

Selected pathobiological features and principles of pharmacological pain management

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Abstract

Pain induced by inflammation and nerve injury arises from abnormal neural activity of primary afferent nociceptors in response to tissue damage, which causes long-term elevation of the sensitivity and responsiveness of spinal cord neurons. Inflammatory pain typically resolves following resolution of inflammation; however, nerve injury—either peripheral or central—may cause persistent neuropathic pain, which frequently manifests as hyperalgesia or allodynia. Neuralgias, malignant metastatic bone disease, and diabetic neuropathy are some of the conditions associated with severe, often unremitting chronic pain that is both physically and psychologically debilitating or disabling. Therefore, optimal pain management for patients with chronic neuropathic pain requires a multimodal approach that comprises pharmacological and psychological interventions. Non-opioid analgesics (e.g., paracetamol, aspirin, or other non-steroidal anti-inflammatory drugs) are first-line agents used in the treatment of mild-to-moderate acute pain, while opioids of increasing potency are indicated for the treatment of persistent, moderate-to-severe inflammatory pain. N-methyl D-aspartate receptor antagonists, antidepressants, anticonvulsants, or a combination of these should be considered for the treatment of chronic neuropathic pain. This review discusses the various neural signals that mediate acute and chronic pain, as well as the general principles of pain management.

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Introduction

The International Association for the Study of Pain currently defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.” However, the International Association for the Study of Pain has proposed the following new definition of pain: “an aversive sensory and emotional experience typically caused by, or resembling that caused by actual or potential tissue injury.”¹

Pain is a distressing sensation that can be described in terms of quality (e.g., burning, dull, throbbing, cramping, or lancinating), intensity, duration, location, and degree of associated functional disability.^{2–8} Acute pain is a physiological response to direct mechanical, chemical, or thermal stimulation of peripheral nociceptors, typically associated with tissue injury or other factors (e.g., drugs, neurotoxins, or inflammatory states); acute pain is mediated by classical nociceptive signaling to the brain.^{8,9} Nociception is defined as the “neural process of encoding noxious stimuli”; however, it does not necessarily result in pain sensation.⁶ The perception and experience of pain is a function of the brain.^{8,10} Pain can also be generated by dysregulated neural pathways of the peripheral or central nervous systems, with or without direct stimulation.^{2,11} Local sharp, aching pain is typically caused by noxious stimuli or inflammatory processes; in contrast, tingling, burning, or shooting sensations are typically indicative of neuropathic type pain.^{9,12,13}

Chronic pain has been defined as “pain that persists or recurs for more than

3 months”;⁶ it may occasionally evoke anxiety, depression, nausea, or other psychological and physiological overlays. The emotional distress of intense pain is a major determinant of an affected individual’s ability to maintain normal functional activity.^{2–6} Chronic pain is classified by the International Association for the Study of Pain⁷ into two types: chronic primary pain, which is a disease in itself, unrelated to any other chronic pain condition; and chronic secondary pain, which is a symptom of an underlying medical condition.^{6,7,14,15}

Pain is a common symptom of disease, which alerts the affected individual to potential or actual tissue damage. While acute pain is associated with physiological signs of stress (e.g., hypertension, tachycardia, and increased plasma cortisol), chronic pain is associated with emotional distress, particularly depression.^{9,16,17} There is an inherent patient-specific susceptibility to chronic pain; individuals affected by frequent episodes of acute pain are at a greater risk of persistent pain; moreover, genetic factors may contribute to the pathogenesis of persistent chronic pain.^{13,18,19} Inflammatory pain is best treated with paracetamol, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs) and—when necessary—by opioids; in contrast, chronic pain is typically treated with either tricyclic antidepressants (e.g., amitriptyline) or anticonvulsants (e.g., gabapentin), or a combination of the two.^{12,20–23}

Pain is a subjective experience. Under similar circumstances, patients with comparable states of general health who

experience noxious stimuli of similar intensities will report pain of different degrees of intensity, and each patient may require different treatment to achieve pain relief. This is presumably because of patient-specific emotional predispositions and differences in the functional activities of endogenous pain-modulating circuits. Furthermore, similar injuries that occur under different circumstances (e.g., on a battlefield or on a field of sport) may cause different intensities of perceived pain. The pain of a battlefield injury is experienced in the context of a perceived threat to life; in a sporting situation, the pain of an injury is primarily psychological.^{2,16,24,25} The first aspects of treatment for any acute pain are removal of the source and administration of analgesic. For severe persistent chronic pain, a multimodal approach may be necessary, which comprises medication, psychological counseling, physical therapy, and perhaps even regional analgesic block.^{3,5,16,22}

This narrative literature review discusses some of the various neural signals that mediate acute and chronic pain; it also discusses the general principles of pharmacological pain management. To construct this

review, relevant databases and individual authoritative texts were critically analyzed and the findings were integrated. Overall, an understanding of the mechanisms of pain and underlying pain hypersensitivity is essential for clinicians involved in the diagnosis and management of pain.

Neural nociceptive pathways

Primary sensory afferent nerves include large-diameter, low-threshold myelinated ($A\beta$) axons; small-diameter, high-threshold myelinated ($A\delta$) axons; and unmyelinated (C) axons. These axons have cell bodies in the trigeminal ganglion or dorsal root ganglion (Figure 1).^{26,27} The primary afferent cell bodies have two axonal branches: one innervates the peripheral tissues, while the other connects with second-order neurons in the dorsal horn of the spinal cord. The neuropeptides that these neurons synthesize—substance P and calcitonin-gene related peptide (CGRP)—are distributed to both peripheral and central terminals. In the periphery, these neuropeptides mediate neurogenic inflammation and peripheral sensitization, whereas they promote central

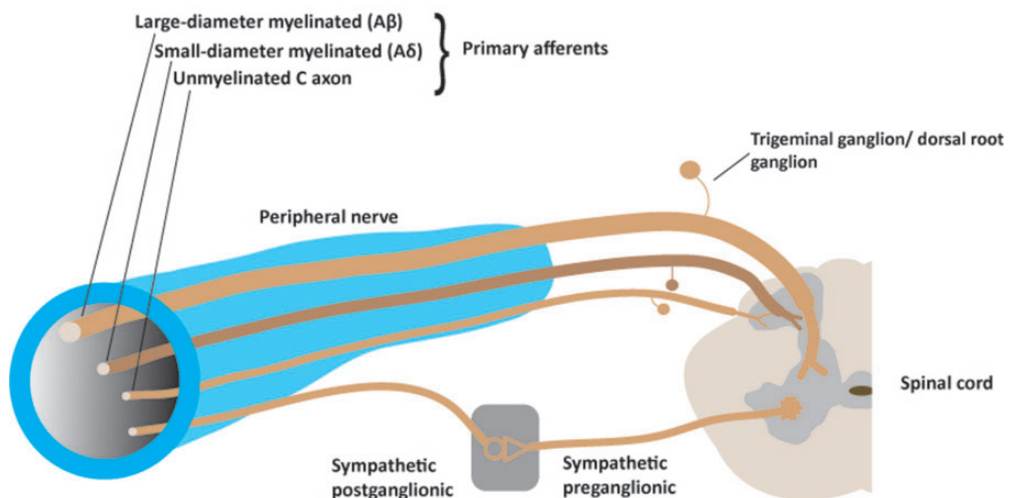


Figure 1. Components of a primary afferent nerve (Adapted from Rathmell and Fields, 2015).¹⁶

sensitization in central terminals.^{24,27,28} Under physiological conditions, activation of low-threshold A β fibers does not generate pain; exposure to noxious chemical, thermal, or mechanical stimuli causes the high-threshold A δ fibers and C fibers to generate nociceptive responses. Within the peripheral nerves, sympathetic postganglionic unmyelinated fibers are present, which may influence the perception of pain (Figure 1).^{13,16,26,27}

The nociceptive pathway begins with the transduction of a noxious stimulus (i.e., mechanical, chemical, or thermal) at peripheral nociceptor nerve endings into an electrical signal, which is transmitted along primary afferent nociceptors to the spinal cord. Functionally and molecularly distinct ion channel receptors are located at primary afferent nociceptors; these receptors are associated with sensitivities to various noxious stimuli; subsets of ion channels are sensitive to either heat, cold, acid, chemical agent, or noxious mechanical stimuli.^{24,26,28,29} For nociceptors to become excited, the stimulus intensity must reach the threshold level. This property enables the nociceptor to distinguish between non-harmful and potentially harmful stimuli, as well as to respond selectively to channel-specific threshold stimuli.^{28,30}

In the dorsal horn of the spinal cord, the central nerve endings of each primary afferent contact many spinal neurons; each spinal neuron receives convergent sensory inputs from multiple primary afferents. This physiological mechanism is essential for the generation of referred pain, which is defined as pain that originates from a noxious stimulus at a specific site, but is mislocalized because multiple inputs from many primary sensory afferents converge on spinal dorsal horn neurons; therefore, the brain may not identify the actual site of noxious stimulus origin.¹⁶

In the spinal cord, primary afferents synapse with neurons of the ascending

contralateral spinal thalamic tract in the anterolateral white matter of spinal cord, lateral edge of medulla, lateral pons, and midbrain,¹⁶ ultimately reaching several regions of the thalamus.^{24,27} From the thalamus, nociceptive pathways diverge to separate regions of the cerebral cortex where distinct aspects of pain (e.g., location, intensity, and quality) are interpreted; these regions determine emotional overlays to pain.^{2,16,27,31} These ascending neural pathways are complex circuits that convey pain and various other types of somatosensory signals, including information regarding non-noxious mechanical and thermal stimuli.^{24,32}

The thalamocortical neural system plays an important role in the transmission and evaluation of sensory, emotional, and motivational aspects of pain. The lateral thalamocortical neural pathway encodes sensory discriminative features (i.e., location and quality of noxious stimuli), while the medial thalamocortical neural pathway encodes distressing aversive emotional features.³³ The hippocampus, hypothalamus, amygdala, nucleus accumbens, medial prefrontal cortex, and periaqueductal gray matter are brain regions commonly involved in the modulation of both emotion and the experience of pain; these aspects affect an individual's state of mind (Figure 2).^{25,34,35}

Physiologically, a subset of postsynaptic receptors is activated by glutamate released from the central terminals of primary nociceptors; these postsynaptic receptors generate excitatory currents in second-order dorsal horn neurons, which may lead to the generation of action potentials with consequent transmission of pain impulses to the brain. Glutamate is the main excitatory neurotransmitter released by primary afferent terminals in the spinal cord, which causes rapid stimulation of dorsal horn neurons; other biological agents (e.g., substance P and CGRP) are also released by

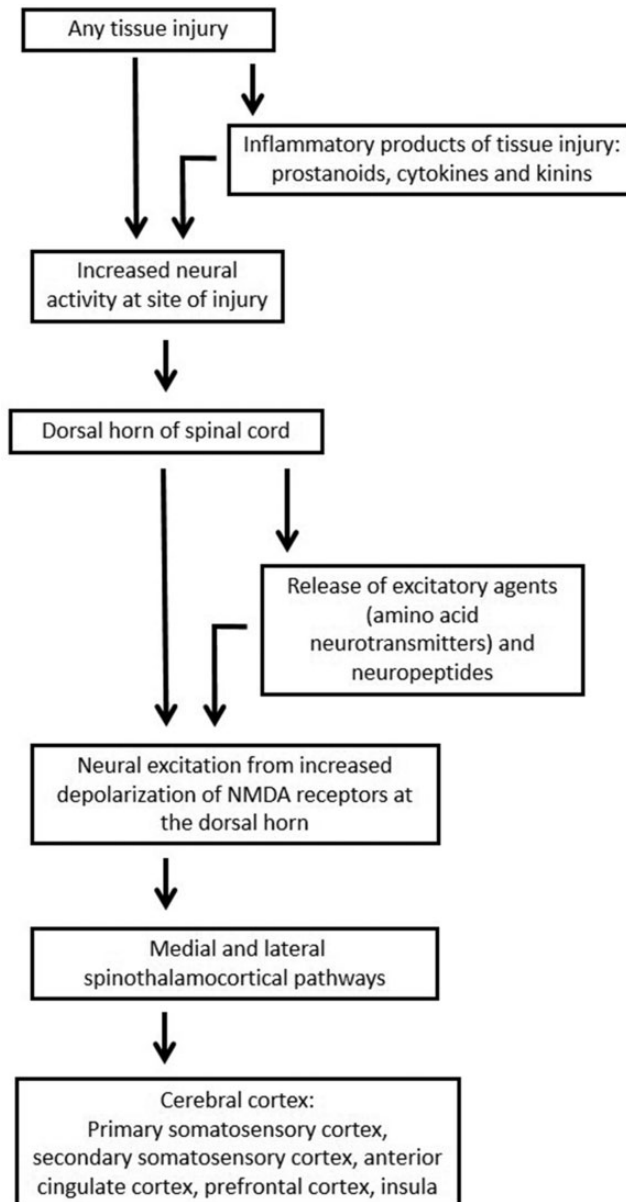


Figure 2. Sequence of neural events caused by injury-induced inflammation (Adapted from Feller et al., 2019).⁶¹

the same central terminals, thereby mediating slower, longer-lasting excitation.^{16,36,37} This classical nociceptive neural circuit is under the control of GABAergic and glycinergic interneurons in the superficial dorsal

horn, both of which inhibit postsynaptic currents of second order neurons.^{20,28}

The activities of nociceptive circuits in the dorsal horn are modulated by neural pathways descending from the cortex,

hypothalamus, midbrain, and medulla to the spinal cord; these neural pathways selectively regulate spinal pain-transmission pathways. Furthermore, these pain-modulating circuits can potentiate or suppress spinal nociceptive circuits, may facilitate induction of pain signals in the absence of peripheral noxious stimuli, and may be influenced by emotional predisposition.^{16,20,28} Endogenous opioids and noradrenaline are inhibitory neurotransmitters in these descending neural pathways; μ -opioid receptor agonists, amine uptake inhibitors (e.g., tricyclic antidepressants), and noradrenalin reuptake inhibitors can upregulate the natural endogenous tonic inhibitory pathways.^{13,20,37,38} However, descending serotonergic pathways facilitate pain through the serotonin 5-HT₃ receptor at the level of the dorsal horn of the spinal cord.^{5,24,39,40} These descending pain modulating pathways also express endogenous opioid peptides (e.g., enkephalins and β -endorphins) that may become activated following surgical procedures, extreme physical exercise, and placebo administration for pain relief.¹⁶

Sensitization

For transduction of nociceptive stimuli and propagation of electrical signals to the central nervous system, depolarization of the membranes of afferent nociceptors must occur, combined with generation of action potentials, by modification of either chemical- or voltage-gated ion channel activity in response to chemical, mechanical, or thermal noxious stimuli.^{13,27,29}

Peripheral sensitization refers to the reduction of activation thresholds of peripheral primary afferent nociceptors, combined with elevation of their membrane excitability, when triggered by mechanical, thermal, or chemical stimuli (Figure 3). Factors implicated in the initiation or promotion of peripheral sensitization include

intense, repeated, or prolonged stimuli; inflammatory mediators (i.e. bradykinin, some prostaglandins, leukotrienes, and nerve growth factor); and noxious products of tissue damage. Upon stimulation, most afferent nociceptors release biological mediators from their peripheral terminals; these mediators include substance P and CGRP, which promote inflammation in the microenvironment, further increasing peripheral sensitization (Figure 3).^{16,22,26,27}

The threshold and hyperexcitability of neurons can also be lowered at the level of the dorsal horn of the spinal cord; this is regarded as central sensitization (Figure 3). Generally, central sensitization is caused by the upregulation of nociceptive activity generated in primary afferent nociceptors in response to peripheral inflammation and/or tissue damage; however, it can also be caused by nerve injury to neural tracts in the dorsal horn. Central sensitization can generate stimulus-independent pain sensation, pain amplification, and pain referral. In this context, the term hyperalgesia refers to elevated pain sensitivity that occurs in response to a noxious stimulus; allodynia refers to sensations of pain that occur in response to normally innocuous stimuli.^{2,13,16,22,27,41,42}

Inflammatory pain

Tissue injury leads to local accumulation of inflammatory cells including neutrophils, macrophages, mast cells, basophils, and platelets. These inflammatory cells, activated nociceptors, and non-neural cells (e.g., endothelial cells and keratinocytes) release the following biological mediators and signaling molecules into the local microenvironment: serotonin, histamine, prostaglandins, bradykinin, substance P, CGRP, chemokines, cytokines, adenosine triphosphate, adenosine, protons, and nerve growth factor.^{13,22,27,28,43-45} These

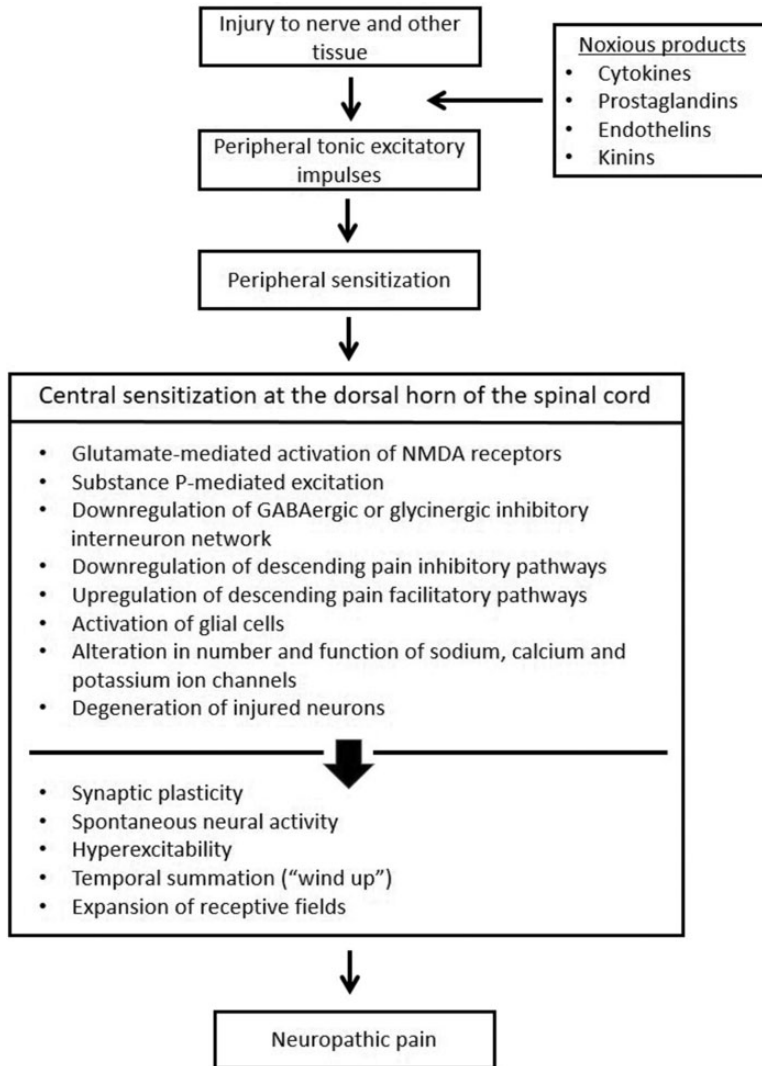


Figure 3. Neural events that lead to chronic neuropathic pain: NMDA receptor activation, substance P-mediated excitation, downregulation of GABAergic and glycinergic inhibitory interneuron network, downregulation of inhibitory and upregulation of excitatory descending pain circuits, activation of glial cells, and alterations in the numbers and/or functions of ion channels and degeneration of injured neurons (singularly or together) may lead to synaptic plasticity and dysfunction of neural connectivity at the level of the dorsal horn of the spinal cord, thereby causing central sensitization. Whereas central sensitization related to inflammatory pain is resolved with the resolution of inflammation, central sensitization is the mechanism that both drives and maintains neuropathic pain.^{8,61}

agents mediate pain sensation by interacting with surface receptors of primary afferent nociceptors, resulting in reduction of their activation thresholds; this causes

membrane hyperexcitability (Figure 2).⁴⁶ While the inflammatory process persists, the neural circuits of pain are hypersensitized and therefore can be

activated by noxious stimuli and by low-threshold innocuous inputs; elevated sensitivity in contiguous non-inflamed receptive fields also occurs as a result of plasticity in peripheral and central nociceptive pathways.^{13,43-45}

Normal healthy tissue and injured inflamed tissue differ with regard to the numbers of sensitive active primary afferent nociceptors in their peripheral receptive fields. Under physiological conditions, some inactive primary afferent nociceptors innervating the skin (i.e., silent nociceptors) are completely insensitive to non-noxious thermal or mechanical stimuli. However, inflammatory mediators recruit and activate these silent nociceptors that then become sensitive to mechanical and thermal stimuli; subsequently, the silent nociceptors promote transduction of pain signals. The mechanisms by which inflammatory mediators activate silent nociceptors are similar (or identical) to those that sensitize “non-silent” nociceptors.^{16,22,27,29,43}

In this regard, prostaglandins synthesized by cyclooxygenase (COX) enzymes can directly increase sodium ion permeability in sensory neurons, thereby resulting in their excitation, the release of substance P, and the spontaneous firing of action potentials. These activities promote nociceptive processing and transmission in the spinal cord; they also mediate the release of other inflammatory agents.^{26,44,47-49} Blocking COX activity by anti-inflammatory drugs reduces prostaglandin production, thereby minimizing both peripheral and central sensitization, which leads to reduction of inflammatory pain.^{21,26,29} Moreover, peripheral inflammatory processes may cause central sensitization with upregulation of nociceptive processes,²⁸ which are relatively long-lasting; however, these processes are reversible and will disappear upon resolution of the inflammatory process.^{13,50}

Neuropathic pain

Neuropathic pain is a severe burning, tingling, or electric shock-like sensation that can be triggered by a very light stimulus (i.e., hyperalgesia or allodynia). It typically arises secondary to damage to peripheral nerve-endings (e.g., in diabetic neuropathy) or to damage to primary afferents (e.g., in herpes zoster). The neural damage causes alterations in signal processing in the central nervous system, and the pain is referred to the region typically innervated by the damaged nerves. Neuropathic pain can also arise secondary to damage to any part of the central nervous system containing central nociceptive pathways (i.e., spinal cord, brainstem, or thalamus). This is typically caused by direct trauma or vascular events.^{2,5,13,16,20} Once established, neuropathic pain does not respond favorably to treatment with COX inhibitors or opioids.^{22,50,51}

Nerve injury presumably increases the excitability of nociceptive pathways, which may then generate neural action potentials in response to very light stimuli, or even spontaneously. In this context, damaged primary afferent nociceptors may show elevated sensitivity to adrenergic agents of the sympathetic system, with consequent central sensitization and hyperexcitability.^{16,24} This hypersensitivity to adrenergic agents, secondary to nerve injury, results from an elevated number of adrenoceptors, an elevated baseline excitability of nociceptors, or both.^{2,16} Thus, central sensory abnormalities associated with neuropathic pain may be dynamically maintained by sympathetic efferent activity, which supports continued tonic activity of nociceptive afferents (Figure 3).^{24,32}

There are several neuropathogenic mechanisms implicated in the development of neuropathic pain. In some instances of neuropathic pain, the injured sensory neurons may cause “phenotypic switching” in the

dorsal root ganglia/trigeminal ganglion, such that the expression levels of some genes encoding biological mediators are upregulated, while others are downregulated. These phenotypic changes may dysregulate the functional activities of both peripheral and central neural pathways, thereby contributing to the development and maintenance of a state of central hyperexcitability and plasticity that promotes the development of neuropathic pain.^{2,13,45,52} Furthermore, peripheral axonal nerve injury may induce structural changes in the dorsal horn, characterized by sprouting of central axonal terminals of injured non-nociceptive, low-threshold A β fibers into nociceptive pathways. These new, formerly non-nociceptive circuits subsequently become engaged in pain transmission, causing hyperalgesia and allodynia.¹³ Healing of the injured peripheral afferents may also be dysregulated, causing formation of neuromas with elevated neural excitability and spontaneous firing.^{5,48}

In the context of persistent injury or intense noxious stimulation, the central afferent nociceptor terminals release biological mediators (e.g., glutamate, substance P, CGRP, and adenosine triphosphate) in the dorsal horn, all of which can activate typically silent postsynaptic NMDA receptors. The activation of NMDA receptors results in elevated excitability of these postsynaptic neurons in the dorsal horn, thereby exaggerating responses to noxious stimuli and causing hyperalgesia. Furthermore, abnormal neural circuits are established in the dorsal horn; because of heterosynaptic facilitation, A β afferents that are typically activated by low-threshold innocuous stimuli (e.g., light touch) become involved in pain transmission. These changes may result in mechanical allodynia (Figure 3).^{5,13,26,28,53}

In neuropathic pain, downregulation or loss of function occurs with respect to GABAergic or glycinergic inhibitory interneuron networks in the dorsal horn.

Physiologically, this system tonically inhibits the glutamate/NMDA-mediated central sensitization. Because of the loss of GABAergic and glycinergic inhibitory tone secondary to injury, central neural sensitivity and hyperexcitability occur, leading to hyperalgesia. Furthermore, pain transmission by non-nociceptive, myelinated A β primary afferents is uninhibited, causing innocuous stimuli to be perceived as noxious; this results in amplification of the pain experience.^{13,28,42,45,53}

Other factors in the pathogenesis of neuropathic pain include changes in pain signaling of descending neural pathways that result in impaired inhibition, increased facilitation, or both, at the level of the dorsal horn of the spinal cord;^{5,19,22,24,40,54} these changes also cause alterations in the numbers and functional activities of sodium, calcium, or potassium ion channels within affected sensory neurons.^{22,30,37,39,46,55}

Last, activated glial cells are important in the induction and maintenance of central sensitization, as well as the subsequent persistence of pain sensation in response to nerve injury; however, the same mechanism is not activated by inflammatory tissue injury. When peripheral nerve injury occurs, microglia (i.e., resident functional macrophages of the central nervous system) are activated by neurotransmitters released from primary afferent terminals in the dorsal horn. The microglia then emit a battery of excitatory biological mediators including cytokines, chemokines, and other signaling molecules, which contribute to neural central sensitization and subsequent persistent pain.^{13,28,45,48,56}

Overall, in patients with neuropathic pain, multiple dysregulated pain mechanisms at multiple neural sites may be involved; therefore, when a single therapeutic agent provides only partial relief, two or more agents should be combined, each targeting a distinct dysregulated pain-associated neural pathway.⁵⁷

Chronic pain

Several risk factors are associated with the change from acute to chronic pain. These include genetic factors, as well as a history of emotional distress, psychological treatment, alcohol or drug abuse, and/or sexual or other forms of physical abuse. Personality traits including low self-esteem or inability to cope with stress, as well as poor social support or job satisfaction, also have been associated with pain chronicity (Figure 4). Furthermore, previous episodes of chronic pain of any origin constitute a risk for further such episodes; elevated pain intensity at the onset of acute pain is associated with subsequent pain chronicity.^{17,27,58,59} Fully functional descending inhibitory pathways are essential for preventing the transition from acute to chronic pain.⁴⁰

When chronic pain develops in the presence of psychosocial stressors, their management is likely to facilitate reduction of chronic pain. The perception and

experience of pain are also influenced by the cognitive appraisal of the nature of the noxious stimuli, which occurs in the prefrontal cortex, then through neural connections from the prefrontal cortex to the limbic system (i.e., amygdala and hippocampus); cognitive mechanisms moderate the emotional component of pain generated in the limbic system (Figure 5).^{25,34,60} Consequently, the management of chronic pain is complex; the physical, emotional, and cognitive aspects of the disease must be addressed in parallel with pharmacological treatment.⁶¹ Cognitive-behavioral therapy, mindfulness/meditation, and physical activity are effective for moderating maladaptive emotions and thoughts, as well as for improving the capacity to cope with chronic pain (Figure 6).⁶²⁻⁶⁵

A variety of typically incurable conditions are causatively associated with severe chronic pain; these include metastatic malignant bone disease, fibromyalgia, osteoarthritis, cerebrovascular events, diabetic neuropathy, and neuralgia.^{5,59,66} Factors

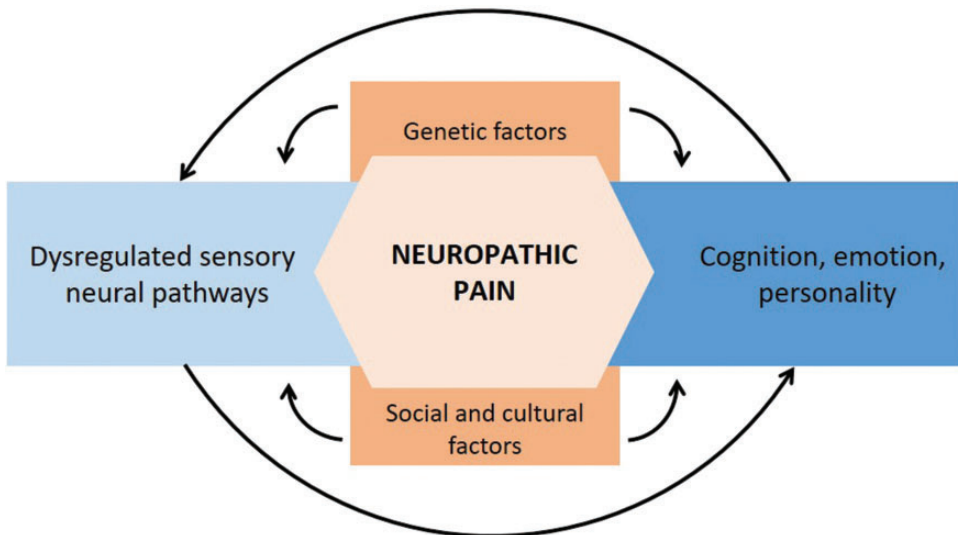


Figure 4. Genetic factors play roles in the functional dysregulation of sensory neural pathways, as well as in determining cognitive processes, emotions, and personality; these genetic factors and related effects, together with social and cultural factors, influence the experience of chronic pain.⁶¹

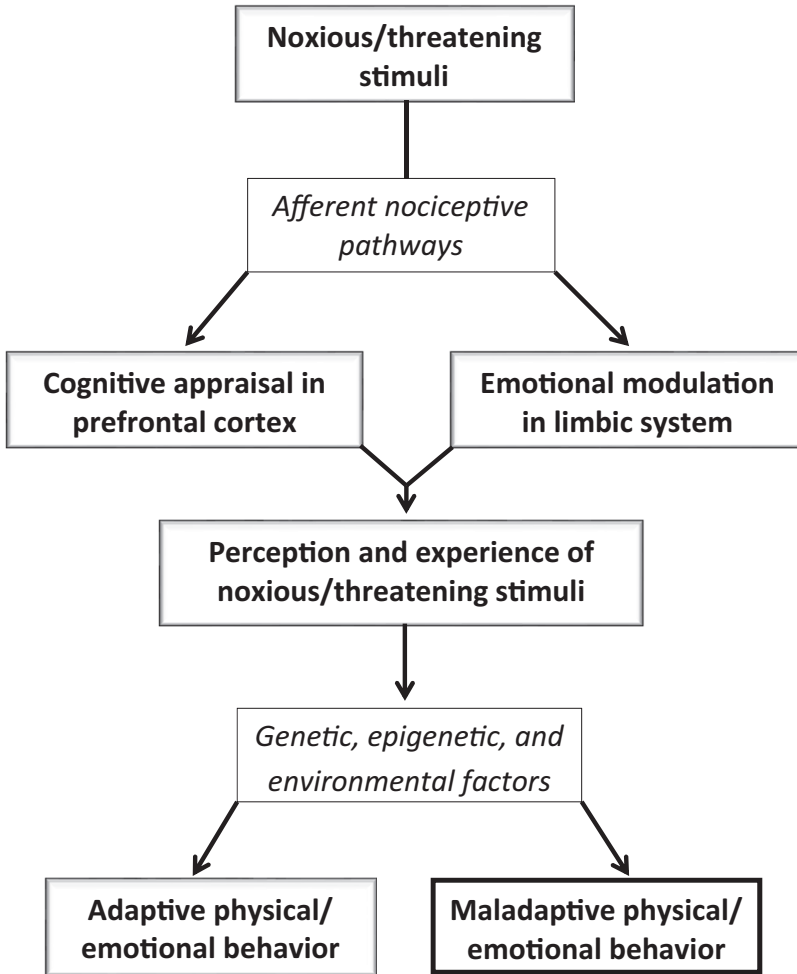


Figure 5. Selected factors that influence physical and emotional responses to chronic pain: the nature of the response to noxious/threatening stimuli is influenced by its severity and duration; by genetic, epigenetic, developmental, and environmental factors; and by the ability to reduce the effect of the stimuli through physical, emotional/spiritual, cognitive, and pharmacological mechanisms (Adapted from Feller et al., 2019).⁶¹

that can perpetuate or exacerbate chronic pain include damage to sensory nerves, elevated sympathetic efferent activity, and a current or recent history of psychological distress.^{16,17} Because chronic pain is associated with both emotional and organic factors, these issues should be addressed concurrently for the best treatment outcome. Therefore, management should ideally be multidisciplinary and should include

pharmacotherapeutic and psychological treatment (Figure 6).^{16,59,67}

Analgesics: principles of treatment

There are three broad categories of analgesics: non-opioids, mild opioids, and strong opioids. Antidepressants and anticonvulsants, NMDA receptor antagonists, and

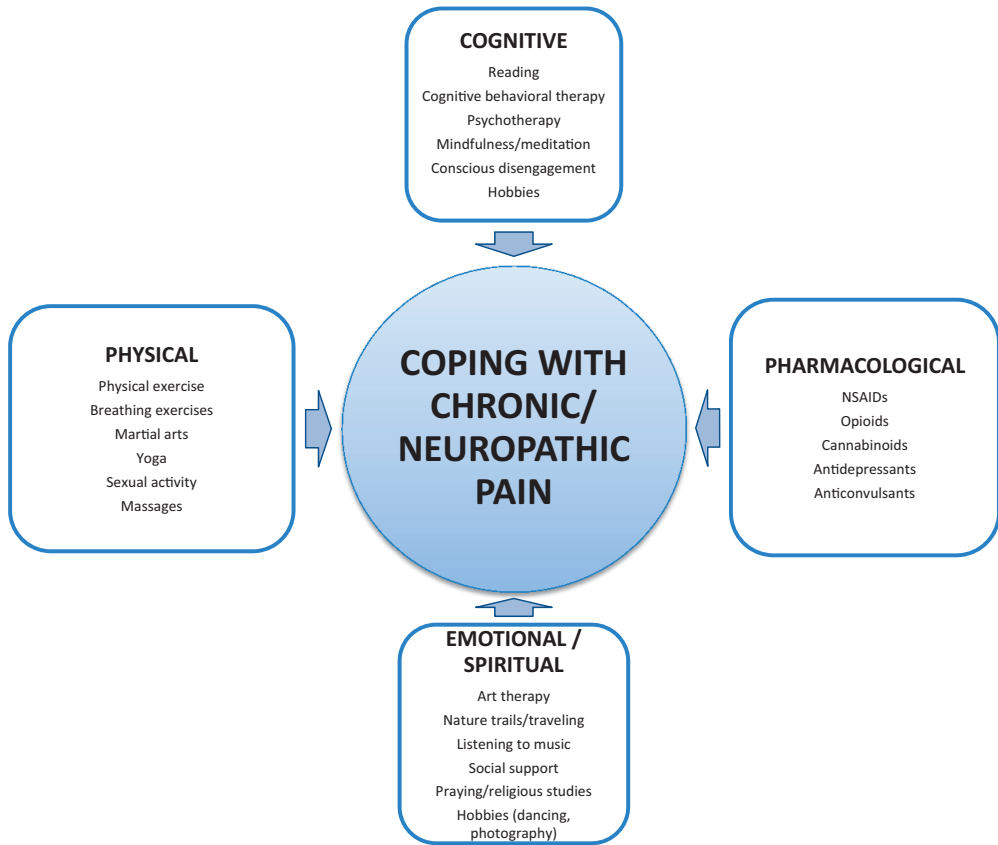


Figure 6. Selected strategies that may help to reduce or control chronic pain.

cannabinoid compounds are also sometimes used as adjuvant agents for treatment of debilitating chronic neuropathic and/or neuralgic pain (e.g., bone cancer pain, post-herpetic neuralgia, diabetic neuropathy, AIDS neuropathy, fibromyalgia, headache, and low-back pain).^{4,5,16,20,22} The symptoms of persistent pain in these conditions are typically similar, which indicates either that different neuropathogenic mechanisms generate similar pain-related symptoms or that the similar pain-related symptoms in different neuropathic conditions are caused by common neuropathogenic mechanisms. Regardless of the cause, there remains no agreed rationale or guideline for treatment because the underlying

mechanisms are not well understood. Relief of chronic neuropathic pain is only partial and temporary.^{5,13} Therefore, more effective and well-tolerated medications are needed, in combination with new therapeutic approaches to the management of chronic neuropathic pain.⁵

Nevertheless, in the context of the limitations of relevant published research regarding pharmacotherapy for neuropathic pain, a recent systematic review and meta-analysis⁶⁸ found that first-line treatment should comprise tricyclic antidepressants, serotonin-noradrenalin reuptake inhibitors, and pregabalin or gabapentin; second-line treatment should comprise lidocaine patches, high-concentration capsaicin

patches, or tramadol (a combined opioid receptor agonist and serotonin-noradrenalin reuptake inhibitor); third-line treatment should comprise strong opioids and botulinum toxin A (Table 1). Topical agents and botulinum toxin A should be reserved for peripheral neuropathic pain.⁶⁸

Non-opioid analgesia: paracetamol (acetaminophen), aspirin, and other NSAIDs

Paracetamol, aspirin, and NSAIDs act through COX inhibition and the resulting reduction of prostaglandins in tissue. While COX-1 is constitutively expressed, COX-2 is expressed in the context of inflammation. COX-1 is essential for the maintenance of gastric mucosal integrity, renal function, and platelet activity. COX-2-selective inhibitors have analgesic effects comparable to those of COX-1 inhibitors; however, COX-2-selective inhibitors cause less gastric irritability and do not impair platelet-mediated blood clotting. However, high doses of COX-2 inhibitors cause nephrotoxicity and increase the risk of untoward cardiovascular events.¹⁶ COX-2 is reportedly expressed by dendrites of excitatory neurons in the spinal cord; moreover, spinal prostaglandins facilitate NMDA-receptor-

dependent nociceptive transmission, whereas COX inhibitors downregulate spinal production of prostaglandins, which causes inhibition of NMDA-mediated nociceptive transmission.⁴⁷

Notably, paracetamol is not an anti-inflammatory agent. Paracetamol, aspirin, and other NSAIDs are all available without prescription and are commonly used for the treatment of mild to moderate pain (Table 1).⁶⁹ However, high doses of paracetamol may be hepatotoxic,⁷⁰ but it does not interfere with platelet function or cause gastric irritation; these toxic effects are caused by use of aspirin and other NSAIDs.^{16,71} Paracetamol is a weak analgesic, but is typically the drug of choice for patients in whom the use of NSAIDs is contraindicated;⁷² moreover, paracetamol is safe for use by pregnant and nursing women. It is typically well tolerated, has good bioavailability, has few drug interactions, and is inexpensive. Paracetamol can be used alone or in combined preparations with other analgesic agents, such as ibuprofen and codeine phosphate.^{69,72,73} Paracetamol, aspirin, and other NSAIDs are all well absorbed from the gastrointestinal tract; they do not produce tolerance or dependence, and have minimal adverse effects if not used with high frequency.

Table 1. Pharmacological agents for treatment of acute and chronic pain.

Pharmacological agents for treatment of chronic/neuropathic pain	
First-line treatment	Tricyclic antidepressants; serotonin-noradrenalin reuptake inhibitors; and pregabalin or gabapentin
Second-line treatment	Lidocaine patches; high-concentration capsaicin patches and tramadol
Third-line treatment	Strong opioids and botulinum toxin A
Pharmacological agents for treatment of acute pain	
Mild-to-moderate pain	
First-line treatment	Paracetamol and/or NSAIDs
Second-line treatment	Paracetamol and/or NSAIDs in combination with a weak opioid (e.g., codeine or dihydrocodeine)
Moderate-to-severe pain	
Third-line treatment	Strong opioids (e.g., morphine or oxycodone)

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.

Although aspirin and other NSAIDs are commonly used beneficially without any untoward effects, gastric irritation is a common limitation, thus limiting the dose and duration of use. These agents are contraindicated for use in patients with pre-existing gastritis or gastric ulceration. Chronic use of aspirin and other NSAIDs can cause—even in healthy persons—stomach erosions and ulcers of the gastric mucosa, as well as possible gastric perforation; because these agents also interfere with the functional activity of platelet COX, bleeding time may increase, resulting in a risk of gastrointestinal bleeding.^{4,16,74} Because NSAIDs may be nephrotoxic or hepatotoxic,⁷² individuals with hepatic or renal dysfunction who frequently use NSAIDs are at a particularly high risk and should be monitored regularly during the course of treatment.^{4,16} When selecting NSAIDs, the following factors should be considered: etiology and severity of pain, any medical condition that may be a relative contraindication to use of the agent (e.g. bleeding, peptic ulcer, and/or renal or hepatic dysfunction), previous history of unfavorable response to the agent, and the clinician's experience with the specific agent.⁴

Opioid analgesics

If non-opioids are ineffective for relief of acute pain, opioids should be introduced (Table 1). These can produce tolerance or dependence with long-term use and their side effects may be dose-limiting. Treatment of acute pain should be initiated with a weak opioid (e.g., codeine, oxycodone, or hydrocodone); if necessary, a more potent opioid (e.g., morphine, hydromorphone, methadone, levorphanol, or fentanyl) should be used.⁴ Because non-opioid analgesics potentiate the effects of opioids, the use of combinations of COX inhibitors—if they are well tolerated—and

opioids allow the administration of lower doses of each agent to achieve adequate pain relief.^{2,16} Opioids combined with NSAIDs constitute the main treatment option for acute inflammatory pain, such as burns or acute postoperative pain.⁷⁵

Typically, patients who experience intermittent severe episodic pain benefit most from use of short-acting opioid agents when needed; patients with severe ongoing pain will benefit from long-acting opioid agents.^{16,76} The analgesic effects of opioids are mediated by activation of pain-inhibitory neurons in the central nervous system via opioid μ -receptors, as well as by direct inhibition of pain-transmitting neurons.²² Notably, opioids are the most potent and effective analgesic agents available for the treatment of severe acute pain. Side effects of opioids are common and include nausea, vomiting, pruritis, sedation, delirium, and constipation; these side effects can be reversed or relieved by using the narcotic antagonist naloxone.^{77,78} Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening if it occurs.⁷⁹ Therefore, close monitoring is needed for patients with any form of respiratory compromise who must receive opioid treatment.¹⁶

The side effects of distinct opioid preparations are unpredictably variable. Because of patient-specific differences in drug absorption, metabolism, and functional activities of opioid receptors, if insufficient pain relief or significant side effects are observed with a specific agent, it is advisable to switch to a different opioid preparation; however, the resulting benefits or side effects cannot be reliably determined before administration of the new agent.^{2,80} Furthermore, because pain is a subjective experience, patients with comparable pain severity using the same opioid preparation may require different doses and routes of administration to achieve an equivalent analgesic effect.^{4,80}

When prescribing an opioid, the following factors must be considered: the etiology and severity of pain, the potency and pharmacokinetics of the agent to be used, the required duration of analgesic effect, the known side effects of the particular agent, and any prior experience the patient may have had with the chosen agent. For any opioid, it is prudent to begin with a low dose; select the most convenient route of administration; increase the dose judiciously; and monitor for pain relief, tolerance, or dependence.^{4,80}

Opioids are effective for treatment of both acute and chronic pain. However, considering the side effects and potential risks of overdose, abuse, and addiction, opioids should not be used as a first-line treatment for chronic neuropathic pain; in contrast, they should be used only when other medications are ineffective.^{5,20,22,77,78}

Antidepressants

Amine uptake inhibitors (e.g., tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors) upregulate endogenous pain inhibition pathways by increasing intrinsic levels of noradrenalin and serotonin.^{5,13} Even in patients who are not depressed, tricyclic antidepressants (e.g., nortriptyline and desipramine) are beneficial in the treatment of neuropathic conditions such as postherpetic neuralgia, diabetic neuropathy, central post-stroke pain, chronic low back pain, and migraine headaches; because tricyclic antidepressants appear to potentiate or enhance opioid analgesia, they are used in combination with opioids in the treatment of severe cancer pain.^{4,16,77}

Tricyclic antidepressants are inexpensive and their once-a-day dosage encourages compliance; however, they have significant side effects including memory impairment, orthostatic hypotension, cardiac conduction delay, urinary retention, drowsiness,

and constipation.^{77,78} Selective serotonin-noradrenaline reuptake inhibitors (e.g., duloxetine, venlafaxine, or milnacipran)^{77,78} have fewer and less serious side effects, but are generally less effective for pain relief, compared with tricyclic antidepressants.¹⁶

Tramadol

Tramadol is a combined μ -opioid receptor agonist and serotonin-noradrenalin reuptake inhibitor, which is beneficial for treatment of neuropathic pain, particularly of peripheral origin; however, it is less effective than strong μ -opioid receptor agonists, such as morphine or oxycodone.⁷⁸ Notably, serotonin mediates descending excitatory pathways through its 5-HT₃ receptors in the dorsal horn of the spinal cord,^{24,37,39,40} thereby facilitating neuropathic pain and reducing the efficacy of tramadol.

Tapentadol is a newer drug, a combined μ opioid receptor agonist and noradrenalin reuptake inhibitor, that lacks the pain-facilitating activity of elevated serotonin, secondary to serotonin reuptake inhibition.^{57,81} Noradrenalin reuptake inhibition results in upregulation of the functional activities of descending pain inhibitory pathways through α 2-adrenergic receptors in the spinal dorsal horn;^{40,57} when combined with the descending pain inhibitory effects of the μ opioid receptor agonist, administration of this agents provides a beneficial treatment outcome.²⁰

Anticonvulsants

Anticonvulsants are effective for treatment of various types of neuropathic pain, but are particularly beneficial for treatment of lancinating pain. For example, the brief, shooting, electric shock-like pain of trigeminal neuralgia, as well as the postherpetic neuralgic pain caused by upregulated nociceptor neural activity, can both be reduced

by the use of anticonvulsants (e.g., phenytoin and carbamazepine, voltage-gated sodium channel blockers) and newer preparations (e.g., gabapentin and pregabalin, voltage-gated calcium channel blockers).^{16,19}

The analgesic effects of gabapentin or pregabalin are mediated through interactions with the $\alpha 2\delta 1$ subunit of calcium voltage-gated channels; this causes downregulation of neurotransmitter release, with reductions of dorsal root ganglia neuron excitability and central sensitization.^{5,45,82,83} Low to moderate doses of anticonvulsants, combined with a tricyclic antidepressant or an opioid, result in beneficial clinical outcomes; these low-dose combination treatments are typically better tolerated than high-dose monotherapies.⁵

NMDA receptor antagonists

Because there is evidence that activated NMDA receptors in the spinal cord are essential for establishing central sensitization in response to nerve injury, NMDA receptor antagonists should be effective for treatment of neuropathic pain.⁸⁴ However, adverse effects of NMDA receptor antagonists are substantial, thus limiting their usage in clinical practice. These adverse effects include profound mood shifts, agitation, hallucinations, nightmares, dizziness, fatigue, headache, respiratory depression, gastrointestinal symptoms, and cardiovascular derangement. The psychomimetic effects of NMDA receptor antagonists are presumably caused by the disinhibition of certain excitatory circuits in the central nervous system.⁸⁵⁻⁸⁷ In patients with neuropathic pain, the treatment outcomes of clinical use of NMDA receptor antagonists vary according to therapeutic agents (e.g., ketamine, memantine, or d-methadone), types of pain (e.g., neuralgia, post-amputation phantom pain, diabetic neuropathy, or HIV neuropathy), and

genetic variations in the molecular structure of the NMDA receptor.^{20,84-86}

Cannabinoids

At present, laws in many countries prohibit and criminalize the use of cannabinoids for any purpose, but there has been considerable public support for the introduction of cannabinoids for medicinal use. Medicinal cannabinoids are active compounds of cannabis (marijuana) that have relatively recently been added to the armamentarium of drugs used in the treatment of various medical conditions (e.g., cancer pain, fibromyalgia, rheumatoid arthritis, multiple sclerosis, and other types of pain including neuropathic, chronic, and post-surgical).⁸⁸

Physiologically, the naturally operating endogenous cannabinoid system in humans comprises cannabinoids and their receptors, which presumably play functional roles in pain modulation, memory and cognition, and immunoinflammatory responses.⁸⁹ The analgesic mechanisms of cannabinoids are not well understood, but have been proposed to involve anti-inflammatory properties and antinociceptive action in descending inhibitory pain pathways,⁸⁸ when cannabinoids are administered in combination with opioids, an additive analgesic effect can be observed.⁸⁹

Although cannabinoids can cause addiction, the risk is much lower than with nicotine, alcohol, heroin, or cocaine. Side effects depend on the botanical strain, molecular characteristics of the active extract, and the dose and frequency of use; these effects include tachycardia, hypotension, bronchodilation, and central nervous system symptoms (e.g., impaired cognition, memory, judgment, and attention, as well as enhanced relaxation, hunger, and euphoria).^{88,89} The safety of long-term continual use of medicinal cannabinoids is unknown.²⁰

Botulinum toxin type A

Subcutaneous injections of controlled doses of neurotoxin botulinum toxin A are effective, safe, and generally well tolerated for the treatment of peripheral neuropathy. The mode of action of this agent is not well understood, but is presumed to involve inhibition of both peripheral and central neural pathways of pain transmission through downregulation of peripheral and central neurotransmitters.^{20,22,90}

High concentration capsaicin patches (8%)

Capsaicin is an alkaloid that provides the hot and spicy flavor in chili peppers.^{59,91} Topical capsaicin can bind to the transient receptor potential vanilloid subfamily member 1 ion channels of small-diameter, peripheral sensory fibers, resulting in desensitization and partial loss of function in afferent nociceptors.^{5,20,59} The long-term benefits and safety of continual capsaicin use are unknown.^{5,20,77}

Topical lidocaine patches

For the treatment of peripheral neuropathies, patches of lidocaine 5% are effective, safe, and well tolerated. Because there is no substantial systemic absorption, adverse effects and drug interactions are minimal. The mode of action of lidocaine involves blockage of the sodium channels of damaged neural fibers under the patch, thereby reducing the firing of affected nerves.^{5,20}

Conclusion

The initiation and persistence of chronic pain involve interactions among multiple factors including dysregulated sensory neural pathways; dysregulated cognitive, emotional, and motivational neural circuits; and the balance between degenerative and regenerative neural events. While acute pain

is of short duration, pain that persists or recurs for more than 3 months is considered chronic. Because multiple determinants are involved in the pathogenesis of persistent chronic pain, optimal management should be multidisciplinary, thus targeting different aspects of the disease. Further research is needed to understand the mechanisms by which persistent chronic pain can cause cognitive deficits, maladaptive emotional behavior, and alterations in the structural integrity of some regions of the brain, as well as how to increase an individual's endogenous ability to control persistent chronic pain.

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