# 29 PAIN

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Pain is ubiquitous in life, usually serving as a warning sign of impending or actual injury to the organism. As such, pain is older than humans, dating back to our most primitive ancestors. Pain is also a vital diagnostic clue for physicians. Physicians should be intimately familiar with pain because it is the most common symptom for which patients seek medical attention. According to the U.S. government's annual report on Americans' health, one in four adults suffered a day-long bout of pain within the past 30 days, and 10% suffer from pain every day. Among the various types of pain, back pain is the most common, followed by headaches and arthralgias. Spinal pain is the leading cause of disability in industrialized nations, with the economic costs exceeding $100 billion annually in the United States by some estimates. Special populations at particular risk for chronic pain include elderly people and individuals with physical and psychological morbidities. Several conditions characterized by chronic pain, such as irritable bowel syndrome, interstitial cystitis, fibromyalgia, and complex regional pain syndrome, are more prevalent in females than males.

## DEFINITION

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This definition recognizes that pain may be experienced in some circumstances in the absence of ongoing tissue damage, such as phantom pain after a healed amputation. One implication of this construct is the assumption that pain is always subjective; hence, a patient's report of pain should always be accepted at face value in the absence of evidence to the contrary.

## PATHOBIOLOGY

### Classification of Pain States

Multiple classifications have been used to describe pain states based on duration, anatomic source, or etiology. *Acute pain* usually results from injury or inflammation, has survival value, and may play a role in the healing process by promoting behaviors that minimize reinjury. In contrast, *chronic pain* is perhaps best construed as a "disease" that serves no useful purpose. Although there is no clear threshold at which acute pain transitions to a chronic state, it is generally accepted that pain persisting beyond the expected healing period is pathologic. In most cases, this period is between 3 and 6 months. The intensity of pain can be classified as mild (1 to 3), moderate (4 to 5), or severe (≥6 on a 0 to 10 numerical rating scale).

### Somatic and Visceral Pains

Pain can originate from somatic or visceral structures. *Somatic pain* is well localized and generally results from injury or disease of the skin, musculoskeletal structures, and joints. *Visceral pain* arises from internal organ dysfunction and can result from inflammation, ischemia, occlusion of flow resulting in capsular or organ distension (e.g., renal stones, bowel obstruction, cholecystitis) or from functional pathology (e.g., irritable bowel syndrome). In contrast to somatic pain, visceral pain is usually diffuse and poorly localized, is often referred to somatic regions (e.g., myocardial ischemia radiating into the arm), and tends to be associated with exaggerated autonomic reflexes and greater emotional features.

### Neuropathic, Nociceptive, and Mixed Pain

Pain can be etiologically classified as neuropathic, nociceptive, or mixed (Table 29-1). *Neuropathic pain* has been defined as pain resulting from disease or injury to the peripheral or central nervous somatosensory system. Common neuropathic pain states include postherpetic neuralgia, diabetic neuropathy, and radicular pain. *Nociceptive pain* usually results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. Pain associated with cancer can result from the tumor itself or can be a consequence of therapy (e.g., surgery, chemotherapy, and radiation therapy). In light of the often multiple different etiologies, advanced cancer pain is a typical example of a mixed pain state.

### Dysfunctional Pain

There is a group of pain syndromes that have been characterized by amplification of pain signaling in the absence of either inflammation or injury (as in nociceptive pain) or damage to the nervous system (as in neuropathic pain). These conditions include pain states such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis. The precise pathophysiologic mechanisms of pain in these disorders are unclear, although they share some features of neuropathic pain. Other chronic pain states, such as primary erythromelalgia and paroxysmal extreme pain disorder, are perhaps best described as hereditary channelopathies associated with mutations of the voltage-gated sodium channel Nav1.7. These mutations lead to increased excitability of nociceptive

**TABLE 29-1 CLASSIFICATION AND PREVALENCE OF COMMON PAIN CONDITIONS**

| *Neuropathic* | | *Nociceptive* | | |
|---|---|---|---|---|
| **PERIPHERAL** | **CENTRAL*** | **SOMATIC** | **VISCERAL** | **MIXED** |
| Peripheral neuropathy (1-3%) | Central post-stroke pain (8%) | Arthritis (25-40% in people >40 years) | Endometriosis (10% in women of reproductive age) | Headache (15% for migraine, 20-30% for tension-type) |
| Postherpetic neuralgia (annual incidence 0.1-0.2%) | Spinal cord injury (30-50%) | Myofascial pain (5-10%) | Irritable bowel syndrome (5-15%) | Cancer§ (lifetime prevalence 30-40%) |
| Chronic postsurgical pain (2-10% after surgery) | Multiple sclerosis (25%) | Fibromyalgia† (2-4%) | Interstitial cystitis (0.2-1% of women) | Low back pain‖ (point prevalence 10-30%) |
| Phantom limb pain (30-60% of patients with major limb amputation) | Parkinson's disease (10%) | Connective tissue disorders (0.2-0.5%) | Ulcers/gastritis/esophagitis (3-9%) | Neck pain‖ (annual incidence 20-30%) |
| Trigeminal neuralgia (0.01%) | Seizure disorder (1-3%) | Burn pain‡ (annual incidence of burns requiring hospitalization 0.01%) | Cholecystitis/appendicitis | Ischemic pain¶ |
| Radiculopathy/spinal stenosis (3-10%) | | | | |
| Complex regional pain syndrome (0.03%, 3-20% after orthopedic surgery) | | | | |
| Nerve entrapment syndromes (e.g., carpal tunnel, thoracic outlet, meralgia paresthetica; 2-4%) | | | | |

*Prevalence rates represent proportion of patients with condition who develop pain.
†Some cases may represent a variant of central pain.
‡Third-degree burns often associated with neuropathic pain.
§Neuropathic pain occurs in 20-50% of cases and may occur secondary to tumor invasion, surgery, chemotherapy, and radiation treatment.
‖Neuropathic pain may accompany nociceptive pain in 10-35% of cases.
¶Typically nociceptive, but long-standing pain may result in ischemic neuropathy.

afferent fibers and ongoing activity in sensory neurons, resulting in spontaneous pain.

### Pain Mechanisms

Pain results from activation of specialized peripheral receptors (*nociceptors*) by a noxious event (stimulus). These stimuli fall into one of three categories: *mechanical* (e.g., pressure, tumor growth, incision), *thermal* (e.g., hot or cold), or *chemical* (e.g., ischemia or infection). The stimulus is then converted into an electrical nerve signal (*transduction*), which is conveyed along the axons of thinly myelinated (A-delta) or unmyelinated (C) nerve fibers through specific pathways (*transmission*). *Modulation* refers to the attenuation of pain signals through intrinsic inhibitory activity within the peripheral and the central nervous systems before being perceived as an unpleasant sensation (*perception*). *Pathologic pain* is the result of injury- or disease-induced changes in the peripheral or central nervous system leading to alterations in the pain signaling process. One important example of pathologic pain from injury to the nervous system is *peripheral sensitization*. This form of pain is characterized by the development of spontaneous ectopic activity in injured nerves and dorsal root ganglion cells, as well as enhanced sensitivity to mechanical, thermal, or chemical stimuli. Recent studies have shown an important role for cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins, released by macrophages and other inflammatory cells, in the peripheral sensitization process.

The prolonged and repeated activation of nociceptive afferent fibers produces *central sensitization*, a state of increased sensitivity of central pain signaling neurons. Activation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate is thought to be an important mechanism for central sensitization. Recent studies indicate that in addition to functional changes in neurons, microglia and astrocytes may also play an important role in the central sensitization process. Other central neuroplastic changes that may contribute to neuropathic pain states include deafferentation hyperactivity that may occur after spinal cord or avulsion injuries, loss of large fiber afferent inhibition, reorganization of central connections of primary afferent fibers, and excitatory descending modulatory mechanisms. Central and, to a lesser extent, peripheral sensitization are considered to be the prime culprits responsible for pain induced by innocuous stimuli (*allodynia*), and increased pain to normally noxious stimuli (*hyperalgesia*), that are commonly observed in neuropathic pain states.

## DIAGNOSIS

### History

Similar to the work-up of any symptom, the evaluation of pain begins with a thorough history. One of the primary tenets of pain assessment is that subjective complaints should always be taken seriously. There is currently no diagnostic test that can measure pain or even ascertain its existence. The most promising techniques involve functional brain imaging that reflects cerebral metabolism. Presently, these techniques are research tools that have helped us understand that the brains of chronic pain patients undergo morphologic alterations such as a diminution in gray matter in the areas involved in pain perception. A comprehensive history should include the anatomic region of pain, its quality, exacerbating and relieving factors, temporal aspects, associated symptoms and signs (e.g., numbness or weakness), interference with activities of daily living, and response to current and prior treatments. The temporal aspects of pain can provide valuable clues to etiology and help guide treatment. Most cases of acute pain develop subsequent to a specific inciting event (e.g., surgery, trauma), whereas chronic pain conditions are usually more insidious in onset. Because acute pain tends to be self-limited and the relationship to a precipitant event is more tangible, it may be better tolerated and associated with fewer psychological sequelae.

The severity of pain can be measured through a variety of different rating scales. Some of the more common instruments include categorical scales, verbal and numerical rating scales (0 to 10), and the visual analogue scale, in which a 10-cm line is anchored on each side by two points designated as "no pain" and "worst possible pain." Because there are subtle differences between different types of scales, repeat assessments and response to therapy are ideally gauged using the same instrument. For young children and mentally incapacitated patients, the use of age-appropriate substitute scales or facial expressions has been validated.

Recent guidelines from experts across multiple specialties and sectors have concluded that pain scores represent only one component of pain management. Other important aspects of treatment include assessments of functional capacity (e.g., Oswestry disability index for back pain), psychological and emotional functioning (e.g., SF-36), satisfaction ratings, adverse treatment effects, and disposition (i.e., work status). It is therefore imperative that realistic goals are established, and individually tailored treatment regimens are developed to achieve these ends.

**TABLE 29-2 CATEGORIZATION OF NEUROPATHIC AND NOCICEPTIVE PAIN**

| CLINICAL CHARACTERISTIC | NEUROPATHIC PAIN | NOCICEPTIVE PAIN |
|---|---|---|
| Etiology | Nerve injury or peripheral/central sensitization | Tissue or potential tissue damage |
| Descriptors | Lancinating, shooting, electrical-like, stabbing | Throbbing, aching, pressure-like |
| Sensory deficits | Frequent (e.g., numbness, tingling, pricking) | Infrequent and, if present, in nondermatomal or non-nerve distribution |
| Motor deficits | Neurologic weakness may be present if motor nerve affected | May have pain-induced weakness |
| Hypersensitivity | Pain frequently evoked with nonpainful (allodynia) or painful (exaggerated response) stimuli | Uncommon except for hypersensitivity in the immediate area of an acute injury |
| Character | Distal radiation common | Distal radiation less common; proximal radiation frequent |
| Paroxysms | Exacerbations common and unpredictable | Exacerbations less common and associated with activity |
| Autonomic signs | Color changes, temperature changes, swelling, and/or sudomotor (sweating) activity occur in one third to one half of patients | Autonomic signs uncommon in chronic nociceptive pain |

Distinguishing between neuropathic and nociceptive pain can have important treatment implications (Table 29-2). Neuropathic pain is characterized by positive and negative symptoms. Negative symptoms, such as a loss of sensation, are usually the result of axon and neuron loss, whereas the positive symptoms reflect abnormal excitability of the nervous system. Numbness, tingling, and other symptoms suggestive of sensory dysfunction are strongly indicative of neuropathic pain, especially when they occur in a dermatomal or solitary nerve distribution. Descriptors such as "burning," "shooting," and "electrical" are more apt to be associated with neuropathic pain, whereas adjectives such as "squeezing," "throbbing," and "aching" tend to be strongly identified with nociceptive pain states such as acute inflammatory pain or arthralgias. Other positive symptoms observed in neuropathic pain states include pain evoked by normally innocuous stimuli (allodynia) and an exaggerated or prolonged pain to noxious stimuli (hyperalgesia or hyperpathia). Although neuropathic pain tends to be more intermittent than nociceptive pain, mechanical spinal pain is classically exacerbated by movement. As alluded to earlier, some conditions such as cancer may be characterized by aspects of both nociceptive and neuropathic pain.

The proper evaluation of the patient in pain includes a psychosocial history. Between one half and two thirds of chronic pain patients exhibit varying degrees of major psychopathology, with depression being the most common comorbidity, followed by anxiety disorders, somatoform disorders, and substance abuse. Many of these coexisting psychological conditions have been associated with poor treatment prognosis. People seeking chronic pain care may also be more likely to carry a concomitant axis II diagnosis (i.e., personality disorder). Patients with axis II diagnoses are more likely to be designated as "difficult patients," which can act as an additional barrier to effective treatment. Potential social factors that can negatively affect treatment should be identified, including low job satisfaction, secondary gain, and ongoing litigation. A focused psychosocial history that includes prior psychiatric diagnoses, suicidal ideation, work history, legal history, and substance abuse, is therefore essential in the formulation of a treatment plan.

### Physical Examination

Examination of the patient in pain should encompass all bodily systems because pain is a frequent manifestation of systemic disease. A physical

examination finding by itself is almost never pathognomonic but usually functions to confirm suspicions garnered from the history and to select patients for imaging studies or invasive diagnostic testing. Unlike acute pain, *chronic pain is usually not associated with increased vital signs or facial grimacing.* Thorough neurologic and musculoskeletal examinations are particularly useful in evaluating pain. Sensory symptoms can precede other neurologic findings by months or weeks. The most common forms of neuropathy are associated with sensory deficits in a glove-stocking distribution, but other patterns occur as well (Chapter 428). Numbness in the distribution of a nerve root or single nerve strongly suggests neuropathic pain, but nondermatomal sensory changes can accompany nociceptive pain (e.g., fibromyalgia or arthritis) as well. Allodynia and hyperalgesia are hallmarks of neuropathic pain. Postural and gait abnormalities may be either causative factors for rheumatologic conditions (e.g., bursitis) or consequences of the underlying condition.

A careful evaluation of passive and active range of motion is useful because generalized and regional pain complaints are often accompanied by decreases in range of motion. Distinctions should be drawn between pain-induced and neurologic weakness, with the latter often occurring in conjunction with muscle atrophy or asymmetry in reflexes. Sometimes, reflex assessment is the only way to distinguish between a true neurologic condition and nonorganic etiologies; hence, deep tendon reflexes are a useful component of the pain exam.

## Diagnostic Tests

Imaging has largely supplanted history and physical examination as the gold standard for diagnosing pathology, but is not without drawbacks. There is a poor correlation between findings on magnetic resonance imaging (MRI) and the intensity of spinal pain, with greater than 50% of asymptomatic individuals having abnormalities on lumbar, thoracic, and cervical films. Previous studies found that neither radiographs nor MRI studies affect treatment outcomes and are unlikely to affect decision making; in fact, redundant imaging can lead to unnecessary procedures. Absolute indications for MRI in patients with back pain are (1) serious or progressive neurologic deficits, (2) new-onset bowel and bladder dysfunction, (3) suspected metastatic disease, or (4) when referring patients for procedural interventions. The presence of "red flags" suggestive of more serious pathology (e.g., extremes of age, trauma history, immunosuppressed state, persistent fever, infection, or history of intravenous drug abuse) should also alert the practitioner to seek further evaluation. Electromyography and nerve conduction studies (Chapter 428) can be used to diagnose injury to large nerve fibers. However, because these studies are associated with significant false-negative and false-positive rates and are not sensitive in detecting impairment of small fiber (nociceptive afferent fibers) function, a normal neurophysiologic study does not rule out neuropathic pain. For small fiber neuropathies, a skin biopsy demonstrating decreased density of epidermal nerve fibers is a sensitive test.

For nonspinal pain conditions, MRI is ideal for detecting inflammation and soft tissue pathology, whereas computed tomography (CT) scanning is indicated for disease processes associated with bone destruction or ossification. The main advantages of ultrasound are that it is safe, is inexpensive, does not utilize ionizing radiation, and is relatively cheap.

## TREATMENT Rx

The goals of treatment should include elucidating the cause of pain and alleviating suffering. Consequently, the goal of pain treatment should not be limited to pain reduction but should encompass improving functional status, mood, and social interactions (i.e., quality of life). Chronic pain may result from diverse etiologies, including physical trauma, disease, infection, and therapies such as radiation, chemotherapy, and surgery. It has been argued that treatment should be mechanism based rather than etiology based, but at the present time, simple clinical tools to correlate symptoms and signs with mechanisms are lacking. Hence, treatment is primarily etiology based, or symptomatic. The future development and validation of diagnostic methods to identify mechanisms (e.g., intravenous infusion tests) may help develop novel target-specific pharmacologic agents.

Pain is a complex perceptual experience affected by a multitude of factors that include not only activation of nociceptors but also emotions (e.g., fear, anxiety), memory and cognition, social and cultural context, and expectations. Thus, it is not surprising that despite a paucity of studies evaluating a multidisciplinary approach to pain management, a strong consensus exists that this approach is beneficial.

## Pharmacologic Therapies

### Antipyretic Analgesics

Today, aspirin (Chapter 36) is the most widely used analgesic in the world. Along with its pharmacologic cousins, nonsteroidal anti-inflammatory drugs (NSAIDs) and the antipyretic drugs acetaminophen and phenacetin, this group forms the backbone of pharmacologic pain treatment. Antipyretic analgesics exert their antinociceptive effects by the inhibition of cyclooxygenase, the rate-limiting enzyme in the production of prostaglandins, which are lipid-based compounds that sensitize nociceptors and regulate inflammation. There are several pharmacologic distinctions between NSAIDs and their counterparts, phenazone and acetaminophen. Whereas NSAIDs act both centrally and peripherally, making them effective topical agents for nociceptive inflammatory conditions, the primary site of enzyme inhibition for acetaminophen is in the central nervous system. Acetaminophen is also a weaker analgesic than NSAIDs and is largely devoid of anti-inflammatory effects.

The main drawback of nonopioid antipyretic analgesics is their ceiling effect, which can render them ineffective as stand-alone agents for severe pain. For cancer pain, the World Health Organization treatment paradigm advocates adding opioids to an analgesic regimen uncontrolled by NSAIDs, not replacing them. NSAIDs may act synergistically with opioids and have proven opioid-sparing effects. It is well acknowledged that aspirin, NSAIDs, and acetaminophen are more effective in treating nociceptive than neuropathic pain, although a significant proportion of neuropathic pain sufferers regularly take NSAIDs.

The second major concern about nonopioid antipyretic agents is side effects. For NSAIDs, these include bleeding, gastrointestinal ulceration, renal toxicity, and an increased risk of cardiovascular events. Although the use of cyclooxygenase-2 selective inhibitors like celecoxib and rofecoxib may attenuate the risk of bleeding and ulcers, the risk of renal failure and cardiovascular events from these drugs remains a significant cause of morbidity and mortality. These risks are significantly increased in elderly patients and with polypharmacy. In view of its more favorable safety profile, acetaminophen is often considered a first-line therapy ahead of NSAIDs, even for pain conditions associated with inflammation.

### Adjuvant Analgesics

Multiple evidence-based guidelines for the treatment of chronic pain states, particularly neuropathic pain, have been recently published. In general, these suggest that antidepressants and anticonvulsants should be the two first-line classes of medications for chronic neuropathic pain. Depending on the particular drug and condition, these medications have been demonstrated to provide significant pain relief above and beyond that observed with placebo in 20 to 40% of ideal pharmacologic candidates (i.e., number needed to treat is between 2.5 and 5 in randomized trials). Whereas opioids have shown similar efficacy for neuropathic pain, anticonvulsants and antidepressants carry a lower risk of serious adverse events (e.g., addiction) and long-term tolerance, rendering them preferable to opioids for long-standing noncancer pain (Table 29-3). In terms of efficacy, tricyclic antidepressants (TCAs) are superior to serotonin-norepinephrine reuptake inhibitors, which in turn are more effective than serotonin-specific reuptake inhibitors. Among the various TCAs, amitriptyline is the most studied but is probably comparable in efficacy to its metabolite nortriptyline and its cousin imipramine. However, the latter two drugs' more favorable side effect profiles (e.g., less sedation and anticholinergic activity) make them the preferred choices for neuropathic pain. In patients who cannot tolerate TCAs, serotonin-norepinephrine reuptake inhibitors such as duloxetine can be beneficial. In addition to neuropathic pain, antidepressants have also been shown to be effective in headache prophylaxis, chest pain, abdominal and pelvic pain, fibromyalgia, arthritis, and spinal pain.

Anticonvulsants are probably effective for neuropathic pain by virtue of their membrane-stabilizing-properties. Although anticonvulsant drugs may be slightly more effective than antidepressants for prototypical "lancinating-type" neuropathic pain, antidepressants may be more versatile in that they have proven benefit in myriad other pain conditions. Owing to their high efficacy and favorable side-effect profiles, gabapentin and its pharmacologic relative pregabalin are first-line agents for most forms of neuropathic pain. In addition to independent pain-relieving properties, these drugs may act synergistically with opioids, provide anxiolysis, and exhibit preemptive analgesic effects when administered before surgery.

When gabapentinoid drugs are ineffective or intolerable, alternative anticonvulsants that act through different cellular mechanisms such as lamotrigine and oxcarbazepine may be employed. For trigeminal neuralgia, carbamazepine remains the treatment of choice, although adverse effects, such as the risk of agranulocytosis, limit its utility for other conditions. Other classes of adjuvants that may be effective in certain contexts include topical creams (e.g., NSAIDs, capsaicin, lidocaine), *N*-methyl-D-aspartate antagonists (e.g., dextromethorphan), skeletal muscle relaxants (e.g., baclofen, cyclobenzaprine), cannabinoids, and antiarrhythmics (mexiletine). Topical lidocaine patches have been shown to reduce the pain and allodynia in patients with postherpetic neuralgia, and anecdotal evidence has suggested lidocaine may be useful in the treatment of certain types of back pain. Recently, a

## TABLE 29-3 ADJUVANT ANALGESIC DRUGS FOR CHRONIC PAIN

| DRUG | DOSAGE | INDICATIONS | ADVERSE EFFECTS | COMMENTS |
|---|---|---|---|---|
| **TRICYCLIC ANTIDEPRESSANTS** | | | | |
| Amitriptyline, imipramine, desipramine, nortriptyline | 10-150 mg/day | Peripheral neuropathy, postherpetic neuralgia, other types of peripheral neuropathic pain, central pain, facial pain, fibromyalgia, headache prophylaxis, irritable bowel syndrome, and chronic low back pain with or without radiculopathy | Sedation, dry mouth, confusion, weight gain, constipation, urinary retention, ataxia, cardiac conduction delay (QTc prolongation) | First-line agents for neuropathic pain and headache prophylaxis<br>Secondary amine drugs (e.g., nortriptyline) have fewer side effects than tertiary amines (e.g., amitriptyline)<br>Contraindicated in glaucoma |
| **SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS** | | | | |
| Venlafaxine | 75-225 mg/day | Peripheral neuropathy, headache prophylaxis | Sedation, dry mouth, constipation, ataxia, hypertension, hyperhidrosis | Dose adjustment in patients with renal dysfunction |
| Duloxetine | 60-120 mg/day | Peripheral neuropathy, fibromyalgia, chronic back pain | Sedation, dry mouth, constipation, hyperhidrosis | U.S. Food and Drug Administration (FDA) approved for fibromyalgia and diabetic neuropathy<br>Contraindicated in glaucoma |
| **ANTICONVULSANTS** | | | | |
| Gabapentin | 600-3600 mg/day | Peripheral neuropathy, postherpetic neuralgia, other types of peripheral neuropathic pain, central pain, pelvic pain, headache prophylaxis, radiculopathy, chronic postsurgical pain | Sedation, weight gain, dry mouth, ataxia, edema | First-line agent for neuropathic pain<br>FDA approved for postherpetic neuralgia<br>Effective preemptively for postoperative pain |
| Pregabalin | 150-600 mg/day | Peripheral neuropathy, postherpetic neuralgia, central pain, fibromyalgia | Sedation, weight gain, dry mouth, ataxia, edema | First-line agent for neuropathic pain<br>FDA approved for diabetic neuropathy, postherpetic neuralgia, fibromyalgia<br>Effective preemptively for postoperative pain<br>Same mechanism of action as gabapentin |
| Carbamazepine | 200-1600 mg/day | Facial neuralgias, diabetic neuropathy | Sedation, ataxia, diplopia, hyponatremia, agranulocytosis, diarrhea, aplastic anemia, hepatotoxicity, Stevens-Johnson syndrome | First-line agent and FDA approved for trigeminal and glossopharyngeal neuralgia<br>Contraindicated in patients with porphyria and atrioventricular conduction block |
| Topiramate | 50-400 mg/day | Headache prophylaxis, chronic low back pain with or without radiculopathy | Sedation, ataxia, diplopia, weight loss, diarrhea, metabolic acidosis, kidney stones | First-line agent and FDA approved for migraine prophylaxis<br>Often used as appetite suppressant |
| **CORTICOSTEROIDS (SYSTEMIC)** | | | | |
| Prednisone | 5-60 mg/day | Inflammatory arthritis, other inflammatory pain conditions (e.g., inflammatory bowel disease), traumatic nerve injury, complex regional pain syndrome | Myriad psychiatric, gastrointestinal, neurologic, and cardiac side effects; immunosuppression, weakness, edema, weight gain, elevated glucose, poor wound healing, others | Stronger evidence supports local (i.e., injection) administration<br>More effective for acute pain<br>Strong anti-inflammatory effects |
| **MISCELLANEOUS** | | | | |
| Muscle relaxants | Variable depending on drug | Skeletal muscle spasm, acute spinal pain, temporomandibular disorder<br>Baclofen effective for spasticity, dystonia, and trigeminal neuralgia | Sedation, ataxia, blurred vision, confusion, asthenia, xerostomia and other gastrointestinal effects, palpitations | First-line agents for acute back pain and skeletal muscle spasm |
| Lidocaine patch | 1-3 patches every 12 hr | Postherpetic neuropathy, peripheral neuropathy, other types of neuropathic and possibly myofascial pain associated with allodynia | Minimal systemic side effects when applied appropriately | Second-line agent and FDA approved for postherpetic neuralgia |
| Capsaicin cream | 0.025% applied 3 or 4 times per day | Postherpetic neuralgia, peripheral neuropathy and other types of neuropathic pain, chronic postsurgical pain, arthritis and other musculoskeletal conditions | Burning on application<br>Minimal systemic side effects when applied appropriately | FDA approved for arthritis<br>Second-line agent for postherpetic neuralgia and third-line agent for peripheral neuropathy<br>Single application 8% patch providing up to 3 months of pain relief was recently approved for postherpetic neuralgia |
| Cannabinoids | Variable depending on drug and delivery route | Strongest evidence is for multiple sclerosis<br>May be effective for peripheral neuropathy and other types of neuropathic pain spasticity | Myriad psychiatric, neurologic, and cardiac effects; xerostomia, abdominal pain, and other gastrointestinal effects | Fourth-line agent with narrow therapeutic index<br>Modest analgesic effect comparable to codeine |

high-concentration (8%) topical patch of capsaicin (the pungent chemical in chili pepper) has been approved for the treatment of postherpetic neuralgia. A single 1-hour application of the capsaicin patch can result in attenuation of pain for up to 12 weeks. Topical NSAIDs (e.g., diclofenac) have been shown to be effective in the short term for the treatment of osteoarthritis and other rheumatologic disorders and have been touted as having fewer adverse effects than systemic NSAIDs.

## Opioid Analgesics

Opioid analgesics, such as morphine, oxycodone, hydromorphone, and methadone, are the cornerstone of treatment for cancer pain (Table 29-4). Several randomized studies have also demonstrated their usefulness in noncancer pain conditions such as chronic osteoarthritis and neuropathic pain states. Maximizing the therapeutic effects of opioid analgesics requires careful attention to balancing the beneficial effects with the undesirable adverse effects. Understanding the clinical pharmacology of opioids, including their relative potency, duration of action, oral bioavailability, and pharmacokinetics, is essential for rational use (see Table 29-4). Their use for chronic pain management is limited primarily by their myriad side effects that include nausea, vomiting, constipation, sedation, itch, respiratory depression, and endocrine deficiency leading to sexual dysfunction and accelerated osteoporosis. Attentive treatment to opioid-induced side effects can facilitate dose titration, maximize analgesia, and minimize adverse effects. Aggressive management with stool softeners and agents that enhance bowel motility such as docusate, lactulose, and senna, can minimize constipation. Whereas most opioids are devoid of end-organ toxicity, an exception is meperidine. A metabolite, normeperidine, can accumulate after several days of treatment, causing myoclonus and anxiety; at higher concentrations, confusion, delirium, and seizures can ensue. Opioids that are predominantly renally eliminated, such as morphine, should be used with caution in patients with renal dysfunction. Two metabolites of morphine, morphine-6-glucuronide, which contains analgesic properties, and morphine-3-glucuronide, which may amplify pain in certain contexts, can accumulate in patients with renal dysfunction and are largely responsible for the adverse effects of morphine. Alternate drugs in such patients are fentanyl and methadone.

For treatment of acute pain (e.g., postoperative pain) or an acute exacerbation of chronic pain in hospitalized patients (e.g., sickle cell crisis), patient-controlled analgesia (PCA) provides a convenient means of administering opioids. Intravenous morphine, fentanyl, or hydromorphone is commonly administered using an infusion device designed to prevent overdose. With or without a basal infusion (which can be used to replace a sustained-release opioid in a patient who is NPO), the bolus dose, lockout time interval between doses, and the maximal dose per hour can be programmed in and adjusted based on clinical circumstances. PCA devices are safe and allow patients to control their pain management with less dependence on health care providers. Studies comparing PCA with conventional administration of opioids have generally found PCAs to be associated with better pain relief and higher satisfaction rates, albeit with larger amounts of medication consumed.

The long-term use of opioids can be associated with tolerance and physical dependence. Cross-tolerance among opioids is not complete, and a strategy that is often used when tolerance to an opioid is suspected is rotation to an alternate opioid drug. Although addiction (Chapter 33) to opioids when used

**TABLE 29-4 FORMULATIONS, DOSAGES, AND PHARMACOLOGIC INFORMATION ON COMMONLY PRESCRIBED OPIOIDS**

| DRUG | EQUIANALGESIC DOSAGE (ORAL UNLESS SPECIFIED) | READILY AVAILABLE ROUTES OF ADMINISTRATION | DURATION OF ACTION | COMMENTS |
|---|---|---|---|---|
| Morphine | 30 mg | IV, IM, PO, PR; SR formulation | 3-6 hr for short-acting, 8-12 hr for SR | Reference standard for all opioids<br>Renally excreted active metabolite |
| Oxycodone | 20 mg | PO, PR; SR formulation | 3-6 hr for short-acting, 8-12 hr for SR | Widely available in combination form with nonopioid analgesics; SR form popular among recreational users |
| Hydromorphone | 3-6 mg | PO, PR, IV, IM | 3-6 hr | Higher PO/IV conversion ratio than other opioids |
| Hydrocodone | 30-60 mg | PO | 3-6 hr | Wide variation in morphine equivalent dose<br>Most commonly prescribed opioid in U.S.<br>Typically used in combination form with nonopioid analgesic<br>Formulations containing <15 mg hydrocodone are schedule III in U.S. |
| Methadone | 2-20 mg | PO, PR, IV | 6-12 hr for pain | Morphine: methadone conversion varies according to dose and length of opioid use, ranging from 2 : 1 to >20 : 1 in patients on very high doses<br>Any physician with a schedule II DEA license may prescribe for pain<br>May take 5-7 days to reach steady state due to extended half-life (i.e., accumulation)<br>Electrocardiogram monitoring recommended with higher doses<br>Other properties such as NMDA receptor antagonism and reuptake inhibition of serotonin and norepinephrine may slow the development of tolerance and increase efficacy for neuropathic pain |
| Fentanyl | 12.5 µg/hr (TD)<br>800-1000 µg (TM)<br>200-400 µg (B) | TD, TM, B | 72 hr for TD; 1 hr-2 hr for TM and B | TD, TM, and B formulations may be useful in patients with poor bowel function<br>TD: wide variation in conversion ratios<br>Delivery system may be associated with fewer gastrointestinal side effects<br>TM and B: delivery systems associated with more rapid (10-min) onset than immediate-release oral opioids.<br>U.S. Food and Drug Administration (FDA) approved for breakthrough cancer pain in opioid-tolerant patients |
| Codeine | 200 mg | PO, PR | 3-6 hr | Often used in combination with nonopioid analgesics<br>Efficacy and side effects may be affected by rate of metabolism to morphine<br>Popular as cough suppressant |
| Propoxyphene | 200 mg | PO, PR | 3-6 hr | Wide variation in morphine equivalent dose<br>Often used in combination form with nonopioid analgesic<br>Toxic metabolite may accumulate with excessive use, especially in elderly patients<br>Weak antagonist at NMDA receptor |
| Meperidine | 300 mg | PO, PR, IV | 2-4 hr | Toxic metabolite may accumulate with excessive use, especially in patients with renal insufficiency<br>Associated with tachycardia and hypertension<br>May cause more "euphoria" than other opioids |
| Buprenorphine | 0.4 mg SL | SL, PR, IV, TD | 6-8 hr | Partial opioid agonist that may precipitate withdrawal in opioid-dependent patients<br>Lower abuse potential, and fewer psychomimetic effects, than pure agonists<br>Not readily reversed by naloxone<br>Schedule III drug in U.S.<br>Primary use of SL preparation is to treat addiction |

B = buccal; IV = intravenous; NMDA = *N*-methyl-D-aspartate; PO = oral; PR = rectal; SL = sublingual; SR = sustained release; TD = transdermal; TM = transmucosal.

for the treatment of chronic pain is reported to be relatively uncommon, guidelines for responsible prescribing of opioids have been published as a monograph by the Federation of State Medical Boards. The critical suggested steps in the management of chronic pain patients with opioids include appropriate patient evaluation, creating and maintaining clear and detailed documentation, creating a function-based treatment plan with well-defined patient goals that include an exit strategy, obtaining a written patient-physician agreement that includes informed consent and patient education, periodic review that focuses on progress toward functional goals, and making specialist referrals when managing difficult patients. Diversion of opioids and the increasing abuse of prescription opioids, particularly in teenagers and young adults, is another growing societal concern (Chapter 33).

Tramadol and tapentadol comprise part of a new class of analgesic drugs that have a dual mechanism of action. Tramadol is a weak agonist and inhibits the reuptake of norepinephrine and serotonin. Along with the usual side effects associated with opioids, seizures have been reported with tramadol, and adverse drug interactions can occur in patients taking warfarin sodium (Coumadin) and selective serotonin reuptake inhibitors (SSRIs). Tapentadol also has a dual mode of action as a μ–opioid agonist and a norepinephrine reuptake inhibitor. Nausea, dizziness, constipation, and sedation are reported side effects of this drug. Tramadol is presently approved for moderate to moderately severe pain, whereas tapentadol, which is currently a schedule II drug in the United States, is approved for moderate to severe acute pain.

Butorphanol, nalbuphine, and pentazocine are opioid agonist-antagonist drugs that can antagonize the actions of μ–opioid agonists and can cause psychotomimetic effects owing to their actions on the κ-opioid receptor. These drugs should be used with caution, particularly in patients receiving other μ–opioid agonists. Buprenorphine, a partial agonist at the μ–opioid receptor and an antagonist at other opioid receptors, is available as a sublingual pill that is approved for the treatment of opioid addiction. A transdermal formulation is approved in Europe for the treatment of chronic pain.

### Combination Therapies

Most clinical trials have studied the effects of individual drugs in specific chronic pain states. However, no one drug is universally effective, and often the drug only provides partial pain relief. In clinical practice, two or more drugs are often used in combination to achieve an additive beneficial effect or to decrease the adverse effects associated with the use of a single drug. The rational use of polypharmacy should include drugs that act at different sites in the pain signaling process or modulate different neurotransmitter systems, or both (Fig. 29-1). Although results are conflicting, a preponderance of recent randomized trials suggest that combination therapy with opioids and either anticonvulsants or antidepressants may be more effective than using either drug class as a stand-alone treatment.[3] Similarly, combining two adjuvant medication classes (e.g., gabapentin and nortriptyline) was recently shown to be more efficacious than giving either drug alone for neuropathic pain,[4] and combination treatment with pregabalin and celecoxib was found to be superior to monotherapy in a mixed population of patients with chronic low back pain.[5] Additional studies are needed to help develop guidelines for rational polypharmacy based on pain pathophysiology, mechanisms of action, and genetic medicine.

## Psychological Treatment

The relationship between pain and psychopathology is complex. The lifetime prevalence rate of coexisting psychiatric illness in chronic pain patients ranges from 50% to upward of 80%. Between 30% and 60% of chronic pain sufferers experience symptoms of depression, making it the most common comorbidity. For anxiety disorders and substance abuse, the coprevalence rates are about 30% and 10 to 15%, respectively.

Viewed from a different perspective, the relationship is even more striking. More than 60% of patients with major depression and more than half of all patients with anxiety and substance abuse disorders experience moderate to severe chronic pain. Although it is widely acknowledged that disease states and injuries that result in chronic pain can predispose patients to depression, anxiety, and even self-destructive behavior, what is less commonly appreciated is the effect preexisting psychiatric conditions have on pain perception. There is a plethora of literature demonstrating that coexisting psychopathology is a strong predictor for the development of chronic pain after an acute, traumatic event (e.g., back pain episode, surgery, motor vehicle crash).

It is necessary to screen all pain patients for psychological conditions that can adversely affect treatment (Table 29-5). Not only major psychiatric conditions such as depression and generalized anxiety but also maladaptive behaviors and secondary diagnoses such as somatization disorder and poor coping skills can negatively influence treatment. Psychological screening is mandated for pain patients being considered for neuromodulation (e.g., spinal cord stimulation), and many spine surgeons will defer surgery until major psychiatric issues are adequately addressed.

Relaxation techniques such as biofeedback, self-hypnosis, and guided imagery have proved effective in a wide array of acute and chronic pain conditions but may be especially useful in those with high levels of anxiety. Cognitive behavioral therapy is a highly structured form of psychotherapy predicated on the replacement of negative thought patterns and behaviors with more positive, constructive ones. These therapies may enhance the modulation of afferent pain signals. Ideal candidates include educated, motivated patients in whom distorted thinking (e.g., "catastrophization") and counterproductive behaviors serve to amplify pain behavior. In patients with personality disorders and ingrained maladaptive behaviors, long-term psychotherapy may be necessary.

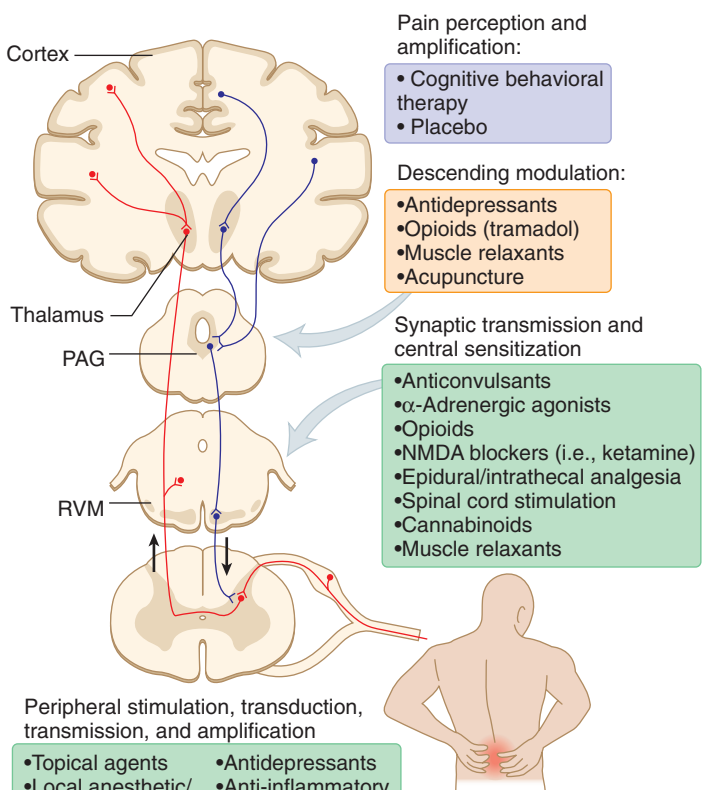


**FIGURE 29-1. Rational choice of combination therapies for pain should be based on the mechanisms of drug actions.** Combining drugs with disparate actions can have additive or synergistic analgesic effects and minimize adverse effects. NMDA = *N*-methyl-D-aspartate; PAG = periaqueductal gray; RVM = rostral ventromedial medulla.

**TABLE 29-5 PSYCHOSOCIAL FACTORS ASSOCIATED WITH CHRONIC PAIN**

| |
|---|
| Multiple pain complaints |
| Poor job satisfaction/low pay |
| Inadequate coping skills |
| Fear-avoidance behavior |
| Manual labor/physically stressful job |
| Obesity |
| Somatization |
| Smoking |
| Low baseline activity levels |
| Ongoing litigation |
| Low education level |
| Greater baseline disability |
| Anxiety |
| Depressed mood |
| Emotional distress |

## Interventional Therapies: Nerve Blocks, Neuromodulation, and Neurosurgery

### Nerve Blocks

Nerve blocks and injections may be done for therapeutic, diagnostic, and sometimes prognostic purposes (i.e., to select candidates for surgery or radio

frequency denervation). Mechanistically, injections performed with local anesthetic may work by releasing entrapped nerves, enhancing blood flow, and interrupting processes involved in central sensitization (i.e., "breaking the cycle of pain"). Additional benefits of adding corticosteroid to local anesthetic include blocking the inflammatory cascade, suppressing ectopic discharges from injured nerves, and inhibiting the synthesis of prostaglandins, some of which serve to sensitize nociceptors.

Nerve blocks are almost never a panacea for noncancer pain, but in appropriate candidates, blocks may provide intermediate-term pain relief, facilitate rehabilitative therapy, and improve quality of life for several weeks to months. Translating this relief into long-term improvement inevitably necessitates addressing the underlying etiologies and predisposing factors, which often entails physical therapy, psychotherapy, and rehabilitation. Injections that can afford benefit in well-selected individuals include trigger point injections with local anesthetic for myofascial pain and nerve blocks with corticosteroid for entrapment syndromes (e.g., carpal tunnel syndrome, occipital neuralgia). Among spinal injections, the strongest evidence is for epidural steroid injections in patients with radicular pain of less than 6 months' duration. Neurolytic procedures, such as celiac plexus neurolysis with alcohol or phenol, have been shown to provide significant pain relief lasting several months in patients with pain associated with cancer of the pancreas, liver, and gastrointestinal tract.

### Spinal Cord Stimulation

Spinal cord stimulation is an effective, minimally invasive neuromodulatory technique for managing a variety of chronic pain states refractory to more conservative measures. It was developed based on the gate-control theory, which postulates that activation of peripheral sensory A-fibers can attenuate pain signaling by slower-conducting pain C-fibers. Common indications include failed back surgery syndrome, complex regional pain syndromes, and outside of the United States, ischemic pain.

### Surgery

Surgical interventions are often advocated in chronic pain patients who have failed more conservative measures, but surgery is fraught with the same limitations as nerve blocks. A traumatic neuroma is an inexorable consequence of cutting or burning a nerve, formed as a result of unregulated and disorganized nerve regeneration. Neuromas have been shown to fire ectopic pain signals and are often quite painful. Hence, neurolytic procedures are rarely successful in the long-term treatment of neuropathic pain. Part of the challenge in deciding when operative therapy is indicated revolves around the difficulty involved in establishing a causative relationship between the targeted pathology and pain. Roughly 10% of women of reproductive age have endometriosis, but many patients with endometriosis have minimal symptoms, and pelvic pain is a frequent occurrence in young females with no detectable pathology. With respect to inguinal hernia repair and spinal decompression, the incidence of chronic postsurgical pain is inversely correlated with the size of the bowel and disc herniation, respectively. This illustrates that in many of these individuals, the targeted pathology may not have been the primary cause of symptoms. On a similar note, scar tissue is a predictable sequela of surgical treatment, but lysis of adhesions is only infrequently associated with long-term symptom palliation because of the high recurrence rate and absence of any means to correlate the presence of adhesions with pain. Not surprisingly, surgery done solely to remove a painful body part (e.g., hysterectomy, orchiectomy) rarely results in long-term benefit.

### Back Pain

Back pain is the leading cause of disability in people younger than 45 years in the industrialized world and thus deserves separate mention when discussing interventional therapies. In patients who present with serious spinal pathology (primarily infection, tumor, and trauma), decompression, stabilization, and fusion can be highly beneficial, but outcomes are strongly dependent on the primary pathology and patient. Decompression procedures done for spinal stenosis or radiculopathy are also effective for short-term relief, but the benefits diminish with time.[1,2] With respect to fusion or disc replacement done for axial pain associated with common degenerative changes, less than 40% of patients can expect a highly functional outcome.

## Physical Treatments

The use of "physical" therapies to provide pain relief and enhance function forms a cornerstone in the multimodal approach to the patient with pain. Physical therapists evaluate, educate, and provide minimally invasive and noninvasive procedural interventions to patients to help prevent and alleviate the pain and dysfunction associated with physical and mental maladies. These interventions include both addressing causative mechanisms of pain (e.g., core strengthening, correcting gait and postural abnormalities) and providing treatments (e.g., ultrasound, hot and cold packs, joint manipulation).

Exercise has been used for decades as a treatment for chronic pain and as a means to prevent injury. Exercise may work through a variety of mechanisms, including enhancing blood flow, releasing endorphins, exerting anti-inflammatory effects, activating descending inhibitory pathways, and improving sleep and mood. Whereas the largest body of research has been conducted in patients with spinal pain, benefits have also been demonstrated in those with fibromyalgia, headaches, arthritis, neuropathic pain, and cancer.

## Complementary and Alternative Therapies

Physicians are referring patients for complementary and alternative medical (CAM) treatments with increasing frequency, with utilization rates exceeding one third for certain conditions. CAM therapies have been used to treat myriad pain conditions, including cancer and noncancer pain and both neuropathic and nociceptive conditions (Chapter 38). Some of the most popular and studied CAM modalities are acupuncture, chiropractic, yoga, and dietary supplements, all of which have been shown in clinical trials to reduce pain and improve functional capacity in certain contexts. However, the effect size tends to be modest for these treatments, and there is little evidence to support the superiority of any one "proven" modality over another.

## Pain Management in Older Persons

Older adults often have varied and multiple pain conditions that exist with other comorbidities. Pharmacologic management of pain in this population can be challenging because of the potential for drug-drug and drug-disease interactions. The potential for drug-related adverse effects is the basis for the popular recommendation of "start low and go slow" in the titration of analgesic drugs. The potential interaction between anticoagulants, such as warfarin and aspirin, and NSAIDs can result in an increased risk for bleeding. Age-related decrease in hepatic blood flow and decreased first-pass effect can result in higher bioavailability of opioids, such as morphine. Significant interactions between analgesic drugs metabolized hepatically by CYP2D6, such as codeine, hydrocodone, oxycodone, tramadol, and antidepressants, may result in decreased metabolism and increased toxicity. Several drugs used for the management of chronic pain and their active metabolites, such as duloxetine, gabapentin, pregabalin, oxycodone, and tramadol, are primarily renally eliminated. Their dose should be adjusted accordingly. An updated guideline for the pharmacologic management of persistent pain in older persons based on a synthesis of the best available evidence has been recently published.

# FUTURE DRUGS AND PREVENTION OF PAIN

Much research is being done to develop new routes of drug administration, abuse-deterrent opioids, and novel nonopioid drug treatments, which can optimize outcomes and reduce risks and side effects for pharmacotherapy. Two other areas ripe for investigation are the development of drugs that exploit the unique genetic makeup of pain patients, and refining selection criteria for various therapies. The conceptual appeal of these and other endeavors is that treatment tailored to individuals is likely to result in greater benefit and less risk than the "shotgun" approach to pain treatment that is too often used.

Regenerative therapies, which seek to facilitate the body's ability to repair, replace, restore and regenerate diseased or damaged tissue, is another frontier in pain medicine. These treatments are currently in preliminary stages of development but may someday be used to treat central, joint, and spinal pain.

Finally, identifying patients at high risk of developing pain and employing strategies to either prevent pain or minimize the disease burden represent other areas that have been henceforth underinvestigated. In patients at high risk for chronic postsurgical pain (e.g., young patients with preexisting pain and psychological comorbidities), these measures might include the use of preemptive analgesics, such as NSAIDs and anticonvulsants, and employment of surgical techniques associated with less trauma. For patients with musculoskeletal complaints, this might entail educational initiatives, extensive rehabilitation, fall-reduction classes, and increased reimbursement for walking aids and wheelchairs.

Grade A


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## SUGGESTED READINGS


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