a single, subcutaneous injection of 150 mg.

Urate-lowering therapy should be initiated in all patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares [189]. Therapy should be started within 24 to 36 hours of the onset of an acute gout attack unless otherwise contraindicated. Urate-lowering therapy is not recommended for patients experiencing their first flare, or for patients with asymptomatic hyperuricemia (serum urate >6.8 mg/dL) with no prior gout flares or subcutaneous tophi [189]. Allopurinol (≤100 mg/day) is the preferred first-line agent. Febuxostat (≤40 mg/day) is an acceptable alternative [189]. Probenecid may be used as an alternative to allopurinol or febuxostat if there is contraindication or intolerance to these preferred agents. However, probenecid should be avoided in patients with a history of urolithiasis [184; 188; 189].

Clinicians may also consider screening for the HLA-B*5801 allele, which is associated with high risk of severe allopurinol hypersensitivity reaction. High-risk persons include Koreans with an estimated glomerular filtration rate <60 mL/min/1.73 m^2 or those with Han Chinese or Thai ancestry [36].

Anti-inflammatory prophylaxis (against precipitating an acute flare) is recommended when initiating urate-lowering therapy in asymptomatic patients [189]. Colchicine was once the treatment of choice but is now less commonly used than NSAIDs because of its narrow therapeutic window and risk of toxicity [190]. To be effective, colchicine therapy is ideally initiated within 36 hours of onset of the acute attack [179]. In the case of colchicine intolerance or contraindication, prednisolone may be used [189]. Prophylaxis should continue after achieving target serum urate level for three months in patients without tophi, for six months in patients with resolved tophi, and with any remaining signs of gout activity in all patients [189].

Patients with intermittent symptoms or chronic synovitis with tophi (chronic tophaceous gouty arthritis) should be treated with a single-agent XOI, such as allopurinol, at a dose to achieve and maintain the serum urate level within normal range [184; 188]. If the serum urate target is not achieved or disease activity persists, a uricosuric agent may be added to the XOI. Pegloticase therapy should be considered if the serum uric target is not achieved, disease activity persists, more than seven attacks occur per year and no tophi, two or more attacks per year and tophi, or chronic tophaceous gouty arthritis is present [36; 189].

HEADACHE

Headache is perhaps the most common of all pain syndromes. One-half of the general population reports having had a headache within a given year; more than 90% recall having had a headache sometime during life [191]. The direct and indirect socioeconomic costs of headache are estimated to be $14 billion per year [191]. Chronic headache, defined as headache 15 or more days per month, occurs in 3% to 5% of the population and can be severely disabling [191]. Headache ranks among the top reasons for primary care contact [192].

Headache types are generally grouped as either primary or secondary. Primary headaches have a poorly understood etiology and are classified by clinical pattern, while secondary headaches are those caused by an underlying disorder [193; 194; 195].

The second edition of the International Classification of Headache Disorders (ICHD-II) was published in 2004 by the International Headache Society to provide an international standard. A third edition (ICHD-III) beta version was released in 2013, with the purpose of promoting more field testing before presentation of the final ICHD-III. The final ICHD-III was published in 2018 [194]. A 2012 assessment compared the reliability and validity of the ICHD-II against recent diagnostic and classification systems and affirmed the continuation of its standard universal use. The evidence was reviewed again in 2015, and no changes to recommendations were made [193]. These classifications will be used throughout this section.

Primary headache accounts for most headaches seen in primary care. Although tension-type headache has the highest prevalence rate, migraine headache is the most common type requiring medical attention [195]. In evaluating patients suspected to have primary headache, the key to proper classification lies with the patient's history, as the neurologic exam is usually normal and thus of limited value [195].

Before reaching the diagnosis of primary headache, other potentially serious pathologic causes should be carefully considered and evaluated by clinical examination. Underlying disorders that commonly present with secondary headache include hypertension, subarachnoid hemorrhage, brain tumor, meningitis, encephalitis, temporal arteritis, idiopathic intracranial hypertension, cerebral venous thrombosis, primary angle-closure glaucoma, and cervical spine pathology [196]. Assessment for warning signs should be performed in all patients, regardless of previous headache history, as the presence of these signs suggests another underlying condition requiring thorough diagnostic follow-up. Warning signs include [195]:

- Aspects of the headache
  - Subacute with progressive worsening over weeks to months
  - Distinctly different quality of the headache
  - Headache described as worst ever
  - Headache with maximum severity at onset
  - New onset after 50 years of age
  - Persistent headache triggered by cough or sneeze, bending, or exertion
- Evidence of systemic disease
  - Fever
  - Hypertension
  - Myalgias
  - Weight loss
  - Scalp tenderness
- Seizures
- Neurologic signs
  - Meningismus
  - Confusion, memory loss
  - Altered level of consciousness
  - Papilledema
  - Visual field defect
  - Cranial nerve asymmetry

- Extremity drifts or weaknesses
- Clear sensory deficits
- Reflex asymmetry
- Extensor plantar response
- Gait disturbances

Secondary headaches are managed by symptom control, principally with analgesic medication, while the underlying cause is being identified and addressed in a definitive manner.

The treatment of primary headache syndromes involves a two-prong approach: the acute (abortive) relief of discomfort, followed by preventive (prophylactic) therapy. Both are required in patients with frequent and/or severe attacks. Acute treatment attempts to reverse or halt the progression of a headache that has already begun. Preventive treatment, taken when the patient is asymptomatic, is intended to reduce or eliminate the frequency and severity of subsequent attacks, or to make acute attacks more responsive to treatment, and thus improve the patient's quality of life. Prevention is the foundation of managing migraine and cluster headache, as these headaches are severe even if short-lived [197].

MIGRAINE

Migraine is one of the most disabling disorders and remains underdiagnosed and undertreated [198]. In the United States, more than 30 million people have one or more migraine headaches per year. This corresponds to approximately 18% of women and 6% of men. Migraine accounts for 64% of severe headaches in women and 43% of severe headaches in men [199]. The economic cost resulting from migraine-related loss of productive time in the workforce is more than $13 billion per year [199]. According to the American Migraine Study, more than 85% of women and 82% of men with severe migraine have some headache-related disability [200]. Women experience higher past-year rates (13% to 18%) than men (5% to 10%). In the United States, chronic migraine prevalence is inversely correlated with household income and education [199].

The severity and frequency of migraine attacks tend to diminish with increasing age. After 15 years of suffering migraines, approximately 30% of men and 40% of women no longer have migraine attacks [199]. Comorbid conditions may occur with migraine, including anxiety and mood disorders, allergies, other chronic pain disorders (e.g., fibromyalgia, low back pain), hypertension, and epilepsy. Migraine with aura is also a risk factor for ischemic stroke, especially in women with frequent attacks [199]. Negative prognostic factors include early age at onset, psychosocial stressors, and psychiatric comorbidity [199].

The main clinical feature of migraine is a unilateral or bilateral throbbing or pulsating headache of moderate-to-severe pain, often preceded by an aura. Other symptoms include GI disturbances (e.g., nausea or vomiting) and intense sensitivity to light or sound. The features that best differentiate migraine from other headache types are the presence of nausea and/or vomiting with photophobia, phonophobia, and/or osmophobia. Migraines typically last 4 to 72 hours [193].

Migraine is subgrouped by the presence or absence of aura. A typical aura is characterized by visual, sensory, and/or dysphasic speech symptoms that include positive symptoms (e.g., flickering lights, spots, zig-zag lines, tingling, pins and needles sensation) and/or negative symptoms (e.g., visual loss, numbness). Aura develops in five or more minutes, persists for up to 60 minutes before migraine onset, and then fully resolves. Different aura symptoms may occur in succession. Aura may also occur in the absence of a migraine headache [193; 196].

Migraine with or without aura is further qualified as episodic (<15 headache days per month) or chronic (≥15 headache days per month for longer than three months) [193]. A variant is menstrual-related migraine, which consists of migraine manifesting primarily between two days before and three days after the onset of menstruation. Diagnosis involves patient documentation in a headache diary and requires this headache pattern in at least two of three consecutive menstrual cycles [193].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement asserts that migraines occurring in association with menses and not responsive to standard cyclic prophylaxis may respond to hormonal prophylaxis with the use of estradiol patches, creams, or estrogen-containing contraceptives.

(https://www.icsi.org/wp-content/uploads/2019/01/Headache.pdf. Last accessed August 19, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Pathophysiology

Migraine is a complex heterogeneous disorder with pathogenic mechanisms that are only now being elucidated [199]. A likely primary pathway leading to migraine-associated pain involves trigeminovascular system activation. This system is comprised of nociceptive nerves from the first or ophthalmic region of the trigeminal ganglia, major blood vessels that regulate cerebral blood flow, and smaller vessels in the pain-sensitive meninges. In the trigeminal ganglion, Aδ and C fibers transmit nociceptive impulses from meningeal blood vessels to the caudal brain stem or high cervical cord, resulting in headache pain. Sensitization and excitation of trigeminal nerves, the result of inflammatory mediator release from CNS dysfunction, promote neurogenic inflammation and generation of pain stimuli. This trigeminal nociceptor activation triggers neuropeptide release, including calcitonin gene-related peptide, substance P, and neurokinin A, from primary sensory neurons involved in the transmission of pain signaling [199; 201; 202].

Aura is believed to be related to cortical spreading depression, a process that transiently compromises cortical function resulting from a spreading (2–6 mm/min) wave of neuronal excitation in cortical gray matter. This cellular depolarization and resultant aura activate trigeminal fibers to initiate headache. The basis of cortical spreading depression involves the release of potassium or glutamate from neural tissue, which depolarizes adjacent tissues that release more neurotransmitters to propagate cortical spreading depression [203]. Cortical spreading depression may be responsible for the upregulation of genes, such as those encoding for metalloproteinases. The activation of these enzymes leads to leakage of the blood-brain barrier, allowing potassium, nitric oxide, adenosine, and other products to reach and sensitize the trigeminal afferent endings. Increased net activity of matrix metalloproteinase-2 has been demonstrated in patients with migraine [199].

Treatment

As with most conditions, the foundation of migraine headache treatment is patient education and self-care [195; 199]. The history, or a log kept by the patient, may reveal one or more environmental, food, or medication sources that act as "triggers" of a migraine attack [193]. Common triggers include intense temperature, an odor, bright light, stress, poor sleep, foods containing monosodium glutamate or nitrates (e.g., aged cheeses, beer, red wine), citrus, aspartame, oral contraceptives, estrogen therapy, nifedipine, and nitroglycerin. Resting in a quiet, dark room can help alleviate some migraines. Regular aerobic exercise and smoking cessation are encouraged. Patients should also keep a headache diary in order to identify triggers and assess treatment efficacy [193]. Acute medication should not be used more than nine days per month, which should be possible with adherence to the prophylactic treatment regimen. For persons who experience troublesome nausea with their attack, it is helpful to keep on hand a prescription antiemetic such as metoclopramide, prochlorperazine, or promethazine [193]. Caffeine may also be a useful adjunct.

Acute Attacks

For patients experiencing mild symptoms of a migraine, initial treatment consists of over-the-counter NSAIDs or aspirin (with or without caffeine) [193; 195]. Triptans (e.g., naratriptan), lidocaine nasal spray, or sumatriptan/naproxen sodium combination therapy may also be used. In 2013, the FDA approved a sumatriptan iontophoretic transdermal system for acute treatment of migraine with or without aura in adults [204].

For moderate symptoms, guidelines recommend the use of NSAIDs, triptans, lidocaine nasal spray, dihydroergotamine mesylate (DHE), or combination acetaminophen, isometheptene, and dichloralphenazone [193; 195]. Severe symptoms may be treated with prochlorperazine, chlorpromazine, DHE, ketorolac IM, magnesium sulfate IV, or triptans. If the migraine is known to be related to menstruation and does not respond to first-line therapies, use of frovatriptan or zolmitriptan is indicated [193].

If symptoms persist for more than 72 hours, the treatment of choice is DHE; however, DHE should never be given within 24 hours of ingesting any triptan or ergot derivative [193; 195]. Other absolute contraindications to DHE use include pregnancy, history of ischemic heart disease, history of variant angina, severe peripheral vascular disease, cerebrovascular disease, hemiplegic or basilar-type migraine, and onset of chest pain following DHE test dose. In these cases, treatment consists of chlorpromazine, valproate sodium IV, magnesium sulfate IV, or prochlorperazine.

Intractable migraine pain may be managed with an opioid (not meperidine) or dexamethasone. If at all possible, clinicians should avoid opioids. The brief pain-relief window, induction of inflammatory neurochemical release, and vasodilatation are counterproductive to treatment issues and migraine pathophysiology. Meperidine is not recommended because its neurotoxic metabolite normeperidine may promote seizures [195].

Prophylactic Treatment

The criteria for migraine prophylactic treatment are three or more severe migraines per month with inadequate response to symptomatic therapy, less frequent but prolonged attacks that are disruptive to quality of life, and patient desire [195; 199]. Several classes of drugs with established efficacy are available, the selection of which depends on individual patient response and tolerance [195; 205; 206]:

- Divalproex sodium
- Sodium valproate
- Topiramate
- Beta blockers (metoprolol, propranolol, or timolol)
- Frovatriptan
- Timolol

If the patient's response is unsatisfactory, it may help to switch to an alternate class, combine a beta blocker with a TCA, or add a second-line medication [195]. Second-line agents are considered probably effective according to available evidence and may be employed for patients who do not respond to initial therapy. These medications include [195; 205; 206]:

- Venlafaxine
- Amitriptyline
- Atenolol, nadolol
- Naratriptan, zolmitriptan
- Naproxen, naproxen sodium

Good studies have demonstrated the effectiveness of the herb butterbur (*Petasites hybridus*) in preventing migraines [199]. Butterbur may be useful to patients with migraine to reduce the frequency and severity of migraine attacks. Patients on butterbur require monitoring of liver enzymes [206]. Additionally, the AAN/AHS found moderate evidence of effectiveness for riboflavin, magnesium, and feverfew [206].

TENSION-TYPE HEADACHE

The lifetime prevalence of tension-type headaches are common, ranging between 30% and 78%. Onset occurs during the teenage years and affects women more frequently, at a ratio of 3:2 [207]. Previous studies in the United States show that tension-type headaches peak in the fourth decade of life. However, European studies show that these headaches persist into the sixth decade of life [207].

The main clinical features of tension-type headache are bilateral mild-to-moderate intensity described as a pressing or tightening sensation in the scalp (not a pulsating sensation). A frequent description is that of a tightening band around the head, with forehead pain sometimes extending into the neck. Routine physical activity, such as walking or climbing stairs, does not worsen tension-type headache pain. The pain can last from several hours to several days. Photophobia, phonophobia, or mild nausea may be present [193].

Tension-type headache is further subtyped based on frequency of symptoms. These headaches are classified as episodic tension-type headache (<15 headache days/month) or chronic (≥15 day/month for 3 months) [193].

Tension-type headache diagnosis is based on the patient's description of an otherwise "featureless" headache and normal neurologic examination. Manual palpation may reveal tenderness of pericranial muscles, the most common objective finding in tension-type headache. Additional symptoms other than headache heighten the importance of further diagnostic workup. Patients reporting an increasing pattern of headache frequency should be evaluated further for medication (analgesic) overuse headache, as chronic tension-type headache is often associated with this behavior [207].

Pathophysiology

Muscular and psychogenic factors contribute to tension-type headache etiology. Patients with chronic tension headaches (longer than five years) have shown lower cortisol levels, likely due to hippocampal atrophy resulting from the effects of chronic stress [207]. Combined myofascial dysfunction and central nociceptive dysregulation is also thought to contribute to tension-type headache, with increasing central nociceptive alteration resulting in progression of tension-type headache from episodic to chronic [208; 209].

Treatment

The treatment of acute tension headache generally consists of over-the-counter pain relievers, including NSAIDs, acetaminophen, aspirin, and combination medications [193; 195; 196]. Patients who experience more than 15 tension headaches per month require prophylactic treatment with venlafaxine XR, amitriptyline, or another TCA [193]. Acupuncture has also been shown to improve symptoms. Codeine and stronger opioids are not indicated, and botulinum toxin is ineffective [193; 195; 196].

CLUSTER HEADACHE

The exact prevalence of cluster headache in the United States is unknown but is estimated to be 0.4% in men and 0.08% in women. The age of onset is typically 20 to 40 years of age but has been reported in patients as young as 1 year and up to 79 years of age [210].

The main clinical feature of cluster headache is severe and excruciating pain that is more severe than any other headache type, which has earned cluster headache the term "suicide headache." In fact, there are reports of suicidal behavior in patients frantically desperate to stop the pain. Other clinical features include unilateral distribution around and above the eye and along the side of the head or face; pain sensation described as sharp, boring, burning, throbbing, or tightening; and a restless or agitated state during the headache [193].

Autonomic features are associated with cluster headache, including ipsilateral conjunctival injection and lacrimation, rhinorrhea or nasal blockage, and ptosis [196]. Although all may not be present, the presence of one or two secures a cluster headache diagnosis. Cluster headache is subtyped as episodic, with daily attacks lasting 15 to 180 minutes for several weeks followed by a period of remission, or chronic, whereby attacks occur without significant remission. The average patient experiences a cluster period of 6 to 12 weeks, followed by remissions as long as 12 months. Cluster headache is diagnosed by patient history and physical examination, with imaging studies used only to rule out other causes [193].

Pathophysiology

Although the underlying pathophysiology of cluster headache is incompletely understood, an underlying mechanism in cluster headache is thought to involve trigeminovascular nociceptive pathway activation and reflex cranial autonomic activation. Central sensitization induces alteration in trigeminal-facial neuronal circuitry and dysregulation in serotonergic raphe nuclei-hypothalamic pathways. Functional imaging has confirmed the highly specific activation of hypothalamic gray in cluster headache attacks, suggesting its involvement in initiating the pain process [210; 211].

Sensory-motor impulses generated in the maxillary and ophthalmic divisions of the trigeminal nerve are relayed to the sphenopalatine ganglion and interior carotid perivascular sympathetic plexus. This signaling is propagated by substance P neurons, and somatostatin inhibits substance P to reduce the duration and severity of cluster headache. Vascular dilatation, secondary to primary neuronal discharge, contributes to cluster headache pathogenesis, and the sudden release of histamine (or serotonin) seems to play a role [212; 213].

Treatment

Acute cluster headache is treated with subcutaneous sumatriptan or intranasal zolmitriptan, interventions proven highly effective for these patients [195; 196]. Some have studied 20-mg sumatriptan nasal spray, but this route is not recommended. Other possible approaches include DHE and supplemental oxygen [195]. A 2014 literature review of six studies (five randomized-controlled studies) found that flow rates of 7–12 L/min effectively treated cluster headaches in approximately 80% of participants [214]. Oxygen inhalation is highly effective when delivered at the onset of an attack with a nonrebreathing facial mask at a flow rate of 7–15 L/min [195]. Analgesics, ergotamine tartrate, and orally administered triptans are ineffective and should not be used [193; 195; 196].

Galcanezumab, a humanized monoclonal antibody, was approved by the FDA in 2018 for migraine prophylaxis. It acts by blocking the CGRP pathway by targeting the ligand itself [36]. Studies have shown galcanezumab to be efficacious in reducing monthly migraine headache days, monthly migraine headache days with acute medication use as well as improving response rates and functional and disability scores [215; 216]. Other monoclonal antibodies targeting the CGRP pathway include fremanezumab (approved in 2018) and eptinezumab (approved in 2020), which target the ligand, and erenumab (approved in 2018), which blocks the receptor [217]. These three agents, as well as galcanezumab, are approved for migraine prevention [36]. Galcanezumab is the only agent shown to be efficacious in cluster headache as well [218].

Bridge treatment for quick suppression of attacks until maintenance treatment reaches therapeutic level consists of corticosteroids, oxygen, and occipital nerve block. For sustained suppression of attacks over the expected cluster cycle, the first-line medications are verapamil, corticosteroids, lithium carbonate, divalproex sodium, and topiramate [195; 196; 212]. Antihistamines may also be helpful. Patients should also be advised to avoid alcohol, tobacco smoke, and certain foods during the cluster cycle [212].

MEDICATION OVERUSE HEADACHE

Medication overuse headache is a chronic headache resulting from treatment of any primary headache, most commonly migraine.

Medication overuse can alter the clinical features of the underlying primary headache by increasing headache frequency such that episodic headache (<15 headache days/month) progresses to chronic headache (≥15 headache days/month for more than three months); increasing the pain distribution, with unilateral headache becoming bilateral; and altering pain sensation, with the typical pulsating migraine pain changing into dull pain [195]. If ingested more than 10 days per month, NSAIDs, acetaminophen, ergotamines, compound analgesics, triptans, and opioids can all lead to overuse headache. The risk of overuse headache differs between substances; ergotamines, opioids, and triptans are associated with greater risk than over-the-counter analgesics [195]. The diagnosis of medication overuse headache is based on headache improvement/resolution, usually within days, when the offending drug(s) is withdrawn [193].

ENDOMETRIOSIS

Endometriosis is an estrogen-dependent syndrome that is a major cause of pelvic pain in women of reproductive age [219]. Symptomatic endometriosis is believed to occur in approximately 6% to 10% of women of childbearing age, although this figure is probably an underestimate, as confirmation of the disease requires an invasive diagnostic procedure [220; 221]. Risk factors for endometriosis include an anomalous reproductive tract that obstructs menstrual outflow, nulliparity, and infertility [222].

Endometriosis is characterized by benign aberrant growth of endometrial tissue outside the uterus in the dependent region of the pelvis. These abnormal tissues are sometimes referred to as ectopic growths. They develop in the ovaries in roughly 66% and the pelvic lymph nodes in roughly 30% of cases [223].

Endometriosis is usually diagnosed via laparoscopy to further investigate patient complaints of secondary dysmenorrhea and dyspareunia. The most common symptoms include pelvic pain before and/or during menstruation, pain during/after sexual activity, fatigue, infertility, heavy bleeding, intestinal upset, painful bowel movements, and low back pain during periods [4; 224].

Many patients experience pain disproportionate to the presence or extent of endometriotic lesions. This pain syndrome is diagnosed on the basis of chronic or recurrent pelvic pain in patients with confirmed endometriosis that persists despite adequate endometriosis treatment. It is often associated with negative cognitive, behavioral, sexual, or emotional distress and often with symptoms suggestive of lower urinary tract, sexual, bowel, or gynecologic dysfunction. Roughly 20% of patients with endometriosis experience comorbid pain conditions, including irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, vulvodynia, migraine, fibromyalgia, and/or autoimmune disorders [4; 221]. The chronicity and absence of correlation with the menstrual cycle suggests that these associated pain syndromes reflect, in part, alterations within the CNS [225]. Epidemiologic data indicate an association between endometriosis and chronic pelvic pain, with endometriosis found in one-third of younger women who undergo surgery for chronic pelvic pain versus 5% in those who do not have infertility or chronic pelvic pain [225].

PATHOPHYSIOLOGY

The pain of endometriosis is in part caused by a chronic, localized inflammatory disorder involving dysregulated immune and endocrine function. Significant immune system alterations have been found that facilitate survival and growth of displaced endometrial tissue. In brief, the immune response is elicited by displaced endometrial tissue that fails to clear the menstrual debris yet retains the capacity to generate proinflammatory cytokines and chemokines that stimulate ongoing inflammation.

Under these conditions, endometrial cells exhibit a hypersensitivity to inflammatory stimuli, which serves to propagate tissue growth within the peritoneal cavity [221; 226]. In addition, the usual endometrial responsiveness to progesterone is blunted, resulting in the loss of local immunosuppressive activity of this steroid and disordered communication between endocrine and immune systems. It is unclear whether progesterone resistance is the cause or effect of disease progression. It is possible that, in some women, altered immune function produces progesterone resistance, while in others, resistance represents an endometrial phenotype that promotes the persistence and progression of the inflammatory state [220].

A key factor in the perpetuation of endometriosis pain is central sensitization by persistent nociceptive input from the affected tissue, manifested by somatic hyperalgesia and an increase in referred pain areas [219; 226]. Findings indicative of CNS mediation of pain include relapsing pain in cases initially alleviated by surgical resection, even in the absence of new lesions; lack of association between pain severity and extent of disease; and an inverse relationship between the likelihood of relapse and the initial extent of disease. These and other findings reflect CNS remodeling such that pain reappears in the absence of obvious nociceptive input from new endometrial lesions [225]. Multiple factors influence the risk for and extent to which CNS sensitization follows local tissue neuronal stimulation and whether central sensitization remains dependent upon, or becomes independent of, peripheral disease activity. Such factors include menstruation, uterine and ovarian function, hormone levels, parity, vaginal delivery, peritoneal fluid, and lesion type and location [225].

Ectopic growths become innervated by an ingrowth of nerves from adjacent tissues. The resultant sensory and autonomic nerve input leads to an alteration of neuronal activity in the spinal cord and brain, which augments endometriosis pain perception [227]. Sensory C, sensory A-delta, sympathetic, and parasympathetic nerve fibers have been observed in the functional layer of endometrium of most women affected by endometriosis. Nerve fiber densities were also greatly increased in the myometrium of women with endometriosis and in endometriotic lesions compared with normal peritoneum [227]. An active research field in endometriosis is the investigation of the distribution and genesis of nerve fibers in ectopic endometrium and the use of endometrial nerve fiber density for diagnostic purpose. This field may help elucidate the molecular mechanisms underlying endometriosis-associated pain and open new avenues for diagnostics and therapeutics [228].

TREATMENT

Numerous pain therapies have been endorsed in practice guidelines by national and international organizations. The recommendations discussed in this section for the treatment of endometriosis pain were published by the Society of Obstetricians and Gynaecologists of Canada, the American College of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, the World Endometriosis Society, and the National Institute of Child Health and Human Development [222; 229; 230; 231; 232].

Unfortunately, the available analgesic, anti-inflammatory, surgical, and hormonal therapies all have unpleasant side effects and often prove unsatisfactory in providing durable pain control for many patients [222]. This is due in large part to the focus on treating or eliminating tissue growths, which is not necessarily effective in ameliorating the pain. For many, painful endometriosis is a chronic and potentially debilitating disease that requires a multidimensional therapeutic approach [222].

Effective management of chronic pain for these patients requires a shift in emphasis from ectopic tissue resection to a recognition of the role played by peripheral and central nervous sensitization in perpetuating the discomfort. This approach is in its infancy, and research efforts are just beginning to explore novel compounds that target growth factors, inflammation, angiogenesis inhibitors, and the endocannabinoid system [225].

Lifestyle Interventions

Lifestyle and dietary interventions have been recommended for all women with endometrial pain. Preliminary evidence supports a diet emphasizing vitamins, minerals, salts, lactic ferments, and fish oil as a postsurgical intervention. Fish oil supplementation (for omega-3 fatty acids) has also been suggested. Some studies have found positive results with a gluten-free diet, but confirmation with RCTs is necessary [222; 229; 230; 231; 232].

Pharmacotherapy

First-line pharmacotherapy often includes the use of NSAIDs and/or acetaminophen for acute pain relief. However, a series of Cochrane analyses found no evidence that NSAIDs are effective in managing pain caused by endometriosis and that they may cause unintended effects [233]. A comparative review of eight widely used guidelines found agreement on the use of combined oral contraceptive pills and progestins (e.g., medroxyprogesterone acetate, norethisterone, dienogest) [234]. If this approach is not effective in managing painful episodes, second-line options include [221; 222; 229; 230; 231; 232]:

- Opioids
- Gonadotropin-releasing hormone (GnRH) agonists with add-back hormone replacement
- Levonorgestrel-releasing intrauterine system
- Depot progestins
- Aromatase inhibitors
- Selective progesterone receptor modulators
- GnRH antagonists

Third-line therapies, reserved for women who do not respond to first- and second-line approaches, include gestrinone (not available in the United States) and danazol [36; 222; 229; 230; 231; 232]. However, a Cochrane review found no benefit from ovulation suppression in subfertile women with endometriosis who wish to conceive [235].

Several complementary therapies have been assessed for efficacy in addressing symptoms of endometriosis. Both acupuncture and high-frequency transcutaneous electrical nerve stimulation (TENS) have shown promise. Two randomized studies evaluated specific versus sham acupuncture for endometriosis pain and both reported significantly better pain relief with true acupuncture [236; 237]. No RCTs supporting the utility of TENS have been published [222; 229; 230; 231; 232]. Chinese herbal medicine may be helpful, although almost all supporting evidence has been published in Chinese journals and may be difficult to replicate.

Surgery

The guidelines agree that laparoscopic surgical removal of ectopic endometrial tissue is first-line therapy for painful endometriosis [222; 229; 230; 231; 232]. Laparoscopic surgery is preferred over laparotomy in most cases. Lesions should be excised after identification, especially in cases of deep endometriotic lesions. Laparoscopic excision is preferred for ovarian endometriomas to minimize recurrence of endometrioma and pain. However, the best surgical approach to deep endometriosis is not known. Highly specialized surgical expertise is required for surgery of deep endometriosis and should only be performed within specialized centers [222; 229; 230; 231; 232].

Adding laparoscopic uterine nerve ablation to laparoscopic removal of endometriosis is considered ineffective. Presacral neurectomy may benefit a small number of women, but potential harms outweigh benefits [222; 229; 230; 231; 232].

SICKLE CELL DISEASE

In the United States, an estimated 100,000 people are afflicted by sickle cell disease and 2,000 infants are born with sickle cell disease annually [238; 239]. Sickle cell disease is predominantly found in persons of African descent; other groups with heightened risk include those of South or Central American, Caribbean, Mediterranean, Indian, and Saudi Arabian descent (typically areas in which malaria is endemic) [239; 240]. The condition is chronic and lifelong and is associated with a decreased lifespan. Median survival in the United States is 42 years for men and 48 years for women, although innovations in disease management are improving long-term survival [241].

There are three main types of sickle cell disease defined by the specific genetic combination [239]. The most severe form is HbSS, commonly referred to as sickle cell anemia. Patients with this type have inherited one sickle cell gene from each parent. Persons who have inherited a sickle cell gene from one parent and a gene for abnormal hemoglobin from the other parent have the HbSC type. This is usually a milder form of sickle cell disease. The final type is HbS beta thalassemia, which is characterized by inheritance of a sickle cell gene from one parent and a gene for beta thalassemia, another type of anemia, from the other parent. This type of sickle cell disease is most common among persons of Mediterranean descent and, as with HbSC, tends to be a milder form [239].

Even more prevalent than sickle cell disease is sickle cell trait. This condition is present in persons who inherit a sickle cell gene from one parent and a normal gene from the other parent. The ratio of infant carriers of hemoglobin variant traits to infants with sickle cell disease is approximately 50:1 [242]. Those with sickle cell trait are usually asymptomatic and live a normal life, but they can pass the trait on to their children.

Pain is the primary reason that medical care is sought by persons with sickle cell disease, usually during an acute pain crisis. Acute pain crises are commonly triggered by dehydration, infection, stress, and changes in body temperature and unfold in four distinct phases [238]:

- Prodromal: Lethargy and mild localized pain may develop, but hematologic changes have not yet occurred.
- Initial infarctive: Pain intensity increases from mild to moderate, hemoglobin decreases, and alterations in mood develop. Laboratory findings lag behind patient self-report of symptoms. Prompt physician attention to patient report of symptom onset is essential to initial management.
- Post-infarctive/inflammatory: Severe pain peaks, with intensity that causes patients to seek emergency department or hospital care for pain relief. Laboratory changes include increases in reticulocyte count, lactate dehydrogenase, and C-reactive protein. During crisis, C-reactive protein levels can rise to 70 mg/L, compared with an average 32.2 mg/L in patients with sickle cell disease not in crisis and 10 mg/L in persons without sickle cell disease.
- Resolution: Pain during crisis returns to a moderate intensity following adequate fluid hydration and intravenous analgesics.

In patients with sickle cell disease experiencing pain crises, the lower back, knee/shin area, and hips are the sites most often affected. A higher number of pain sites are found in patients with depression and in those 45 years of age and older [243].

PATHOPHYSIOLOGY

A single nucleotide mutation is the underlying basis of sickle cell disease. It involves alteration of the glutamate for valine in the sixth position of the beta-globin protein, which predisposes hemoglobin to polymerize when deoxygenated, causing red blood cells to assume the characteristic sickle shape. This red blood cell deoxygenation and sickling accounts for sickle cell disease characteristics of anemia, hemolysis, and acute and chronic complications from vascular occlusion that affect multiple organs [244]. The deformed red blood cells tend to clump together to increase blood viscosity, leading to microvascular blockage and ischemia. Pain during an acute crisis is due to ischemic occlusion of the microcirculation from red blood cell aggregation and resultant decreased blood flow to distal tissues. The most common cause of recurrent pain episodes is vaso-occlusion of the microcirculation and destruction of bones, joints, and visceral organs [245]. Chronic pain can occur from complications of sickle cell disease such as avascular necrosis or ankle ulcers superimposed on acute sickle cell pain. Additionally, frequent episodes of acute pain in sickle cell disease can resemble chronic pain [245].

Chronic sickle cell disease pain involves modulation of the afferent nociceptive pathways in the spinal cord (such as the spinothalamic tract) that transmit pain from the periphery to the brain for processing [238]. Neuropathic pain is uncommon [239]. Chronic pain from sickle cell disease can be physically and psychologically debilitating; consistent with chronic pain from other conditions, chronic sickle cell disease pain involves sensation, emotion, cognition, memory, and context [239].

The most common chronic pain syndromes in sickle cell disease include [239]:

- Arthritis
- Arthropathy
- Aseptic (avascular) necrosis
- Leg ulcers
- Vertebral body collapse

TREATMENT

No single treatment is effective for all people with sickle cell disease; instead, appropriate treatment options are determined according to symptom severity [239]. Nonpharmacologic prevention includes avoiding dehydration, extreme temperatures, high altitudes (including flying), and low oxygen levels from intense exercise or athletic training [246].

For prevention of acute pain episodes, hydroxyurea is most often used [240]. This agent acts by ribonucleotide inhibition and induction of fetal hemoglobin, which possesses superior affinity for oxygen binding. It is FDA-approved for use in adults and children 2 years of age and older and is the only treatment for sickle cell disease that modifies the disease process. Hydroxyurea is effective in reducing pain crises, painful symptoms, need for blood transfusion, and mortality. As such, it represents the backbone of sickle cell disease management. The usual daily oral dose is 15–35 mg/kg [36; 240]. Inconsistent adherence reduces its efficacy, and patient adherence can be challenged by the three- to six-month delay between treatment initiation and the onset of clinical response. More frequent follow-up contact with support and encouragement may be needed in some patients.

According to the National Heart, Lung, and Blood Institute, adults with sickle cell anemia who have three or more sickle cell-associated moderate-to-severe pain crises in a 12-month period should be treated with hydroxyurea.

(https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Last accessed August 19, 2022.)

Strength of Recommendation/Level of Evidence: Strong recommendation, high-quality evidence

Management of acute pain episodes requires stronger analgesic agents, with codeine and tramadol useful for moderate pain and morphine, oxycodone, hydrocodone, and hydromorphone more effective in treating severe and breakthrough pain [239]. For first-time opioid therapy for severe pain, the use of morphine sulfate or hydromorphone is favored. With recurrent pain, the best initial choice of opioid and dose for severe sickle cell pain is that which previously provided adequate analgesia. Intravenous administration is recommended in severe pain. Patients and clinicians may prefer a 5–10 mg loading dose of parenteral morphine or equivalent [239].

Adjunctive medications may also be indicated. Parenteral NSAIDs can reduce opioid requirements and provide greater ease in transition to oral analgesics [238]. Parenteral corticosteroids can be beneficial during crisis phases, but efficacy data beyond the initial 48 hours is lacking.

Intraspinal analgesics should be considered only with insufficient response to maximum-dose systemic opioids and adjuvant medications. Epidural anesthetics alone or with fentanyl can be effective in acute refractory pain [238].

For chronic pain associated with sickle cell disease, long-acting and short-acting opioids, NSAIDs and acetaminophen, and adjuvant medications form the basis of long-term management [238]. Aspirin should be avoided due to the risk of Reye syndrome. Codeine, low-dose oxycodone, or low-dose hydrocodone are preferred for treatment of moderate chronic pain.

In patients requiring chronic opioid therapy, extended-release, sustained-release, or long-half-life opioid formulations are favored because of ease in administration and more consistent analgesia. Specifically, transdermal fentanyl is effective for chronic pain management in patients who are opioid tolerant. Short-acting opioids may be used for rescue dosing early in the treatment regimen, for acute episodes of breakthrough pain or for analgesic bridge until steady-state is achieved with a long-acting formulation [239].

Adjunctive therapy with SNRIs and TCAs can alter pain perception in the spinothalamic tract. Blood transfusion may be necessary for severe anemia. Common antecedents for transfusion necessity include sudden worsening of anemia due to infection and splenomegaly [239; 246].

Massage therapy may be effective as a therapy adjunct. Participants in one trial reported significant decreases in pain intensity following massage with a mean pain scale score of 9.6 before massage versus 2.8 after massage [247].

Transplantation is the only known cure for sickle cell disease and involves blood or bone marrow stem cell transplantation. To prevent potentially severe complications, donor-recipient stem cells should be closely matched using human leukocyte antigen (HLA) tissue typing. Unfortunately, only a small number of patients with sickle cell disease are appropriate candidates for stem cell transplantation [246].

In 2023, the FDA approved two cell-based gene therapies, Casgevy and Lyfgenia, for the treatment of sickle cell disease in patients 12 years and older [326]. These are first-in-class approvals, and Casgevy is also the first FDA-approved treatment to utilize a type of novel genome editing technology, signaling an innovative advancement in the field of gene therapy. Both products are made from the patients' own blood stem cells, which are modified, and are given back as a one-time, single-dose infusion as part of a hematopoietic stem cell transplant [326].

POSTHERPETIC NEURALGIA

Postherpetic neuralgia is persistent or relapsing pain in an area affected by herpes zoster, also known as shingles. Herpes zoster is a late reactivation of chickenpox, caused by the varicella-zoster virus (VZV). It presents clinically as an acute vesicular skin eruption of dermatomal distribution preceded or accompanied by pain of variable intensity. Patients experience an intense sharp, prickly, or burning sensation, often with tingling and numbness or itching. A cluster rash of fluid-filled vesicles develops within a few days that

usually follows a pattern of thoracic, abdominal, or cranial dermatomal distribution. Although resolution of the rash usually occurs within two to four weeks of onset, approximately 20% of patients will develop the severe intractable pain condition of postherpetic neuralgia [248].

Much of the population in the United States has been infected with chickenpox and carries dormant VZV. A chickenpox vaccine was released in 1995 with the belief that it could greatly reduce the number of shingles cases in individuals who received the vaccine [248]. The weakened attenuated virus strain used in the preparation is not likely to survive well over many decades in the body.

Although difficult to estimate, 500,000 to 1 million people are believed to be currently afflicted with postherpetic neuralgia [249]. The risk of developing postherpetic neuralgia following acute zoster is strongly associated with age. The incidence of postherpetic neuralgia is 5% in those younger than 60 years of age, 10% in those 60 to 69 years of age, and 20% in those 80 years of age or older [250]. Other risk factors for postherpetic neuralgia include [248; 251]:

- Intensity of zoster pain at onset
- Severity of the rash
- Presence and duration of pain before onset of rash
- Psychosocial factors, such as depression
- Female sex
- Immunocompromise

Postherpetic neuralgia can be challenging to manage due to its severity, duration, and potential to induce profound pain and debilitation. The exact definition of postherpetic neuralgia varies, but in general, it is defined as persistent pain at two to four months after the onset or the healing of associated rash. Postherpetic neuralgia pain can be severe and is described as a sensation of continuous burning, throbbing, or electric shock-like discomfort. More than 90% of patients with postherpetic neuralgia experience allodynia, and many also report hyperalgesia or spontaneous pain in areas of lost or impaired sensation. Chronic pruritus may also be present [249].

PATHOPHYSIOLOGY

The onset of herpes zoster begins with reactivation of latent/dormant VZV particles within the trigeminal or spinal dorsal root ganglia. Virus then travels via the neuronal axon to infiltrate sensory terminals in the skin, producing pain and initiating the vesicular eruption. Inflammation leads to nociceptor sensitization, lower activation threshold, and abnormal spontaneous discharge. Neuron damage followed by neurolytic lesions develop in areas of high viral load. Endoneurial inflammation and hemorrhage release virus from infected neurons into adjacent tissues. Injury-associated sensory stimulation and amplified signaling from sensitized nociceptors release glutamate in spinal cord dorsal horn neurons and activate NMDA receptors, resulting in central sensitization [252]. Although risk factors have been identified, the exact mechanisms associated with VZV reactivation remain unknown [253].

While herpes zoster results in neuronal damage in all patients, only some progress to postherpetic neuralgia, indicating that neuronal injury alone is not sufficient for the development of postherpetic neuralgia [252]. The neuritic inflammatory response to the initial viral replication results in necrosis, fibrosis, and destruction of neuronal tissue from peripheral afferent fibers to the spinal cord. The pathophysiology of postherpetic neuralgia remains to be fully understood, but it is thought to involve peripheral and central mechanisms that result from virus-induced damage of peripheral afferent neurons and changes from viral replication and immune responses in central afferent neurons and efferent pain-modulating neurons [251].

Pathologic features of postherpetic neuralgia include severe peripheral axonal loss, nociceptor degeneration, multisegmental dorsal horn atrophy, clinically nonsymptomatic contralateral changes in skin innervation, and deafferentation and strengthening of existing synaptic connections between central pain pathways and peripheral A fibers. How these features initiate or contribute to postherpetic neuralgia pain is not yet understood [251; 252].

TREATMENT

Although several therapeutic approaches have shown efficacy in clinical trials and are endorsed for use by clinical practice guidelines, actual pain relief achieved in clinical practice is often unsatisfactory. Some patients show a partial response but discontinue treatment because the side effects offset the level of pain reduction. The incomplete understanding of pathophysiologic mechanisms in postherpetic neuralgia pain hampers the ability to deliver more widely effective, targeted therapies for pain control [251].

The most important strategy for postherpetic neuralgia is prevention of herpes zoster and neuralgia with the VZV vaccine, approved by the FDA in 2006 and indicated for use in adults 50 years of age and older with a history of chickenpox. A second, more effective vaccine was licensed by the FDA in 2017, also for use in adults 50 years of age and older [248]. Two doses of the vaccine decreases the incidence of herpes zoster by 98% and reduces the incidence of severe varicella by 100% [248]. Moreover, the vaccine also reduces the incidence and severity of postherpetic neuralgia by two-thirds in patients who do develop zoster after vaccination [248]. However, the vaccine remains seriously underused due to provider and patient unawareness and other factors. With postherpetic neuralgia potentially leading to severe, life-altering chronic pain, the vaccine should be offered to every patient older than 50 years of age with a history of chickenpox [248; 254].

The severity of pain and duration of a zoster flare can be significantly reduced (50%) by treatment with an oral antiviral drug if started within 72 hours of onset [248]. Three such antivirals are available: acyclovir (the least expensive), valacyclovir (often preferred because of less frequent dosing), and famciclovir. These antivirals may also decrease the risk of postherpetic neuralgia and the frequency of recurrences if taken prophylactically [248].

Other therapies with a strong evidence base for acute zoster pain include opioid analgesics (e.g., morphine, oxycodone, methadone, tramadol) for moderate or severe pain, a short course of systemic corticosteroid therapy in non-immunocompromised patients, and sympathetic nerve block [255].

The American Society of Anesthesiologists Task Force on Chronic Pain Management/American Society of Regional Anesthesia and Pain Medicine, the European Federation of Neurological Societies, and the American Academy of Neurology also recommended gabapentin, pregabalin, amitriptyline, nortriptyline, desipramine, and/or lidocaine patch as possibly effective therapeutic options for postherpetic neuralgia pain [18; 256; 257]. Alternatives include capsaicin 8% patch, opioids, and valproate (weak positive evidence). Lidocaine cream, spray, and gel are also effective [248].

More intense therapies are available for treatment-refractory pain, but significant side effects are possible. Established guidelines indicate that intrathecal preservative-free steroid injections, intrathecal ziconotide infusion, or spinal cord stimulation are potential options. A trial of neuraxial opioid should be performed before considering permanent implantation of intrathecal drug delivery systems. However, a 2013 small-sample replication study found no benefit from intrathecal methylprednisolone and was halted early over lack of efficacy and safety concerns [258].

The results of two other publications suggest the utility of additional therapeutics in the treatment of postherpetic neuralgia pain. A single-dose RCT found a very high rate of clinically meaningful pain reduction and sleep improvement with botulinum toxin A vs. placebo that persisted for a mean of 16 weeks [259]. In another study, tramadol (50–200 mg/day) was compared to a topical combination of 3.33% doxepin and 0.05% capsaicin for four weeks, and although significant reduction in pain intensity was found in both groups, greater pain reduction was found with tramadol [260].

POST-AMPUTATION PAIN

In the United States, an estimated 2 million people are living with an amputated limb, and 185,000 amputations occur each year [261]. Populations that experience a significant percentage of these amputations include patients with vascular disease (54%), including peripheral artery disease and diabetes; patients with traumatic injuries (45%); and patients with cancer (less than 2%). In comparison, combat-related major limb amputations among U.S. armed forces peaked in 2011 at 260, with a 2001–2015 total of 1,645 [262].

Of individuals with limb amputation, 60% to 80% experience phantom limb pain [263]. Post-amputation pain can manifest in the residual limb or be referred from a site in the former limb. Phantom-limb pain is commonly confused with pain in the area adjacent to the amputated body part, which is referred to as residual limb pain or stump pain. Residual limb pain and phantom limb pain can co-occur. It is important to note that the term "residual limb pain" is not strictly a diagnosis, as it does not acknowledge the underlying mechanism [264].

Residual limb pain is pain experienced in a part of the limb that was not surgically removed and is considered a normal process during the acute postsurgical period. Persistence of residual limb pain beyond tissue healing or reappearance at a later point is often the result of mechanical factors such as poor prosthetic socket fit, bruising of the limb, chafing or rubbing of the skin, or poor perfusion with ischemic pain. The development of post-amputation neuromas can also cause residual limb pain [265]. The main clinical characteristic involves sharp, often jabbing pain in the stump that develops several weeks to months after amputation and will persist indefinitely if untreated. Residual limb pain can be aggravated by pressure on or infection in the stump. Tapping over the neuroma in the transected nerve or nerves often elicits a pain response [29].

Phantom limb pain is pain experienced in the amputated part of the limb(s) and is the most difficult form of post-amputation pain to manage. As noted, phantom limb pain is experienced by 60% to 80% of amputees, and up to 40% report significantly bothersome symptoms 1 year after amputation [263]. Phantom pain is associated with the intensity and duration of preoperative pain [265].

Phantom sensations commonly occur in amputees and are considered normal. The onset of phantom limb pain can occur months to years following amputation, and the severity and frequency of pain varies greatly. It is subjectively experienced as cramping, aching, burning, or shock-like. A distorted image of the lost limb almost always accompanies phantom limb pain [29].

Phantom sensations should receive medical attention only if they result in discomfort or functional limitation. Altered CNS processing is thought to be the underlying mechanism [265].

PATHOPHYSIOLOGY

As noted, residual limb pain is largely the result of neuroma development in the stump, although the noxious nociceptive input from the neuroma may contribute to and increase the level of central reorganization to elevate the risk of phantom limb pain development [65; 266].

The finding that optimal perioperative analgesia reduces the intensity, prevalence, and frequency of phantom limb pain at six-month follow-up is consistent with findings in other pain syndromes that sufficient control of acute pain reduces the risk of chronic pain. This suggests that unchecked pain before and after amputation is likely to induce neuronal plasticity, central sensitization, and aberrant processing of pain and sensory input [267].

The underlying sustaining mechanisms in phantom limb pain are believed to originate from changes along the neuraxis. At the spinal level, these alterations include increased dorsal horn neuron excitability, reduction in inhibitory processes, and structural changes at the central nerve endings of the primary sensory neurons, interneurons, and projection neurons. Changes at the supraspinal level occur in the brainstem, thalamus, and cortex. Imaging studies have demonstrated reorganization in the somatosensory cortex and at the thalamic level that mediates the representation of the phantom limb and perception of phantom limb pain [65].

The somatosensory cortex is also the site that mediates the development and activation of somatosensory memory. Two types of somatosensory memories have been identified in patients with phantom limb pain: memories resulting from long-lasting, intensely distressing pre-amputation pain and those arising from flashbacks with pain a component of the trauma memory. It is believed that inappropriately stored or chronically activated pain memories may play a significant role in the maintenance of phantom limb pain. This forms the basis of interventions in phantom limb pain that are effective with other populations in facilitating reprocessing and disengagement from traumatic memories [268].

Psychological factors are likely to play a role in modulating phantom limb pain. The pain may be exacerbated by stress, and patients who lack adaptive coping skills or have little social support are likely to report higher levels of phantom limb pain [65].

TREATMENT

Residual limb pain can be managed by [29]:

- Switching or adjusting the prosthesis to avoid pressure on neuromata
- Resecting the neuromata so it no longer occupies the pressure areas
- Neurosurgical intervention involving rhizotomy and ganglionectomy
- Spinal cord or peripheral nerve stimulation in properly selected patients

Recommendations for pharmacotherapy in phantom limb pain are complicated by the paucity of trials comparing different therapeutics and routes of administration. The few published RCTs have shown inconsistent results [269]. This modest evidence base has resulted in few evidence-based practice guidelines being published, and treatment recommendations have often been based on expert opinion and uncontrolled studies [263].

Findings that neuroplastic changes in the CNS contribute to phantom limb pain, that CNS neuroplasticity can be reversed, and that reversal is correlated with extent of pain reduction has led to novel neuromodulatory treatment strategies. Evaluation of these approaches is in the early stages, and mirror therapy has received the most evaluation of these approaches [270].

Phantom limb pain should be managed using a multidisciplinary approach that combines evaluative management, desensitization, psychotherapy, and pharmacotherapy. Evaluative management includes optimal prosthetic fit and resolving residual limb pain or inflammation, remote hip pain, or lower back pain, as these can exacerbate phantom limb pain. The Veterans Administration/Department of Defense (VA/DoD) guideline for rehabilitation of lower limb amputation recommends that risk reduction for phantom limb pain begin prophylactically with sufficient pre- and postamputation pain control [265]. Opioid analgesics should be considered in

the immediate postoperative phase. The VA/DoD recommends against initiation of long-term opioid therapy for chronic pain and instead recommends alternatives to opioid therapy, including self-management strategies and other nonpharmacologic treatments. Nonopioids are recommended over opioids [265]. Transition to non-opioid pharmacotherapy combined with physical, psychological, and mechanical modalities should be considered throughout the rehabilitation process and should be tailored based on risk assessment and individual patient needs and characteristics [265]. Treatment should target pain related to the residual and/or phantom limb and address pain in other anatomic areas from a primary care approach. Desensitization is believed to reduce pain in the residual limb and may help the amputee accept his or her new body image. Desensitization involves the use of TENS, and guideline authors recommend that TENS be used as part of a multimodal approach to pain management for phantom limb pain [18]. However, the VA/DoD finds insufficient evidence to support the use of TENS [265].

Psychotherapy has been found effective in reducing pain from amputation and can inform the pain physician of the underlying mechanism (e.g., muscle spasm or vascular insufficiency) and thus assist in pharmacologic selection [263]. Mirror therapy, which involves the patient viewing the reflection of their intact limb as he or she performs exercises with the amputated limb, is efficacious in upper and lower extremity phantom limb pain; however, most experts agree that further research is needed [271; 272; 273; 274]. A pilot study evaluated pain outcomes in 10 patients with phantom limb pain using eye movement desensitization and reprocessing, a psychological treatment directed at reprocessing emotional and somatosensory memories. At three-months follow-up, four were pain-free and four had reduced pain. At 2.8-years (mean) follow-up, three were pain-free and two had reduced pain (and four dropped out). These encouraging results require larger-scale replication [268].

No single drug has shown universal effectiveness in phantom limb pain control [269]. However, evidence of morphine and tramadol efficacy is robust and consistent, and both received an efficacy rating of "A" by the European Federation of Neurological Societies Task Force [256]. Patients with phantom limb pain may require higher-dose morphine and tramadol; the daily effective dose was found to be 70–300 mg and 523 mg, respectively [269].

Gabapentin can be effective in reducing pain in some patients, particularly when combined with opioids or TCAs in patients who show partial response to monotherapy with the same agents [269; 275]. Two RCTs found that gabapentin led to significant reduction in pain intensity and decreased the use of rescue pain medication compared to placebo [275]. However, a third study found no pain advantage over placebo.

Other possible pharmacotherapies include clonidine and tizanidine. In one study, clonidine combined with morphine and bupivacaine as preoperative epidural infusion led to a significantly reduced incidence of phantom limb pain and phantom limb sensation [269]. In another, tizanidine at 12 mg/day induced a significant analgesic effect [269].

DIABETIC NEUROPATHY

Estimates from 2021 indicate that diabetes affects 37.3 million Americans, or 11.3% of the population, with 1.4 million new cases diagnosed each year [276]. Of persons with diabetes, 5% have type 1 diabetes mellitus, a disease involving autoimmune destruction of pancreatic islet cells and loss of pancreatic insulin production. Type 2 diabetes mellitus accounts for the remaining 95%. Type 2 diabetes is a metabolic disease involving high pancreatic insulin output in the context of diminished muscle, fat, and liver cell response to insulin (i.e., insulin resistance) [276; 277].

Among patients with diabetes, as many as 50% of patients have mild-to-severe nerve damage (diabetic neuropathy), and roughly 50% of those 40 years of age and older have impaired foot sensation [278]. Pain with diabetic neuropathy, termed painful diabetic neuropathy, usually involves sensory-motor neurons and is experienced as burning, shooting, or stabbing pain. The feet or lower legs are almost always the sites of pain, and when pain occurs in the arms or hands, it is usually preceded by leg symptoms. Some patients may experience tingling, numbness, or loss of feeling in the extremities [279; 280]. In one study, the prevalence of painful diabetic neuropathy in adults with type 2 diabetes was found to be 26.4% [281]. Another study found a prevalence of 21%; however, painful symptoms, with or without diagnosed neuropathy, occur in one-third of all patients with diabetes [282].

Risk factors for diabetic neuropathy include poor glycemic control in type 1 diabetes and hypertension, obesity, and dyslipidemia in type 2 diabetes. Smoking and diabetes duration are likely risk factors in both diabetes forms [277; 278; 283].

Diabetic neuropathy may involve sensory, motor, or autonomic nervous systems and manifest in several focal or diffuse patterns. Pain is determined by the type of neuropathy and the affected nerves [279]. Diabetic neuropathy is categorized as peripheral, autonomic, proximal, focal, symmetrical, or multifocal.

Diabetic peripheral neuropathy begins as pain or loss of sensation in the extremities, particularly the toes, feet, legs, hands, and arms [279]. Diabetic autonomic neuropathy presents as changes in GI, urinary, cardiovascular, or sexual function. Common autonomic symptoms include resting tachycardia, exercise intolerance, and orthostatic hypotension. Diabetic autonomic neuropathy may impair the normal physiologic response to insulin-induced hypoglycemia (e.g. tremor, palpitations, sweating) that patients with diabetes rely upon as warning signs of hypoglycemia and the need to counterbalance insulin with a good, rapid source of glucose [279].

Diabetic proximal neuropathy usually first appears as unilateral pain in the thighs, hips, buttocks, or legs that results in lower extremity weakness and great difficulty in standing from a sitting position. Older patients with type 2 diabetes are most commonly affected by this type [279].

Diabetic focal neuropathy appears as sudden-onset pain or loss of motor function that involves the head, torso, or leg. Pain may become severe, but the neuropathy usually improves over several weeks or months and does not create long-term nerve or tissue damage [279]. Focal neuropathy that occurs in an extremity is also considered to be peripheral [280].

Focal and multifocal neuropathies can manifest as neuropathies in the cranial nerve, the limb, or in truncal areas. They are most commonly seen in patients older than 50 years of age and in those with diabetes spanning multiple decades. Focal neuropathies are often characterized by inflammatory vasculopathy and may spontaneously resolve or show a relapsing course [284].

Distal symmetrical neuropathy is the most common form and represents more than 90% of cases [285]. This neuropathy involves sensory and autonomic neurons and progresses via a fiber-length-dependent pattern. It can appear as a progressive distal axonopathy, typically manifesting as pain, trophic changes in the feet, and autonomic disturbances [284; 285]. Length-dependent polyneuropathy displays either an aggressive progression or relatively stable severity over time [284].

PATHOPHYSIOLOGY

Diabetic neuropathy is a heterogeneous disorder, and although the pathophysiology is incompletely understood, several contributory factors have been identified.

There are fundamental differences in the development of diabetic peripheral neuropathy in type 1 and type 2 diabetes. In type 1 diabetes, intensive glycemic control substantially reduces the risk of diabetic peripheral neuropathy. In these patients, emphasis should be placed on glycemic control as an effective approach in preserving nerve function and/or reducing the risk of developing diabetic neuropathy [277; 286].

In contrast to type 1 diabetes, intensive glycemic control in type 2 diabetes only modestly reduces risk of diabetic peripheral neuropathy, suggesting that factors other than impaired glucose tolerance contribute to neuropathy development. Obesity, hypertension, dyslipidemia, inflammation, and insulin resistance have been identified as potential mechanisms for the development of neuropathy in type 2 diabetes [287]. With the metabolic syndrome component in type 2 diabetes accounting for the probable mechanism in neuropathy development, risk reduction for neuropathy must address obesity, hypertension, low-density lipoprotein, high-density lipoprotein, and hypertriglyceridemia in patients with type 2 diabetes [277].

In the pathogenesis of diabetic neuropathy, elevated intracellular levels of glucose produce glycosylated end products. The deposition of glycosylated end products around nerve fibers results in demyelination, axonal degeneration, and reduction in nerve conduction velocity. Their deposition around the capillary basement membrane results in basement membrane thickening and capillary endothelial damage. These vascular abnormalities result in diminished oxygen supply and neuronal hypoxia, the onset of neuronal ischemia, and peripheral arterial disease. Activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) results in depletion of NADP, elevation of oxidative stress, and generation of oxidative free radicals that aggravate nerve damage [288; 289].

The mechanisms of pain development in diabetic neuropathy are not fully known, and the degree of nerve damage does not correlate with the presence or severity of pain [289]. Although decreasing pain symptoms may suggest nerve recovery, progression of neuropathy can result in loss of sensation, also experienced as diminution of pain. It is possible that Aδ fiber demyelination is a greater contributor to neuropathic pain than damage to unmyelinated C fibers. Supportive evidence comes from the finding that damaged A fibers release substance P, a neurochemical associated with allodynia that is normally released only from C fibers [290]. Pathologic changes leading to nerve damage may become permanent, resulting in peripheral and central sensitization. With repeated nerve stimulation, the excitatory neurotransmitter glutamate is released in the dorsal horn, resulting in enhanced postsynaptic effects and disproportionate pain signaling [290].

Nerve damage and pain in distal symmetrical neuropathy primarily involve small-fiber Aδ and C fibers. Small fiber neuropathy manifests in sensory symptoms reflecting peripheral deafferentation. Negative symptoms include thermal and pinprick hypoesthesia, and positive symptoms include burning pain, allodynia, and hyperalgesia [291]. Vascular changes and distal nerve fiber loss in small fiber neuropathy precede loss of nerve fibers in the nerve trunk of lower extremities. The polyol pathway, glycation, reactive oxygen species, and altered protein kinase C activity contribute to pathogenesis [292].

TREATMENT

Pain with diabetic neuropathy can be severe and potentially life-impairing. It often intensifies at night and creates sleep deprivation and fatigue that are aggravated by activity. Until the past decade, pain-reducing therapies were limited in effectiveness by burdensome side effect profiles, and none had received FDA approval for pain with diabetic peripheral neuropathy [279].

PRACTICE GUIDELINE RECOMMENDATIONS FOR THE PHARMACOLOGIC TREATMENT OF DIABETIC NEUROPATHY PAIN			
Approach	**Recommended Pharmacotherapy by Recommending Organization**		
	American Academy of Neurology	**Toronto Expert Panel on Diabetic Neuropathy**	**European Federation of Neurological Societies Task Force**
First-line	Pregabalin	TCAs SNRIs Anticonvulsants Opiates Membrane stabilizers Alpha-lipoic acid Capsaicin	Pregabalin Gabapentin Duloxetine TCAs Venlafaxine ER
Second- or third-line	Opioids (e.g., morphine tramadol, oxycodone CR) Venlafaxine Duloxetine Amitriptyline Gabapentin Valproate Capsaicin Dextromethorphan	Opioids (e.g., morphine, tramadol, oxycodone CR) Spinal cord stimulation	Opioids Tramadol Spinal cord stimulation
CR = controlled release, ER = extended release, SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant.			
Source: [256; 293; 294]			*Table 10*

Although it will not reverse neuronal damage, improved glycemic control may modestly slow progression [280]. As such, blood glucose monitoring, meal planning, physical activity, and compliance with oral medication or insulin should be encouraged [279].

Pharmacotherapies are the first-line treatment of pain with diabetic neuropathy. Among the general considerations, lack of efficacy should be judged only after two to four weeks using an adequate dose, as time is necessary to reach full efficacy. Analgesic combinations may be more effective; maximum pain reduction with any one therapy is limited to around 50% [255]. Practice guidelines published by the American Academy of Neurology, the Toronto Expert Panel on Diabetic Neuropathy, and the European Federation of Neurological Societies Task Force recommend a multi-tiered approach in which second- or third-line therapies are indicated for patients lacking response or tolerance to first-line therapies (***Table 10***) [225; 256; 257].

For many of these medications, use for neuropathic pain is off-label; they were approved by the FDA for other indications. Many have been associated with questionable side effects (e.g., increased blood pressure and edema from salt retention with fludrocortisones). Nevertheless, multiple clinical studies show benefit for the use of these medications in the treatment of neuropathic pain. Use of these medications is well within the standard of care in most medical communities [278].

COMMON CLINICAL CHARACTERISTICS OF CRPS		
Autonomic Abnormalities	**Motor Abnormalities**	**Trophic Changes**
Distal extremity swelling, especially in acute phase Hyper- or hypohidrosis Vasodilatation or vasoconstriction Changes in skin temperature	Weakness Coordination deficits Tremor Neglect-like symptoms of disturbed body perception of affected limb Dystonia	Abnormal nail growth Increased or decreased hair growth Fibrosis Thin, glossy skin Osteoporosis

Source: [302; 303] *Table 11*

Alpha-lipoic acid (ALA) bears special mention as the only pain therapy for diabetic neuropathy that potentially addresses the underlying pathophysiologic process (i.e., reduction of oxidative stress) [295]. One study randomized 460 patients with diabetes to oral ALA 600 mg once daily or placebo [296]. Four-year follow-up found significantly greater numbers of ALA patients reporting symptom improvement with fewer showing progression. A 2006 study found that five weeks of oral ALA 600–1,800 mg once daily resulted in significant improvement compared to placebo in stabbing and burning pain, paresthesia and numbness, and overall patient rating of efficacy [297]. However, these studies did not specifically evaluate changes in nerve conductivity. A 2012 systematic review evaluated 15 RCTs of ALA (mostly from Chinese-language journals) that used nerve conduction velocities as an end point for assessing the effectiveness of therapy on the underlying neuropathologic condition [298]. The pooled outcomes indicate that treatment with ALA (300–600 mg/day IV for two to four weeks) can lead to significant improvement in motor nerve conduction velocity, sensory nerve conduction velocity, and painful symptoms. A 2015 randomized withdrawal trial demonstrated painful symptom reduction from an average total symptom score of 8.9 to an average total symptom score of 2.5 over a 20-week period with a 600 mg/day ALA dose [295].

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS), formerly referred to as reflex sympathetic dystrophy, Sudeck's atrophy, causalgia, algodystrophy, or peripheral trophoneurosis, encompasses two highly similar conditions. In CRPS-I, pain is triggered by tissue injury, while nerve injury triggers the onset of pain in CRPS-II [299; 300].

A reported 50,000 new cases of CRPS-I occur annually. CRPS-I has a much higher prevalence than CRPS-II, and the risk of onset increases with age [301]. The incidence of CRPS is greater in women than men by a ratio that varies from 2:1 to 4:1 [302].

The cardinal feature of CRPS is continuous and progressively intense pain that is substantially disproportionate to the severity of the initiating injury or illness. An example is finger or toe injury that results in widespread pain involving the entire arm or leg or that transfers to the opposite extremity. Pain is usually comprised of stimulus-evoked mechanical and thermal allodynia and hyperalgesia and deep somatic allodynia [303]. Emotional stress can exacerbate the pain response [299].

Other sensory, motor, and autonomic abnormalities contribute to CRPS (***Table 11***) [302; 303]. Neurologic symptoms with both peripheral and central elements can increase the diagnostic challenge [304].

Until the last decade, CRPS was believed to progress through three stages and show an overall time-dependent worsening of symptoms. This concept has been replaced by the concept of distinct CRPS subtypes. These subtypes include a limited syndrome with dominant vasomotor symptoms, a limited syndrome with dominant neuropathic pain and sensory abnormalities, and a full-blown CRPS syndrome with chronic severe pain and abnormal sensory, motor, vasomotor, and/or trophic findings. Cluster analysis of signs and symptoms has been somewhat helpful in understanding subtypes, but the true breakthrough will occur when clinical and biomarker profiles are used to identify distinct CRPS subtypes, predict disease severity and progression, and better inform treatment selection [305; 306].

PATHOPHYSIOLOGY

The pathophysiology of CRPS is complex and not fully understood, but substantial progress has been made over the past decade in clarifying the underlying basis. These findings include [65; 301; 302; 303; 306]:

- Alteration in CNS function expressed by central sensitization, reorganization in the primary somatosensory cortex, and motor cortex disinhibition
- Sympathetic nervous system abnormality resulting from up-regulated adrenergic receptors and functional coupling between sympathetic efferent and sensory afferent fibers
- Immunologic factors such as aberrant expression of human leukocyte antigen, substance P, cytokines, and interleukins
- Neurogenic inflammation, edema, vasodilatation, and increased sweating, likely the result of elevations in systemic levels of calcitonin gene-related peptide
- Elevated neuropeptide concentrations contributing to pain and hyperalgesia
- Genetic and psychological mechanisms also contribute to CRPS

In CRPS, NMDA receptor activity plays a fundamental role in central sensitization and immune system modulation and is essential in the development and persistence of pain. To date, the only therapeutic approach with demonstrated efficacy in achieving short-term pain relief and long-term full remission are NMDA receptor antagonists [306].

TREATMENT

The Reflex Sympathetic Dystrophy Syndrome Association published a set of guidelines for CRPS that represent the most comprehensive and current management recommendations [305]. The following treatment recommendations are primarily from this publication.

CRPS should be treated using an interdisciplinary approach, with a focus on functional restoration. Although medication, blocks, and psychotherapy should be available to all patients at treatment onset if warranted, their use is suggested only when patients are unable to make progress in functional improvement. Interdisciplinary pain management techniques stressing functional restoration are the preferred approach because they are the most likely to reset the alteration in central processing and normalize the distal environment [305].

According to the Reflex Sympathetic Dystrophy Syndrome Association, interdisciplinary/multidisciplinary pain management techniques emphasizing functional restoration are thought to be the most effective therapy for chronic pain, perhaps by resetting altered central processing and/or normalizing the distal environment.

(https://rsds.org/wp-content/uploads/2022/06/CRPS-practical-diagnostic-treatment-guidelines-5-edition.pdf. Last accessed August 19, 2022.)

Level of Evidence: 1 (Meta-analysis or systematic reviews)

ANALGESIC SELECTION FOR RECURRENT OR TREATMENT-RESISTANT CRPS	
Reason for Inability to Begin or Progress	**Action**
Mild-to-moderate pain	Simple analgesics and/or blocks
Excruciating, intractable pain	Opioids and/or blocks or more experimental interventions (if continued non-response)
Inflammation/swelling and edema	Steroids, systemic or targeted (acutely), or NSAIDs (chronically); immune modulators
Depression, anxiety, insomnia	Sedative analgesic antidepressant/anxiolytics and/or psychotherapy
Significant allodynia/hyperalgesia	Anticonvulsants and/or other sodium channel blockers and/or NMDA receptor antagonists
Significant osteopenia, immobility, and trophic changes	Calcitonin or bisphosphonates
Profound vasomotor disturbance	Calcium channel blockers, sympatholytics, and/or blocks
NMDA = *N*-methyl-D-aspartate, NSAID = nonsteroidal anti-inflammatory drug.	
Source: [305]	*Table 12*

The sequence of physiotherapies recommended for all patients with CRPS is [305]:

1. Mirror visual feedback, graded motor imagery, reactivation, contrast baths, desensitization, exposure therapy
2. Edema control, active flexibility, isometric strengthening, correction of postural abnormalities, diagnosis and treatment of secondary myofascial pain
3. Stress loading, isotonic strengthening, gentle and passive range of motion, general aerobic conditioning, postural normalization and balanced use
4. Ergonomics, movement therapies, normalization of use, vocational and functional rehabilitation

When patient progress stalls, pharmacotherapy is warranted. Choosing an agent can be difficult, as research regarding CRPS treatment is lacking. Guidance comes from the results of RCTs for other neuralgias, clinical experience, and identification of likely pain generators in the individual patient with CRPS. Pain with ischemic, dystonic, neuropathic, or bony etiology is matched with appropriate analgesic selection (***Table 12***) [305].

Anti-Inflammatory Drugs/Immunomodulators

Some patients with CRPS find NSAIDs effective, although certain NSAIDs may have greater efficacy [305]. Ketoprofen is likely to produce a substantial antibradykinin and antiprostacyclin effect along with the expected antiprostaglandin effect.

A demonstration of modest benefit with IV immunoglobulin suggests potential efficacy in targeting immune function and inflammation in CRPS [305]. Thalidomide, a TNF-α and interleukin-1 and 6 inhibitor, has also shown modest benefit.

Oral corticosteroids are the only anti-inflammatory intervention with support from RCTs. However, most studies involve early/acute cases, when inflammation is prominent [305]. It is unclear if corticosteroids are beneficial for chronic CRPS, in which pro-inflammatory cytokine levels are lower. Chronic steroid use is contraindicated due to serious adverse effects.

Cation Channel Blockers

Gabapentin has shown efficacy in CRPS, while pregabalin has not yet been evaluated. Carbamazepine 600 mg/day over eight days has been found to substantially reduce pain versus placebo [305].

Oxcarbazepine is often used in place of carbamazepine because of a more favorable side effect profile, and although not yet studied in CRPS, it may be beneficial [305]. Phenytoin is a third-line agent to consider, especially in cases involving ectopic nerve firing.

Augmentation of Monoaminergic Neurotransmission

Tricyclic and heterocyclic antidepressants can be highly beneficial in the treatment of CRPS, and side effect profile determines their selection. For example, doxepin may be a good choice in anxious, depressed, underweight, or insomniac patients, while the greater noradrenergic selectivity of desipramine may be a better choice in overweight or hypersomnolent patients.

SSRIs are ineffective in CRPS and are not supported [305]. Data are lacking for combined SNRIs.

Opioids

Neuropathic pain in CRPS does not predictably respond to opioids to the same extent as acute nociceptive pain, often resulting in dose escalation with no added pain relief but accruing adverse effects. However, opioids are a reasonable second- or third-line treatment option in CRPS [305]. Use of short-acting opioids is often inappropriate, and when indicated, therapy should involve extended-release delivery systems and "pure" (not containing acetaminophen) formulations. Short-acting opioids should be reserved for breakthrough pain only.

Methadone has the theoretical advantage of NMDA antagonism and is inexpensive [305]. Likewise, tramadol is theoretically appealing due to its dual serotonin/norepinephrine reuptake blockade. Long-term high-dose use of opioids can exacerbate allodynia and/or hyperpathia.

NMDA Receptor Antagonists

The NMDA receptor antagonists MK-801, amantadine, and dextromethorphan have been evaluated in neuropathic pain and CRPS, but toxicity at effective doses has generally been too high. Oral dextromethorphan may be better tolerated and may augment the effect of opioids to decrease opioid dosing requirements. Ketamine has been used topically, orally, and intravenously and is one of the very few therapies demonstrating substantial and durable pain reduction of treatment-refractory CRPS pain [306]. Ketamine trials have effectively controlled side effects with higher-dose co-administration of midazolam or lorazepam, combined with either the a2-adrenergic agonist clonidine or the 5-HT3 antagonist ondansetron [307; 308; 309; 310].

The most dramatic treatment response involved induction of anesthetic-dose ketamine treatment in 20 patients with CRPS unresponsive to all other pain management approaches, including lower-dose 5-day inpatient or 10-day outpatient ketamine protocols. Over five days, patients were infused with ketamine 7 mg/kg/h, midazolam 0.15 – 0.4 mg/kg/h, and clonidine 0.1 mg. Complete remission from CRPS was observed in all patients at one month, 17 of 20 at three months, and 16 of 20 at six months. Of the 20 patients, 10 remained completely pain free from 5 to 11 years and no longer required any form of pain medication [311]. Consensus guidelines developed by the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists caution that larger studies are needed to quantify efficacy, improve patient selection, refine the therapeutic dose range, and develop a better understanding of the long-term risks of repeated ketamine treatments [312].

Antihypertensives and a-Adrenergic Antagonists

Nifedipine, a calcium channel blocker, has a strong theoretical basis for use in CRPS, and doses up to 60 mg/day can be useful in some patients [305]. Phenoxybenzamine and phentolamine are considered third-line agents for CRPS. Efficacy of phenoxybenzamine is supported, but it is more effective in syndromes under three months in duration. Phentolamine is used much less often due to cost and administration by continuous IV infusion.

Treatment of Bone Pain with Calcitonin or Bisphosphonates

Calcitonin is one of the few CRPS treatments validated by RCTs, and intranasal doses of 100–300 U per day are efficacious for CRPS-related bone pain [305]. Bisphosphonates such as alendronate, ibandronate, risedronate, zoledronate, etidronate, and pamidronate can ease bone pain in CRPS by slowing bone resorption. Alendronate is the most studied in this class [305].

Topical Treatments

A 5% lidocaine patch may have efficacy in some local or focal CRPS phenomena such as allodynia [305]. Dimethyl sulfoxide (50% cream for two months) has been found to significantly reduce pain compared with placebo [305]. Topical capsaicin is often found intolerably painful and unacceptable by patients with CRPS.

Interventional Approaches

Interventional approaches supported for use in patients with CRPS are placed in a three-level sequence. Inadequate or partial response should initiate a stepwise progression moving from less to more invasive, in conjunction with non-interventional therapies [305]. This approach consists of [305]:

- Minimally invasive therapies
  - Sympathetic nerve blocks
  - IV regional nerve blocks
  - Somatic nerve blocks
- More invasive therapies
  - Epidural and plexus catheter blocks
  - Neurostimulation
  - Intrathecal drug infusion, such as baclofen
- Surgical and experimental therapies
  - Sympathectomy
  - Motor cortex stimulation

FIBROMYALGIA

An estimated 10 million adults in the United States are afflicted with fibromyalgia, of whom 75% to 90% are female. However, the condition also occurs in men and children of all ethnic groups [313]. Diagnosis is usually made between the ages of 20 and 50 years, and with increasing age comes increased prevalence [313].

The cardinal features of fibromyalgia are widespread pain and tenderness in multiple regions of the body that are not attributable to another condition. In addition to pain and tenderness, patients with fibromyalgia often experience [314; 315]:

- Morning stiffness
- Tingling or numbness in the extremities
- Headache that may include migraine
- Irritable bowel syndrome
- Sleep disturbances
- Cognitive and memory dysfunction (referred to as “fibro fog”)
- Dysmenorrhea
- Restless legs syndrome

Abnormal reactivity to sensory input is also characteristic of fibromyalgia. This includes [316]:

- Hypersensitivity to painful stimuli applied to somatic structures, including painful and non-painful sites and normal control areas
- Low pain thresholds to thermal, mechanical, electrical, and chemical stimuli
- Pain increases with repeated stimulation (enhanced temporal summation)
- Temperature sensitivity
- Sensitivity to loud noises or bright lights

Patients with fibromyalgia report either a gradual or a post-traumatic onset. Pain with fibromyalgia is described as a persistent, diffuse, deep, aching, throbbing sensation in muscles that is most often continuous [317; 318].

COMMON CLINICAL CHARACTERISTICS OF FIBROMYALGIA	
System	**Contributory Factors**
Autonomic	Decreased heart rate variance, a tendency for syncope, altered cutaneous capillary responsiveness
Neuroendocrine	Hypothalamic-pituitary-adrenal axis dysfunction, including blunted cortisol response, and abnormal growth hormone regulation
Neurotransmitter	Consistently elevated levels of the pro-nociceptive neurotransmitters substance P, glutamate, nerve growth factor, brain-derived neurotrophic factor, and serotonin 2a/3a Consistently decreased levels in pain-ameliorating neurotransmitters serotonin 1a/b, norepinephrine, and dopamine Typically normal endogenous opioid system, helping explain the lack of benefit from opioid analgesics
Neurosensory	Central amplification of pain and/or reduced anti-nociception (central sensitization, abnormalities of descending inhibitory pain pathway function)
Genetic	Strong familial aggregation for fibromyalgia; evidence of polymorphism in the genes encoding serotoninergic, dopaminergic, and catecholaminergic systems in fibromyalgia etiology
Source: [318; 319; 320]	*Table 13*

Other chronic pain syndromes can exist along with fibromyalgia, including chronic fatigue syndrome, endometriosis, inflammatory bowel diseases, interstitial cystitis, temporomandibular joint dysfunction, and vulvodynia. Whether these disorders share an underlying common pathologic basis with fibromyalgia is not known [315].

Rheumatic diseases such as rheumatoid arthritis, lupus, and ankylosing spondylitis are risk factors for fibromyalgia. A genetic contribution is suggested by an increased prevalence in patients with a positive family history of fibromyalgia [315].

PATHOPHYSIOLOGY

Emerging evidence strongly suggests that disordered processing in central afferent neurons accounts for the dominant symptoms of pain and tenderness in fibromyalgia [317; 319]. The contributory role of augmentation in pain signaling through central sensitization is supported by brain imaging findings consistent with abnormal pain response (e.g., decreased thalamic blood flow and accelerated brain gray matter loss) [318; 319]. Dysregulated autonomic, neuroendocrine, neurotransmitter, and neurosensory function and genetic predisposition have all been implicated in fibromyalgia pathophysiology (***Table 13***) [317; 318].

CLASSIFICATION

In the absence of definitive laboratory tests for fibromyalgia, diagnosis relies on patient history and symptom self-report, physical examination, and manual tender point examination, in accordance with the 2010 standardized criteria established by the ACR. With the diverse symptoms and often vague presentation, the typical patient with fibromyalgia fails to receive an accurate diagnosis for an average of five years [317]. Further complicating the diagnostic process is the considerable symptom overlap with other syndromes such as lupus and rheumatoid arthritis [318].Fibromyalgia is a diagnosis of exclusion, and patients should be thoroughly evaluated for the presence of other disorders that could be the cause of symptoms before a diagnosis of fibromyalgia is made [317; 318].

PHARMACOTHERAPY FOR FIBROMYALGIA WITH GREATEST EVIDENCE OF EFFICACY		
Drug	**Dose Range**	**Supporting Evidence**
Amitriptyline	10–50 mg	Several RCTs, guideline recommended
Duloxetine	30–60 mg	FDA approved, several RCTs, meta-analysis
Milnacipran	25–200 mg	FDA approved, several RCTs, meta-analysis
Pregabalin	150–450 mg	FDA approved, long-term efficacy demonstrated, guideline recommended
Gabapentin	1200–2400 mg	RCTs, guideline recommended
Cyclobenzaprine	10 – 40 mg	One meta-analysis
Fluoxetine	20–60 mg	Three small RCTs
Naltrexone	4.5 mg	One small RCT
Paroxetine	20 mg	One large RCT
Tramadol	50–300 mg	Guideline recommended
RCT = randomized controlled trial.		
Source: [322]		*Table 14*

TREATMENT

The treatment goal in fibromyalgia is to decrease pain and associated symptoms and to improve function and quality of life. No cure is available from any single therapy. The overall treatment effects of single interventions are modest at best, and the management approach with greatest evidence involves pharmacologic therapy combined with nonpharmacologic approaches such as education, exercise, and cognitive-behavioral therapy [319]. The atypical nature of fibromyalgia is underscored by it being the only chronic pain syndrome that may be effectively treated with SSRIs [134].

An interdisciplinary pain rehabilitation program that emphasizes behavioral or cognitive-behavioral interventions combined with conditioning exercise is recommended for patients with partial or substantial disability due to fibromyalgia-related chronic pain [134].

Advances in the understanding of pain transmission help to explain the effective pharmacotherapies for fibromyalgia (***Table 14***). The efficacy of TCAs is thought to occur through inhibition of serotonin and norepinephrine reuptake in spinal neurons, increasing their synaptic concentration and resulting in descending pain pathway mediation of analgesia. Amitriptyline is the most extensively studied TCA with fibromyalgia [321].

The three FDA-approved drugs for fibromyalgia—duloxetine, milnacipran, and pregabalin—have been found superior to placebo on many measures, the exceptions being duloxetine for fatigue, milnacipran for sleep disturbance, and pregabalin for depressed mood [323]. Comorbid depression may not respond to the primary agent or the dose used to treat fibromyalgia, and separate antidepressant therapy may be required [322]. A 2012 Cochrane review of monoamine oxidase inhibitor efficacy in fibromyalgia found statistically significant improvement with pirlindole versus placebo in pain, tender points, and patient and physician assessment [324].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Cultural and demographic factors may contribute to lack of effective pain management. Expression of pain and the use of pain medication differ across cultures. For example, Hispanic and Filipino patients have been shown to be reluctant to report pain because of fear of side effects or addiction [325]. Even when effective opioids have been prescribed, access may be difficult, as inadequate supplies of opioids are more likely in pharmacies in primarily non-White neighborhoods. Communication with patients regarding level of pain is a vital aspect of caring for patients in the end of life. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

CONCLUSION

In the past decade, breakthroughs in the scientific knowledge of pain pathophysiology have dramatically transformed our understanding of how pain develops, progresses, persists, and responds to intervention. Consequently, some of the more established past strategies for treating chronic pain are now being challenged by research evidence. In turn, these advances in pain science have the potential to greatly assist healthcare providers in delivering more effective pain management care, partially through greater elucidation of disease-treatment relationships. The prevalence of chronic pain syndromes in the United States is expected to continue rising, in relation to an aging population, increasing rates of obesity and diabetes, continued advances in lifesaving trauma interventions, poorly managed postsurgical pain, and greater public awareness of pain as a condition warranting medical attention.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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