CHAPTER

78 Pain

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KEY POINTS

- Pain is transmitted in pathways involving the peripheral and central nervous systems.
- Specific terminology is used to characterize pain and pain syndromes.
- There is a high rate of psychiatric co-morbidity in patients with chronic pain.
- Psychiatric treatment can be effective for pain and the psychiatric co-morbidities of pain.
- Multimodal and multidisciplinary treatment facilitates provision of the highest quality care for chronic pain.

OVERVIEW

Pain, as determined by the International Association for the Study of Pain (IASP), is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] This chapter will describe the physiological aspects of pain transmission, pain terminology, and pain assessment; discuss the major classes of medications used to relieve pain; and outline the diagnosis and treatment of psychiatric conditions that often affect patients with chronic pain.

EPIDEMIOLOGY

Psychiatric co-morbidity (e.g., anxiety, depression, personality disorders, and substance use disorders [SUDs]) afflicts those with both non–cancer-related and cancer-related pain. Epidemiological studies indicate that roughly 30% of those in the general population with chronic musculoskeletal pain also have depression or an anxiety disorder.[2] Similar rates exist in those with cancer pain. In clinic populations, 50% to 80% of pain patients have co-morbid psychopathology, including problematic personality traits. The personality (i.e., the characterological or temperamental) component of negative affect has been termed *neuroticism*, which may be best described as "a general personality maladjustment in which patients experience anger, disgust, sadness, anxiety, and a variety of other negative emotions."[3] Frequently, in pain clinics, maladaptive expressions of depression, anxiety, and anger are grouped together as disorders of negative affect, which have an adverse impact on the response to pain.[4]

Rates of substance dependence in chronic pain patients are also elevated relative to the general population, and several studies have found that 15% to 26% of chronic pain patients have a co-morbid substance (e.g., illegal drugs or prescription medications) dependence disorder.[5] Prescription opiate addiction is a growing problem that affects approximately 5% of those who have been prescribed opiates for chronic pain (although good epidemiology studies are lacking). Other chapters in this textbook focus more specifically on SUDs. This chapter will concentrate on those with affective disorders and somatoform disorders in the setting of chronic pain.

While many chronic pain patients somatize and have difficulty adapting to it, a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) diagnosis of somatization disorder per se, is less frequently encountered by those who treat patients with chronic pain. The DSM-IV-TR accounts for this distinction by classifying the somatoform component of a pain disorder into several categories (such as pain disorder associated with psychological factors, pain disorder associated with psychological factors and a general medical condition, and somatization disorder).

PATHOPHYSIOLOGY OF PAIN TRANSMISSION

Detection of noxious stimuli (i.e., nociception) starts with the activation of peripheral nociceptors (resulting in somatic pain) or with the activation of nociceptors in bodily organs (leading to visceral pain).

Tissue injury stimulates the nociceptors by the liberation of adenosine triphosphate (ATP), protons, kinins, and arachidonic acid from the injured cells; histamine, serotonin, prostaglandins, and bradykinin from the mast cells; and cytokines and nerve growth factor from the macrophages. These substances and decreased pH cause a decrease in the threshold for activation of the nociceptors, a process called *peripheral sensitization*. Subsequently, axons transmit the pain signal to the spinal cord, and to cell bodies in the dorsal root ganglia (Figure 78-1). Three different types of axons are involved in the transmission of pain from the skin to the dorsal horn.

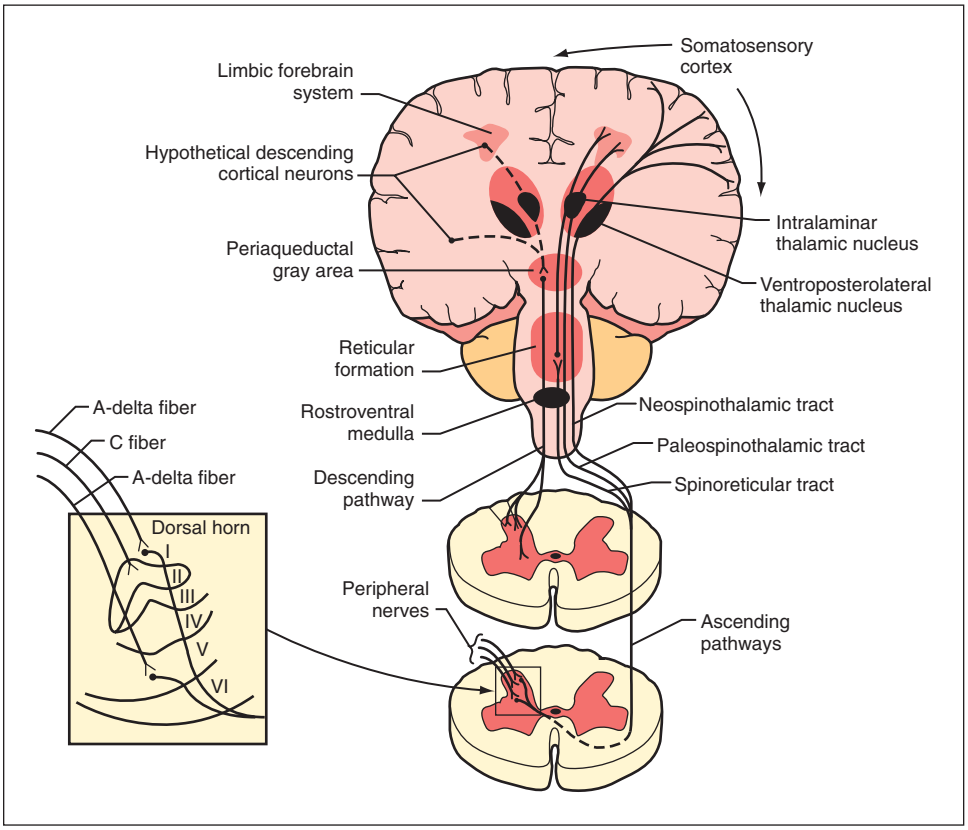

Figure 78-1 Schematic diagram of neurological pathways for pain perception. (From Hyman SH, Cassem NH: Pain. In Rubenstein E, Fedeman DD, editors: *Scientific American medicine: current topics in medicine,* subsection II, New York, 1989, Scientific American. Originally from Stern TA, Herman JB, editors: *Psychiatry update and board preparation,* 2004, McGraw-Hill.)

A-β fibers are the largest and most heavily myelinated fibers that transmit awareness of light touch. A-Δ fibers and C fibers are the primary nociceptive afferents. A-Δ fibers are 2 to 5 mcm in diameter and are thinly myelinated. They conduct "first pain," which is immediate, rapid, and sharp, with a velocity of 20 m/sec. C fibers are 0.2 to 1.5 mcm in diameter and are unmyelinated. They conduct "second pain," which is prolonged, burning, and unpleasant, at a speed of 0.5 m/sec.

A-Δ and C fibers enter the dorsal root and ascend or descend one to three segments before synapsing with neurons in the lateral spinothalamic tract (in the substantia gelatinosa in the gray matter) (see Figure 78-1). Second pain transmitted with C-fibers is integrally related to chronic pain states. Repetitive C-fiber stimulation can result in a progressive increase of electrical discharges from second-order neurons in the spinal cord. NMDA receptors play a role when prolonged activation occurs. This pain amplification is related to a temporal summation of second pain or "wind-up." This hyperexcitability of neurons in the dorsal horn contributes to central sensitization, which can occur as an immediate or as a delayed phenomenon. In addition to wind-up, central sensitization involves several factors: activation of A-beta fibers and lowered firing thresholds for spinal cord cells that modulate pain (i.e., they trigger pain more easily); neuroplasticity (a result of functional changes, including recruitment of a wide range of cells in the spinal cord so that touch or movement causes pain); convergence of cutaneous, vascular, muscle, and joint inputs (where one tissue refers pain to another); or aberrant connections (electrical short-circuits between the sympathetic and sensory nerves that produce causalgia). Inhibition of nociception in the dorsal horn is functionally quite important. Stimulation of the A-Δ fibers not only excites some neurons, but it also inhibits others. This inhibition of nociception through A-Δ fiber stimulation may explain the effects of acupuncture and transcutaneous electrical nerve stimulation (TENS).

The lateral spinothalamic tract crosses the midline and ascends toward the thalamus. At the level of the brainstem more than half of this tract synapses in the reticular activating system (in an area called the spinoreticular tract), in the limbic system, and in other brainstem regions (including centers of the autonomic nervous system). Another site of projections at this level is the periaqueductal gray (PAG) (Figure 78-2), which plays an important role in the brain's system of endogenous analgesia. After synapsing in the thalamic nuclei, pain fibers project to the somatosensory cortex, located posterior to the Sylvian fissure in the parietal lobe, in Brodmann's areas 1, 2, and 3. Endogenous analgesic systems involve endogenous peptides with opioid-like activity in the central nervous system (CNS) (e.g., endorphins, enkephalins, and dynorphins). Different opioid receptors (mu, kappa, and delta receptors) are involved in different effects of opiates. The centers involved in endogenous analgesia include the PAG, the anterior cingulate cortex (ACC), the amygdala, the parabrachial plexus (in the pons), and the rostral ventromedial medulla.

The descending analgesic pain pathway starts in the PAG (which is rich in endogenous opiates), projects to the rostral

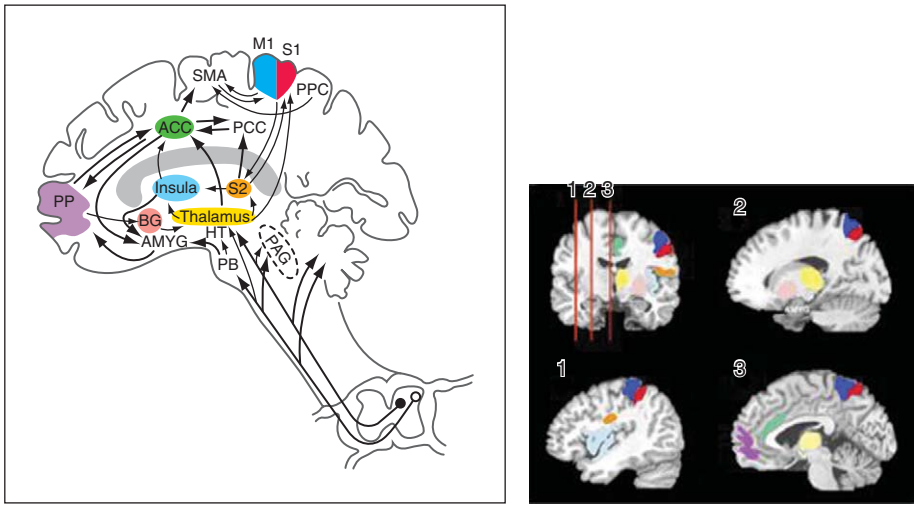

Figure 78-2 Pain processing in the brain. Locations of brain regions involved in pain perception are color-coded in a schematic **(A)** and in an example magnetic resonance imaging (MRI) scan **(B). A,** Schematic shows the regions, their interconnectivity, and afferent pathways. **B,** The areas corresponding to those in part **(A)** are shown in an anatomical MRI, on a coronal slice, and on three sagittal slices as indicated on the coronal slice. The six areas used in meta-analysis are primary and secondary somatosensory cortices (S1 and S2, red and orange), anterior cingulated (ACC, green), insula (blue), thalamus (yellow), and prefrontal cortex (PF, purple) Other regions indicated include primary and supplementary motor cortices (M1 and SMA), posterior parietal cortex (PPC), posterior cingulated (PCC), basal ganglia (BG, pink), hypothalamic (HT), amygdala (AMYG), parabrachial nuclei (PB), and periaqueductal gray (PAG). (Redrawn from Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: Human brain mechanisms of pain perception and regulation in health and disease, *Eur J Pain* 9:463-484, 2005.)

ventral medulla, and from there descends through the dorsolateral funiculus of the spinal cord to the dorsal horn. The neurons in the rostral ventral medulla use serotonin to activate endogenous analgesics (enkephalins) in the dorsal horn. This effect inhibits nociception at the level of the dorsal horn since neurons that contain enkephalins synapse with spinothalamic neurons. Additionally, there are noradrenergic neurons that project from the locus coeruleus (the main noradrenergic center in the CNS) to the dorsal horn and inhibit the response of dorsal horn neurons to nociceptive stimuli. The analgesic effect of tricyclic antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs) is thought to be related to an increase in serotonin and norepinephrine that inhibits nociception at the level of the dorsal horn, through their effects on enhancing descending pain inhibition from above.

CORTICAL SUBSTRATES FOR PAIN AND AFFECT

Advances in neuroimaging have linked the function of multiple areas in the brain with pain and affect. These areas (e.g., the ACC, the insula, and the dorsolateral prefrontal cortex [DLPFC]) form functional units through which psychiatric co-morbidity may amplify pain and disability (see Figure 78-2). These areas are part of the spinolimbic (also known as the medial) pain pathway,[6] which runs parallel to the spinothalamic tract and receives direct input from the dorsal horn of the spinal cord. The interactions among the function of these areas, pain perception, and psychiatric illness are still being investigated. The spinolimbic pathway is involved in descending pain inhibition (which includes cortical and subcortical structures), whose function may be negatively affected by the presence of psychopathology. This, in turn, could lead to heightened pain perception. Coghill and colleagues[7] have shown that differences in pain sensitivity between patients can be correlated with differences in activation patterns in the ACC, the insula, and the DLPFC. The anticipation of pain is also modulated by these areas, suggesting a mechanism by which anxiety about pain can amplify pain perception. The disruption or alteration of descending pain inhibition is a mechanism of neuropathic pain, which can be described as *central sensitization* that occurs at the level of the brain, a concept supported by recent neuroimaging studies of pain processing in the brains of patients with fibromyalgia.[8] The ACC, the insula, and the DLPFC are also laden with opioid receptors, which are less responsive to endogenous opioids in pain-free subjects with high negative affect.[9] Thus, negative affect may diminish the effectiveness of endogenous and exogenous opioids through direct effects on supraspinal opioid binding.

INTERACTIONS BETWEEN PAIN AND PSYCHOPATHOLOGY

The majority of patients with chronic pain and a psychiatric condition have an organic or physical basis for their pain. However, the perception of pain is amplified by co-morbid psychiatric disorders, which predispose patients to develop a chronic pain syndrome. This is commonly referred to as the *diathesis-stress model,* in which the combination of physical, social, and psychological stresses associated with a pain syn-

drome induces significant psychiatric co-morbidity.[4] This can occur in patients with or without a pre-existing vulnerability to psychiatric illness (e.g., a genetic or temperamental risk factor). Regardless of the order of onset of psychopathology, patients with chronic pain and psychopathology report greater pain intensity, more pain-related disability, and a larger affective component to their pain than those without psychopathology. As a whole, studies indicate that it is not the specific qualities or symptomatology of depression, anxiety, or neuroticism, but the overall levels of psychiatric symptoms that are predictive of poor outcome.[10] Depression, anxiety, and neuroticism are the psychiatric conditions that most often co-occur in patients with chronic pain, and those with a combination of pathologies are predisposed to the worst outcomes.

PAIN TERMINOLOGY

Acute pain is usually related to an identifiable injury or to a disease; it is self-limited, and resolves over hours to days or in a time frame that is associated with injury and healing. Acute pain is usually associated with objective autonomic features (e.g., tachycardia, hypertension, diaphoresis, mydriasis, or pallor).

Chronic pain (i.e., pain that persists beyond the normal time of healing or lasts longer than 6 months) involves different mechanisms in local, spinal, and supraspinal levels. Characteristic features include vague descriptions of pain and an inability to describe the pain's timing and localization. It is usually helpful to determine the presence of a dermatomal pattern (Figure 78-3), to determine the presence of neuropathic pain, and to assess pain behavior.

Neuropathic pain is a disorder of neuromodulation. It is caused by an injured or dysfunctional central or peripheral nervous system; it is manifest by spontaneous, sharp, shooting, or burning pain, which may be distributed along dermatomes. Deafferentation pain, phantom limb pain, complex regional pain syndrome, diabetic neuropathy, central pain syndrome, trigeminal neuralgia, and postherpetic neuralgia are examples of neuropathic pain. Qualities of neuropathic pain include hyperalgesia (an increased response to stimuli that are normally painful); hyperesthesia (an exaggerated pain response to noxious stimuli [e.g., pressure or heat]); allodynia (pain with a stimulus not normally painful [e.g., light touch or cool air]); and hyperpathia (pain from a painful stimulus with a delay and a persistence that is distributed beyond the area of stimulation). Both acute and chronic pain conditions can involve neuropathic processes in addition to nociceptive causes of pain.

Idiopathic pain, previously referred to as *psychogenic pain,* is poorly understood. The presence of pain does not imply or exclude a psychological component. Typically, there is no evidence of an associated organic etiology or an anatomical pattern consistent with symptoms. Symptoms are often grossly out of proportion to an identifiable organic pathology.

Myofascial pain can arise from one or several of the following problems: hypertonic muscles, myofascial trigger points, arthralgias, and fatigue with muscle weakness. Myo-

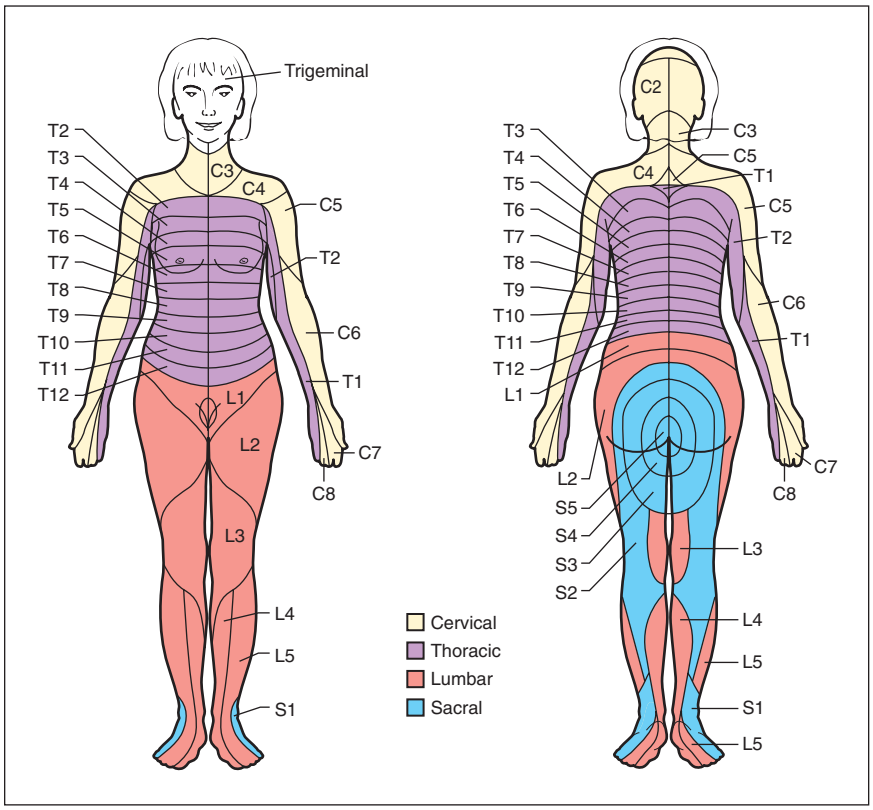

Figure 78-3 Schematic diagram of segmental neuronal innervation by dermatomes. (From Hyman SH, Cassem NH: Pain. In Rubenstein E, Fedeman DD, editors: *Scientific American medicine: current topics in medicine,* subsection II, New York, 1989, Scientific American. Originally from Stern TA, Herman JB, editors: *Psychiatry update and board preparation,* 2004, McGraw-Hill.)

fascial pain is generally used to describe pain from muscles and connective tissue. Myofascial pain results from a primary diagnosis (e.g., fibromyalgia) or, as more often is the case, a co-morbid diagnosis (e.g., with vascular headache or with a psychiatric diagnosis).

ASSESSMENT OF PAIN

The evaluation of pain focuses first on five questions: (1) Is the pain intractable because of nociceptive stimuli (e.g., from the skin, bones, muscles, or blood vessels)? (2) Is the pain maintained by non-nociceptive mechanisms (i.e., have the spinal cord, brainstem, limbic system, and cortex been recruited as reverberating pain circuits)? (3) Is the complaint of pain primary (as occurs in disorders such as major depression or delusional disorder)? (4) Is there a more efficacious pharmacological treatment? (5) Have pain behavior and disability become more important than the pain itself? Answering these questions allows the mechanism(s) of the pain and suffering to be pursued. A psychiatrist's physical examination of the pain patient typically includes examination of the painful area, muscles, and response to pinprick and light touch (Table 78-1).

The experience of pain is always subjective. However, several sensitive and reliable clinical instruments for the measurement of pain are available. These include the following:

1. The *pain drawing* involves having the patient draw the anatomical distribution of the pain as it is felt in his or her body.
2. The *Visual Analog Scale* and *Numerical Rating Scales* employ a visual analog scale from "no pain" to "pain as bad as it could possibly be" on a 10 cm baseline, or a 0 to 10 scale where the patient can rate pain on a scale of 1 to 10. It is also exquisitely sensitive to change; consequently the patient can mark this scale once a day or even hourly during treatment trials, if desired.
3. The *Pain Intensity Scale* is a categorical rating scale that consists of three to six categories for the ranking of pain severity (e.g., no pain, mild pain, moderate pain, severe pain, very severe pain, worst pain possible).

CORE PSYCHOPATHOLOGY AND PAIN-RELATED PSYCHOLOGICAL SYMPTOMS

In patients with chronic pain, heightened emotional distress, negative affect, and elevated pain-related psychological symptoms (i.e., those that are a direct result of chronic pain, and when the pain is eliminated, the symptoms disappear) can all be considered as forms of psychopathology and psychiatric co-morbidity, since they represent impairments in mental health and involve maladaptive psychological responses to medical illness (Figure 78-4). This approach melds methods of classification from psychiatry and behavioral medicine to describe the scope of psychiatric disturbances in patients with chronic pain. In pain patients the most common manifestations of psychiatric co-morbidity involve one or more core psychopathologies in combination with pain-related psychological symptoms. Unfortunately, not all patients and their symptoms fit neatly into DSM categories of illness.

Pain-related anxiety (which includes state and trait anxiety related to pain) is the form of anxiety most germane to pain.[11] Elevated levels of pain-related anxiety (such as fear of pain) also meet DSM-IV criteria for an anxiety disorder due to a general medical condition. Since anxiety straddles both domains of core psychopathology and pain-related psychological symptoms, the assessment of anxiety in a patient with

Table 78-1 General Physical Examination of Pain by the Psychiatrist

Physical Finding	Purpose of Examination
Motor deficits	Does the patient give-way when checking strength? Does the person try? Is there a pseudoparesis, astasia-abasia, or involuntary movements that suggests a somatoform disorder?
Trigger points in head, neck, shoulder, and back muscles	Are common myofascial trigger points present that suggest myofascial pain? Is there evoked pain (such as allodynia, hyperpathia, or anesthesia) that suggests neuropathic pain?
Evanescent, changeable pain, weakness, and numbness	Does the psychological complaint preempt the physical?
Abnormal sensory findings	Does lateral anesthesia to pinprick end sharply at the midline? Is there topographical confusion? Is there a nondermatomal distribution of pain and sensation that suggests either a somatoform or CNS pain disorder? Is there an abnormal sensation that suggests neuropathy or CNS pain?
Sympathetic or vascular dysfunction	Is there swelling, skin discoloration, or changes in sweating or temperature that suggest a vascular or sympathetic element to the pain?
Uncooperativeness, erratic responses to the physical examination	Is there an interpersonal aspect to the pain, causing abnormal pain behavior, as in somatoform disease?

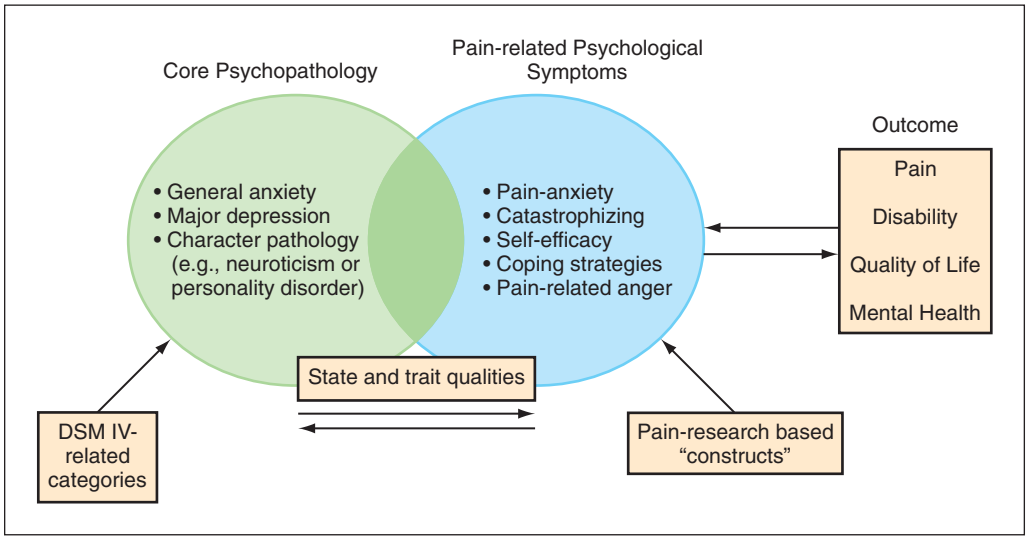

Figure 78-4 Common psychiatric symptoms in patients with chronic pain.

chronic pain (as detailed below) must include a review of manifestations of generalized anxiety as well as pain-specific anxiety symptoms (e.g., physiological changes associated with the anticipation of pain).

Poor coping skills (often involving passive responses to chronic pain [e.g., remaining bed-bound] and mistakenly assuming that chronic pan is indicative of ongoing tissue damage), catastrophization (with cognitive distortions that are centered around pain), and low self-efficacy (i.e., with a low estimate by the patient of what he or she is capable of doing) are linked with pain-related psychological symptoms and behaviors.[12] Poor copers employ few self-management strategies (such as using ice, heat, or relaxation strategies). A tendency to catastrophize often predicts poor outcome and disability, independent of other psychopathology, such as major depression. The duration of chronic pain and psychiatric co-morbidity are each independent predictors of pain intensity and disability. High levels of anger (which occur more often in men) can also explain a significant variance in pain severity.[13]

PAIN AND CO-MORBID PSYCHIATRIC CONDITIONS

Virtually all psychiatric conditions are treatable in patients with chronic pain, and the majority of patients who are provided with appropriate treatment improve significantly. Many physicians who treat pain patients often do not realize that this is the case. Of the disorders that most frequently afflict patients with chronic pain, major depression and anxiety disorders are the most common; moreover, they have the best response to medications. Whenever possible, medications that are effective for psychiatric illness and that have independent analgesic properties should be used. *Independent analgesia* refers to the efficacy of a pain medication (such as a TCA for neuropathic pain), which is independent of its effect on mood.[14]

Regardless of the type of psychopathology present, improvement in psychiatric symptoms results in a reduction of pain levels, in greater acceptance of the chronicity of pain, in improved function, and in an improved quality of life. Chronic pain may precipitate or worsen psychopathology and psychopathology may worsen pain. There is good evidence that psychiatric co-morbidity can be successfully treated, even if pain does not improve. It is important for the physician who treats pain to recognize psychiatric illness early in the course of chronic pain and to treat both conditions. In general, as with most psychiatric illnesses, a combination of pharmacological and psychotherapeutic treatments is more effective in treating depression and anxiety in pain patients than is pharmacological treatment alone.

Major Depression

The diagnosis and treatment of major depression in a patient with chronic pain is not significantly different from the approach to major depression in a patient with another medical illness. As in other patient groups, the combination of medications and cognitive-behavioral therapy (CBT) yields the best outcome.

Symptoms

Major depressive disorder (MDD) can be diagnosed by DSM-IV or similar research criteria in approximately 15% of those who suffer from chronic pain and in 50% of patients in chronic pain clinics. Recurrent affective illness, a family history of depression, and other psychiatric conditions (e.g., anxiety or substance use disorders) are often present. MDD can be distinguished from situational depression (also termed *demoralization* or an *adjustment disorder with depressed mood*) by the triad of persistently low mood, neurovegetative symptoms, and changes in self-attitude that last at least 2 weeks.[15] It may be important to distinguish which neurovegetative signs (such as sleep abnormalities) are the result of pain and which are the result of depression. However, given the high rate of co-morbid depression in chronic pain patients, it is prudent to err on the side of attributing neurovegetative symptoms to depression, particularly if they are accompanied by changes in mood or self-attitude. MDD is a serious com-

plication of persistent pain; if not treated effectively it will reduce the effectiveness of all pain treatments. Even low levels of depression ("subthreshold depression") may worsen the physical impairment associated with chronic pain, and it should be treated.

Medication Treatment

There is some evidence that pain patients with MDD are more treatment-resistant, particularly when their pain is not effectively managed.[16] In general, the first-line agent for a patient in pain is an agent with independent analgesic properties. Among the antidepressants these include the TCAs and SNRIs (duloxetine and venlafaxine). Each has shown efficacy in a variety of neuropathic pain conditions. The details of prescribing a specific antidepressant are covered elsewhere in this text.

Selective Serotonin Reuptake Inhibitors. Since the introduction of fluoxetine (Prozac) in 1987, many selective serotonin reuptake inhibitors (SSRIs) have been developed. The antidepressant efficacy and low side-effect profile of SSRIs have made them the most widely prescribed class of antidepressants. Pain patients whose depression responds to an SSRI may have less pain, a finding that is attributable to improvements in the affective components of their pain; there is little evidence to support the independent analgesic activity of SSRIs. SSRIs should not be prescribed in conjunction with tramadol, because of the heightened risk of seizures.

Other Antidepressants. Bupropion and mirtazapine are atypical antidepressants with unique mechanisms of action. Some preliminary evidence indicates that they have analgesic properties, but further study is required. Bupropion is particularly useful in pain patients because of its energizing effects that lessen fatigue.

Coping and Psychotherapy

Improving coping skills is a mainstay of treatment for any of the psychiatric conditions associated with chronic pain. In addition to improving psychological distress, use of active coping strategies improves pain and function (e.g., remaining active despite pain). Coping involves having adaptive defense mechanisms to negotiate maladaptive thoughts and feelings that arise in response to pain.

The psychodynamic aspects of coping involve conflicts over autonomy and care. Regression can be manifest as noncompliance, help-rejecting complaining, and behaviors akin to the metaphorical "cutting off your nose to spite your face." Pain may make both patients and physicians appear hateful; psychiatrists are well served by clarifying how these problems get played out in the physician-patient relationship. To help the patient cope, the psychiatrist must be sensitive to the unconscious feelings of the patient; in addition, denial must be managed, and family counseling, relaxation, exercise, physical rehabilitation, and pharmacotherapy should be considered.

CBT in conjunction with antidepressant therapy is the most efficacious treatment for MDD, including MDD that worsens in the setting of chronic pain. Typically, CBT improves coping skills and self-efficacy, and diminishes catastrophization. When CBT is used the patient must be properly motivated, have sufficient insight, and have the ego strength to tolerate challenges to his or her beliefs. CBT in pain patients focuses on the thoughts and cognitive distortions that surround chronic pain (such as fear of re-injury, the belief that the only meaningful life is one without pain, and thoughts that the patient's pain is not taken seriously by others).

Anxiety Disorders

Symptoms

Anxiety disorders encompass a broad spectrum of disorders (including generalized anxiety disorder [GAD], panic disorder, obsessive-compulsive disorder [OCD], and posttraumatic stress disorder [PTSD]). In addition, pain-related anxiety is the primary manner in which anxiety disorders are manifest in those with chronic pain.[11] Anxiety is prevalent in chronic pain clinics, with 30% to 60% of the patients experiencing pathological anxiety.[17] Among the anxiety disorders, GAD is the condition that most often afflicts pain patients. More than 50% of patients with anxiety disorders also have a current or past history of MDD or another psychiatric disorder. Alcohol and substance abuse commonly accompany chronic pain; consequently, recognition and treatment of co-morbid depression and substance abuse are critical to long-term treatment outcome.

In pain patients, situational (state) anxiety may be centered on the pain itself and its negative consequences (pain-anxiety). Patients may have conditioned fear, believing that activities will cause uncontrollable pain, causing avoidance of those activities. Pain may also activate thoughts that a person is seriously ill.[11] Questions such as the following can be helpful: "Does the pain make you panic? If you think about your pain, do you feel your heart beating fast? Do you have an overwhelming feeling of dread or doom? Do you experience a sense of sudden anxiety that overwhelms you?"

Anxiety amplifies both the perception and complaints of pain through several bio-psycho-social mechanisms (e.g., sympathetic arousal that lowers the nociceptive threshold, increased firing of ectopically active pain neurons, excessive focusing on pain symptoms, and implementation of poor coping skills). Patients with pathological anxiety are often restless, fatigued, irritable, and concentrate poorly. They may also have muscle tension and sleep disturbances.

Treatment

Overall, CBT demonstrates the best treatment outcomes for anxiety disorders, including pain-specific anxiety in chronic pain patients. Further improvement can be obtained with relaxation therapy, meditation, and biofeedback. Physical therapy by itself, with no other psychological treatment, is an effective therapy for addressing the fear of pain (termed *kinesiophobia*, the fear of movement because of pain). A flexibility program addresses muscle disuse (which by itself creates pain) and imparts several psychological insights: activity and function can be improved, despite high levels of pain; it is more meaningful to be active with pain than to remain inactive with pain; and fear of pain and reinjury can be dimin-

ished. Antidepressants are effective, but many need to be used at higher doses than are typically prescribed for depression. Anxiolytics (such as benzodiazepines and buspirone) are most useful in the initial stages of treatment. However, the side effects and potential for physiological dependency make them a poor choice for long-term treatment.

Antidepressants

Antidepressants may take 2 to 4 weeks until improvement is noted. To improve compliance, escalation of doses must be slow, because anxious patients tolerate side effects poorly. Antidepressants reduce the overall level of anxiety and prevent anxiety or panic attacks, but they have no role in the treatment of acute anxiety. Among antidepressants the SSRIs are most effective. Effective doses are often higher than those used for depression. Of the SNRIs, both venlafaxine and duloxetine have demonstrated efficacy in GAD.[18,19]

Somatoform Disorders

Classification

The somatoform disorders comprise a group of disorders in which complaints and anxiety about physical symptoms are the dominant features. These complaints exist in the absence of sufficient organic findings to explain the extent of a person's pain. Most often there is a physical basis (including functional pathology, such as neuropathic pain) for at least a portion of the pain complaints, in which symptom-reporting is magnified by somatizing. Somatization is best thought of as a process. The spectrum of somatization includes amplification of symptoms, which entails "focusing upon the symptoms, racking with intense alarm and worry, extreme disability, and a reluctance to relinquish them."[20] Pain-related psychological symptoms amplify pain perception and disability. Hence, there is a tremendous overlap between the somatoform component of a chronic pain syndrome and other psychiatric co-morbidities. Four somatoform disorders may involve pain: somatization disorder, conversion disorder, hypochondriasis, and pain disorder (with or without a physical basis for pain). Somatoform disorders without any physical basis for pain are estimated to occur in 5% to 15% of patients with chronic pain who receive pain treatment.[21]

Symptom Presentation

Among somatizers, pains in the head or neck, epigastrium, and limbs predominate. Visceral pains from the esophagus, abdomen, and pelvis are associated with a high rate of psychiatric co-morbidity, particularly somatoform disorders, which can be challenging to diagnose.[22] Missed ovarian cancers, neuropathic pain following inflammatory disorders, and referred pain are often overlooked because of the nonspecific presentations of visceral pain. Sufferers from somatoform disorders often have painful physical complaints and excessive anxiety about their physical illness. The most common co-morbid conditions among somatoform-disordered pain patients are MDD and anxiety disorders. Patients with somatization disorder consume health care resources at nine times the rate of the average person in the United States.

Treatment Concepts

Among sufferers of somatoform disorders, most pain complaints are ill-defined, and a psychiatric diagnosis is often particularly difficult to establish. The treatment approach is similar across the spectrum of somatoform disorders, and the psychiatrist plays a key role in the coordination of care. First, the psychiatrist must work closely with the patient's other physicians to establish the physical basis or diagnosis for the pain, if any. The treatment team must agree on which symptoms, or to what degree the symptoms, are caused by structural or neuropathic pathology. This agreement involves a consensus among the providers not to aggressively pursue (with testing, medication, or procedural treatment) every pain or physical complaint. Other co-morbid psychiatric illnesses must be identified and treated. CBT is used to help the patient appreciate the connections between thoughts, emotions, perceived pain, and pain behaviors. This treatment involves a gradual escalation of activity, with continuous reassurance given that an increase in pain does not signal worsening of the patient's underlying physical condition (if any).

Conversion Disorder

Conversion disorder may be manifest as a pain syndrome with a significant loss of or alteration in physical function that mimics a physical disorder. Conversion symptoms may include paresthesia, numbness, dysphonia, dizziness, seizures, globus hystericus, limb weakness, sexual dysfunction, or pain. If pain or sexual symptoms are the sole complaints, the diagnosis is pain disorder or sexual pain disorder, rather than conversion disorder. Pain, numbness, and weakness often form a conversion triad.

Psychological factors are judged to be etiological for the pain when a temporal relationship between the symptoms and a psychosocial stressor exists; in addition, the person must not intentionally produce his or her symptom. A mechanism of primary or secondary gain needs to be evident before the diagnosis can be confirmed. Presence of *la belle indifference* and histrionic personality traits has little value in making or excluding the diagnosis of conversion. A "conversion V" on the Minnesota Multiphasic Personality Inventory (MMPI) identifies the hypochondriacal traits and the relative absence of depression that often accompanies conversion.

Hypochondriasis

Hypochondriasis involves the persistent belief that one has a serious illness, despite extensive medical evaluation to the contrary. Head and orofacial pains, cardiac and gastrointestinal pains, and feelings of pressure, burning, and numbness are common hypochondriacal concerns. Care of the hypochondriac begins with a complete history and a comprehensive differential diagnosis. The persistence of vague complaints helps to rule out the most serious diseases, and to set the stage for an alliance with the patient by demonstrating an open mind. A pain drawing may help reveal psychotic somatic beliefs. The psychiatrist should reassure, and not reject, the patient.

Pain Disorder

Pain disorder is defined in DSM-IV as a syndrome in which the focus of the clinical presentation is pain that causes significant impairment in occupational or social function, induces marked distress, or both. Organic pathology, if present, does not explain the extent of pain complaints or the degree of associated social and occupational impairment. Pain disorder has three subtypes: psychological (in which psychological factors play the primary role in the onset, severity, exacerbation, or maintenance of the pain); nonpsychiatric pain associated with a general medical condition; and combined type (pain associated with psychological factors and a general medical condition).

Pain disorder has been variously called *psychogenic pain disorder*, *somatoform pain disorder*, and *pain behavior*. When behavioral disability predominates, chronic pain syndrome is the behavioral description of this same syndrome. The meandering history of nomenclature is best understood as reflecting the mix of pain behaviors, as well as interpersonal and affective characteristics, that emphasize disability and entreat attention from others. Psychological antecedents of this syndrome may include a history of physical abuse, counterdependent personal relationships, a family history of alcoholism, and a personal developmental history of attachment problems. Co-morbid diagnoses (particularly depression, anxiety, and substance abuse) should be sought. Treatment must address the triad of self-defeating behavior, affective dysfunction, and psychodynamic conflicts, which causes poor coping, disability, and disrupted rehabilitation efforts.

Factitious Disorder with Physical Symptoms

Factitious disorder with physical symptoms involves the intentional production or feigning of physical symptoms. Onset is usually in early adulthood with successive hospitalizations forming a life-long pattern. The cause is a psychological need to assume the sick role, and as such, the intentional production of painful symptoms distinguishes factitious disorder from somatoform disorders. Renal colic, orofacial pain, and abdominal pain are three of the common presentations for factitious disorder; of these, abdominal pain and a scarred belly herald the diagnosis most often. Despite the seeming irrationality of the behavior, those with factitious disorder are not psychotic.

Pain may be described as occurring anywhere in the body, and the patient often uses elaborate technical detail to intrigue the listener with *pseudologia fantastica*. Multiple hospitalizations under different names in different cities, inconclusive invasive investigations and surgery, lack of available family, and a truculent manner are characteristic features of this disorder. Unfortunately, there is no effective treatment.

GENERAL PRINCIPALS OF MULTIMODAL ANALGESIA

In the medication management of chronic pain, multimodal analgesia is the preferred method, since very commonly multiple receptor systems must be targeted to achieve optimal pain control. By logical extension, successful treatment of chronic pain typically involves the use of more than one medication, nerve blocks, physical therapy, and relaxation or biofeedback techniques (i.e., treatment is conducted by a multidisciplinary team or by an interdisciplinary pain medicine program). In general, treatment goals are reports of pain less than 5 out of 10 and an improvement in function. Typically, this corresponds to a 30% to 50% long-term improvement in chronic pain and an improved quality of life. Studies have shown that at a level of 4 out of 10 or below, most patents are able to perform most of their activities of daily living with satisfaction. A 30% improvement in pain has been shown to be the level that is clinically meaningful, a level at which most patients will feel significantly better. Many of the nerve blocks (such as epidural steroid injections) are effective for acute exacerbations of chronic pain. But their relatively short duration of efficacy (2 to 6 weeks on average) makes them inadequate for the long-term management of chronic pain, if they are used as the only treatment modality. Interventional procedures with longer-term efficacy include spinal cord stimulation, radiofrequency lesioning, and intrathecal pump implantation.

Major Medication Classes

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are useful for acute and chronic pain (such as pain due to inflammation, muscle pain, vascular pain, or posttraumatic pain). NSAIDs are generally equally efficacious (whether they are nonselective or COX-2 inhibitors) and they have similar side effects, but there is great individual variability in response across the different NSAIDs (Table 78-2). Ketorolac (up to 30 mg every 6 hours) intramuscularly (IM) or intravenously (IV) followed by oral dosing has a rapid onset and a high potency, enabling it to be substituted for morphine (30 mg of ketorolac is equivalent to 10 mg of morphine). It should be used for no more than 5 days.

Side Effects. Most NSAIDs can cause bronchospasm in aspirin-sensitive patients, induce gastric ulcers, interact with angiotensin-converting enzyme (ACE) inhibitors (thereby contributing to renal failure), precipitate lithium toxicity, and impair renal function with long-term use. NSAIDs can elevate blood pressure in patients treated with β-blockers and diuretics. The COX-2 inhibitors (e.g., celecoxib) have a lower incidence than nonselective NSAIDs of ulcer disease in the first year of treatment, but not necessarily beyond this time frame.

Muscle Relaxants

These are useful for acute and chronic musculoskeletal pain. Their exact mechanism of action is unknown and mechanisms likely differ among the various compounds. In general, they are thought to enhance inhibition of descending pain pathways. Some of the most frequently prescribed include baclofen (an antispasticity agent), cyclobenzaprine (Flexeril), metaxalone (Skelaxin), orphenadrine (Norflex), and tizanidine (Zanaflex).

Table 78-2 Properties of Aspirin and Nonsteroidal Antiinflammatory Drugs

Drug	Dose (mg)	Dosage Interval (hr)	Daily Dose (mg/day)	Peak Effect (hr)	Half-Life (hr)
Aspirin	81-975	4	2400	0.5-1	0.25
Celecoxib	100-200	12	400	1	11
Diclofenac	25-75	6-8	200	2	1-2
Diflunisal	250-500	12	1500	1	13
Etodolac acid	200-400	6-8	1200	1-2	7
Meloxicam	7.5-15	24	15	2	15-20
Flurbiprofen	50-100	6-8	300	1.5-3	3-4
Ibuprofen	200-800	6-8	2400	1-2	2
Indomethacin	25-75	6-8	150	0.5-1	2-3
Ketoprofen	25-75	6-8	300	1-2	1.5-2.0
Ketorolac*					
Oral	10	6-8	40	0.5-1	6
Parenteral	60 load, then 30	6-8	120	0.5	6
Choline magnesium trisalicylate	500-1000	12	3000	1	2-12
Nabumetone	1000-2000	12-24	2000	3-5	22-30
Naproxen	500 load, then 250-375	6-8	1000	2-4	12-15
Oxaprozin	60-1200	24	1200	2	3-3.5
Piroxicam	40 load, then 20	24	20	2-4	36-45
Sulindac	150-200	12	400	1-2	7-18
Tolmetin	200-600	8	1800	4-6	2

Adapted from *Tarascon pocket pharmacopoeia,* California, 2006, Tarascon Publishers.
*Use no longer than 5 days.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are one of the primary medications used to treat neuropathic pain syndromes; TCAs have both independent analgesic properties and effects as adjuvant agents. A series of studies by Max and others[14] have illustrated the analgesic properties of TCAs, which are independent of their effects on improving depression. TCAs have been shown to be effective for the pain associated with diabetic neuropathy, for chronic regional pain syndromes, for chronic headache, for post-stroke pain, and for radicular pain. While the early studies were done with amitriptyline and desipramine, subsequent studies have confirmed that other TCAs also have equivalent analgesic properties. Of note, the typical doses for the analgesic benefit of TCAs (25 to 75 mg) are lower than the doses generally used for antidepressant effect (150 to 300 mg). Nevertheless, there is a dose-response relationship for analgesia, and some patients benefit from a TCA used in the traditional antidepressant dose range, in conjunction with blood level monitoring. A TCA and an anticonvulsant are often combined for the treatment of chronic pain, and this combination facilitates treatment of mood disorders. Since pain patients are frequently on a variety of medications that may potentially increase TCA serum levels, the value of blood level monitoring, even at low doses, cannot be understated.

Serotonin-Norepinephrine Reuptake Inhibitors

The serotonin-norepinephrine reuptake inhibitors (SNRIs) are a newer group of antidepressants, which, like the TCAs, act by inhibiting serotonin and norepinephrine reuptake. Venlafaxine and duloxetine are the most familiar drugs in this category; they have less alpha-1, cholinergic, or histamine inhibition than the TCAs. This results in fewer side effects than the TCAs, with equivalent antidepressant and potentially equal analgesic benefits. Placebo-controlled studies have demonstrated efficacy in neuropathic pain for both venlafaxine and duloxetine.

Structurally, venlafaxine is similar to tramadol, and in mice, venlafaxine demonstrates opioid-mediated analgesia that is reversed by naloxone. Duloxetine has a Food and Drug Administration indication for both diabetic peripheral neuropathic (DPN) pain and for MDD. Thus, it is an excellent choice for pain patients with psychiatric co-morbidity who have failed to respond to a TCA. It has also shown efficacy in fibromyalgia and GAD. It is started at 30 mg a day for a week (or 20 mg in the elderly), and then increased to 60 mg a day. Up to 120 mg a day can be prescribed for DPN. The most common side effects are nausea and sedation. Its metabolism is similar to that of venlafaxine. Many patients are unable to tolerate the side effects of TCAs, so both venlafaxine and duloxetine are promising agents in patients with co-morbid MDD and chronic pain.

Anticonvulsants

Blocking abnormally high-frequency and spontaneous firing in afferent neurons, in the dorsal horn, and in the thalamus is the putative mechanism for the efficacy of anticonvulsants with regard to pain. The consequence of blocking the hyperexcitability of low-threshold mechanoreceptive neurons in the brain is pain relief. Anticonvulsants are used in this population primarily for treatment of neuropathic pain.

Opioids

Acute, severe, and unremitting pains in cancer patients, as well as non–cancer-related chronic pain, which have been refractory to other medication modalities typically requires treatment with opioids. At times, opioids are the most effective treatment for chronic, nonmalignant pain, such as the pain associated with postherpetic neuralgia, degenerative disorders, and vascular conditions. Nociceptive pain and absence of any co-morbid drug abuse have been associated with long-term opioid treatment efficacy. Morphine is often the initial opioid of choice for acute and chronic pain because it is well known to most physicians and has a good safety profile. Beyond these starting points, the basic principles of opioid treatment are outlined in Tables 78-3 and 78-4.

Tramadol deserves special mention because it does have weak mu-opioid receptor activity, but it is not classified as a controlled substance in the United States. It also has SNRI

Table 78-3 Guidelines for Opioid Maintenance

- Maintenance opioids should be considered only after other methods of pain control have been proven unsuccessful. Alternative methods (which typically include use of NSAIDs, anticonvulsants, membrane-stabilizing drugs, monoaminergic agents, local nerve blocks, and physical therapy) vary from case to case.
- Opioids should not be prescribed for addicts unless there is a new major medical illness (e.g., cancer or trauma) accompanied by severe pain. In such cases, a second opinion from another physician (a pain medicine or addiction specialist) is suggested.
- If opioids are prescribed for longer than 3 months, the patient should have a second opinion, plus a follow-up consultation at least once per year. Monitoring with a urine toxicology screen, at least yearly, is also recommended.
- One pharmacy and one prescriber should be designated as exclusive agents.
- Dosages of opioids should be defined, as should expectations of what will happen if there are deviations from it. For example, abuse will lead to rapid tapering of the drug and entry into a detoxification program. There should be no doubt that the physician will stop prescribing the drug.
- Informed consent as to the rationale, risks, benefits, and alternatives should be documented.
- The course of treatment (in particular, the ongoing indications, changes in the disease process, efficacy, and the presence of abuse, tolerance, or addictive behavior) should be documented.

Table 78-4 Opioid Potencies and Special Features

Drug	Parenteral (mg equivalent)	Oral (mg)	Duration (hr)	Special Features
Morphine	10	30	4	Morphine sulfate controlled release has 12-hr duration
Codeine	120	200	4	Ceiling effect as dose increases, low lipophilic
Oxycodone	4.5	30	4	Every 12 hr oxycontin (10, 20, 40 slow release mg)
Hydromorphone	2	8	5	Suppository 6 mg = 10 mg parenteral morphine
Levorphanol	2	4	4	Low nausea and vomiting, low lipophilic
Methadone	5	10	2-12	Cumulative effect; day 3-5 decrease respiration; equianalgesic ratio varies considerably
Meperidine	100	300	3	κ, proconvulsant metabolite, peristaltic slowing and sphincter of Oddi decrease
Fentanyl	0.1	25 μg SL	1 (patch 72 hr)	50-μg patch = 30 mg/day morphine IM/IV
Sufentanil	Not recommended	15 μg SL	1	High potency with low volume of fluid
Propoxyphene	Not available	325	4	High dose leads to psychosis
Pentazocine	60	150	3	κ, σ agonist-antagonist, nasal 1 mg q1-2hr
Butorphanol	2	Not available 3 (IM), 2 (NS)	μ, κ, σ, agonist-antagonist, nasal 1 mg q1-2hr	
Buprenorphine	0.3	4	4-6	Partial agonist
Tramadol	Not available	150	4	μ agonist, decreased reuptake 5-HT and NE, P450 metabolism
Nalbuphine	10	Not available	3	Agonist-antagonist

5-HT, 5-hydroxytryptamine; *IM,* intramuscular; *IV,* intravenous; *NE,* norepinephrine; *NS,* nasal; *SL,* sublingual.

properties. Its analgesic mechanism is unknown, but it is thought to enhance descending pain inhibition. Tramadol should not be prescribed concurrently with SSRIs because of a unique interaction that results in a dramatic reduction in seizure threshold. Caution should be taken when prescribing it with other medications (such as bupropion, TCAs, and neuroleptics) that also lower the seizure threshold.

Recent evidence suggests that patients should be screened for risk factors for opioid misuse or abuse (e.g., a current or past history of a substance use disorder [SUD], a family history of an SUD, a significant legal history, and a prominent affective disorder) before prescribing them, so that the physician can prescribe and monitor use of opiates appropriately. Once oral doses have been initiated and titrated to a satisfactory level, the analgesic effect needs to be sustained by minimizing fluctuations in blood levels and the variable effects of dosing schedules. Long-acting or controlled-release formulations are ideal for this homeostasis, because they are released more slowly than are short-acting opioids.

For the treatment of chronic pain, dosing with short-acting medications only on an as-needed basis should be avoided since this makes steady relief impossible. It also predisposes the patient to drug-respondent conditioning and to subsequent behavior problems. Typically, long-acting formulations are combined with short-acting agents for breakthrough pain. In those at risk for opioid misuse or with demonstrated aberrant drug behavior, only long-acting (such as a fentanyl patch) agents are preferred to avoid inappropriate self-medication. Other chapters in this text discuss strategies for the prescription of opiates to those with addiction. The most frequently reported side effects of opioid therapy are constipation, dry mouth, and sedation.

Treatment of Neuropathic Pain

Neuropathic pain is responsive to multiple medication classes (such as TCAs, anticonvulsants, and opioids) when used at higher doses than what is typically prescribed for chronic musculoskeletal pain. Multiple medications are often combined with physical therapy and with coping skills training for complete interdisciplinary care.

Sympathetically Maintained Pain

Sympathetically maintained pain is a type of neuropathic pain. Regardless of whether it is due to complex regional pain syndrome, inflammation, postherpetic neuralgia, trauma, or facial pain, sympathetically maintained or mediated pain can respond to sympathetic blockade. Medications often used in the sympathetic blockade are alpha-blocking drugs (e.g., phentolamine, alpha-blocking antidepressants, and clonidine). Intrathecal, epidural, and systemic administration of a local anesthetic or clonidine also produces analgesia and may be useful in some types of vascular or neuropathic pain with a sympathetic component. β-Blockers are not efficacious in the treatment of sympathetically maintained pain except in their use in the alleviation of migraine headaches. Guanethidine, bretylium, reserpine, and phentolamine have also been used to produce a chemical sympathectomy.

TREATMENT OF PAIN BEHAVIOR AND THE USE OF MULTIDISCIPLINARY PAIN CLINICS

Medicare guidelines offer a broad set of criteria to qualify for structured multidisciplinary pain management. The pain must last at least 6 months (and result in significant life disturbance and limited function), it must be attributable to a physical cause, and it must be unresponsive to the usual methods of treatment. Quality control guidelines developed by the Commission on Accreditation of Rehabilitation Facilities (CARF) have led to the certification of more than 100 multidisciplinary chronic pain management programs nationwide. Behavioral treatments are a key component of these programs and can be effective for the relief of pain and can help extinguish the behaviors associated with pain.

Inpatient or outpatient multidisciplinary pain treatment should be considered early in the course of chronic pain. This is particularly important when intensive observation is necessary (e.g., to rule out malingering); no single modality of outpatient treatment is likely to work; the patient has already obtained maximum benefit from outpatient treatments (such as NSAIDs, nerve blocks, antidepressants, and simple physical and behavioral rehabilitation); intensive daily interventions are required, usually with multiple concurrent types of therapy (such as nerve blocks, physical therapy, and behavior modification); and the patient exhibits abnormal pain behavior and agrees to the goals of improved coping, work rehabilitation, and psychiatric assessment.

REHABILITATION

Successful rehabilitation of patients who have chronic pain syndromes may require some combination of psychiatry, physiatry, and behavioral psychology. These treatments include exercise, gait training, spinal manipulation, orthoses, traction therapy, psychotherapy, and yoga. Successful rehabilitation aims to decrease symptoms, increase independence, and allow the patient to return to work. A positive, rapid return to light-normal activities and work is essential if disability is to be minimized. Psychologically, this is the key to coping with acute trauma. There is no evidence that a return to work adversely affects the course of the majority of chronic pain syndromes.

CONCLUSIONS

Pain is an exciting and burgeoning discipline for psychiatrists. Whether the psychiatrist is treating the pain or its psychological sequelae, it is critical to have a firm understanding of the physical basis for the pain complaints in conjunction with a thorough appreciation of how psychiatric co-morbidity interacts with the perceptions of pain. Patients who attend pain clinics have significant psychiatric pathology. This co-morbidity worsens their pain and disability, and this mental distress is an independent source of suffering, further reducing the quality of life. Fortunately, with the boom in psychotherapeutic medications over the past 15 years, and with more effective psychotherapies, significant improvement in pain treatment has been noted.

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