The Mechanism-Based Approach to Pain Management

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

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

Faculty Disclosure

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

Division Planners

John M. Leonard, MD
Margo A. Halm, RN, PhD, ACNS-BC

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

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

Audience

This course is designed for practitioners involved in the care of patients with pain.

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Designations of Credit

NetCE designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

A complete Works Cited list begins on page 18.

Mention of commercial products does not indicate endorsement.

This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 1 MOC point in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

NetCE designates this continuing education activity for 1 ANCC contact hour.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 1 Interprofessional Continuing Education (IPCE) credit for learning and change.

NetCE designates this continuing education activity for 1.2 hours for Alabama nurses.

NetCE designates this continuing education activity for 1 pharmacotherapeutic/pharmacology contact hour.

AACN Synergy CERP Category A.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2025); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide primary care clinicians and nurses with a brief review of current concepts of the pathogenesis and persistence of chronic pain, and the clinical utility of a mechanism-based approach to pain management. The goal is to promote a broader understanding of the underlying neuroscience, and thus a more effective strategy for alleviating the suffering imposed by chronic pain.

Learning Objectives

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

1. Outline the primary pain types.
2. Identify the underlying mechanisms of pain.
3. Evaluate the factors involved in the transformation of acute to chronic pain and the pathways that perpetuate chronic pain.
4. Describe the interaction of pain mechanisms and the importance of central sensitization to devising a strategy for chronic pain management.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

According to the Institute of Medicine, more than 116 million persons in the United States suffer with pain that persists for weeks to years, at an annual cost estimated to exceed $560 million [1]. Clearly, chronic pain is among the most common of afflictions, and relief from pain is difficult to come by. Impediments to effective pain relief are multiple. These include limited access to practitioners with the requisite knowledge, experience, and patience required to effectively manage this difficult clinical issue; patients' misunderstanding of the complex nature of pain and the limitations of prescription analgesia; outmoded or poorly informed clinical practices by some who either overprescribe medication, including opioids, or underprescribe for fear of violating government regulations. The current climate of clinical care for the patient with pain is further challenged by the ongoing epidemic of opioid misuse and diversion. Then, there are differences in expectations and outcomes related to psychologic make-up, life experiences, age, education, and past medical history [1].

Chronic pain is now known to have a distinct pathologic basis, with functional and structural changes in multiple areas of the nervous system that can worsen over time [1; 87]. These adaptive changes may have psychologic and cognitive correlates that add to the complexity of chronic pain and influence response to therapy. A mechanism-based approach (MBA) to the treatment of pain is an emerging strategy driven by discoveries in pain neuroscience. MBA involves therapeutic targeting of the pathologic reorganization in nervous system structure and function that underlies chronic pain. The objective of this approach is to more effectively treat chronic pain and to prevent or minimize the risk of developing chronic pain.

A key foundation of MBA involves the concept of acute versus chronic pain. Traditionally, chronic pain has been defined as acute pain that persists beyond an arbitrarily selected temporal cut-off point (typically three to six months) from onset, or persistent pain beyond expected resolution. However, this concept of chronic pain as a continuation of acute pain no longer appears to be valid. Most chronic pain syndromes, even those that persist following acute injury or inflammation, reflect an acquired, dynamic neurophysiologic condition having multiple, complex mechanisms. Chronic pain is now known to develop from abnormal sensory processing and neuronal plasticity in peripheral and central pain pathways [2; 3; 4]. Based on this understanding, acute pain may persist for extended periods without the underlying mechanism undergoing a "chronification" [5].

The first step in managing pain is to identify the disease, lesion, or injury origin of pain, which until recently comprised the entire diagnostic process [6]. Evidence now strongly supports the use of MBA to classify pain conditions by the type of maladaptive nervous system alteration. This approach provides a comprehensive dual therapeutic focus that targets the pathologic sustaining mechanism of the pain and the original disease, lesion, or tissue injury [6; 7]. Such an approach is now believed to optimize pain diagnosis and treatment by avoiding the limitations associated with the traditional etiology-based approach [3; 4; 9; 10; 11; 12].

Importantly, MBA is not meant to replace the traditional approach of targeting the original anatomic cause of pain, which remains essential when indicated. By addressing the underlying pain pathophysiology, MBA aims to prevent the development of maladaptive plasticity and peripheral and central sensitization that characterize chronic pain and to promote normalized function of pain mechanisms [4; 13; 14].

Knowledge of neuroscience that supports MBA and how it informs treatment selection holds great promise for broader and more effective therapeutic options. Understanding the theoretical and evidence basis of MBA may provide primary care providers with treatment solutions to many vexing problems traditionally encountered in treating chronic pain. These include patient complaints of severe pain in the absence of apparent physiologic or anatomic cause, the failure to achieve a satisfactory therapeutic response to conventional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, and the loss of analgesic effectiveness in patients who have progressed from acute stage to chronic pain syndromes. MBA also explains why some pain therapies are ineffective and informs the clinician regarding potentially effective augmentation strategies to enhance pain control and reduce opioid requirements [3; 4; 6].

Pain neuroscience is exceptionally complex. The material obtained from the scientific literature and presented in this course is greatly simplified and reduced, and effort has been made to highlight pain mechanisms for which known therapies have been identified as targeting.

PRIMARY PAIN TYPES

Most pain syndromes involve multiple, often overlapping, neurobiologic mechanisms determined by the stage of the disease process. Current concepts of pain classify these into four main categories: nociceptive, inflammatory, neuropathic, and centralized [15].

Nociceptive pain is a physiologic response to tissue injury, the perception that arises from intense stimulation of specialized peripheral sensory neurons (nociceptors) that respond only to noxious (pain) stimuli. Nociceptive pain is subgrouped by location of involved tissues into somatic pain (muscle or connective tissue) and visceral pain (visceral structures) [13]. Nociceptive pain is considered adaptive during tissue healing but maladaptive and pathologic when it persists after healing has occurred.

Inflammatory pain occurs in response to tissue injury or infection that activates peripheral nociceptors and initiates the immune response. While the resultant production and recruitment of pro-inflammatory mediators to the injury site may serve to perpetuate discomfort, it also facilitates tissue repair; thus, this is considered an adaptive pain mechanism [15].

Neuropathic pain originates from peripheral or central nervous system injury. Unlike nociceptive and inflammatory pain, the mechanism of neuropathic pain has no adaptive function and is strictly pathologic [4; 16]. Acute pain from somatosensory damage is termed "acute neural injury." The term "neuropathic pain" implies pain that persists beyond the period of expected or actual tissue healing, and the underlying mechanism involves a maladaptive alteration in somatosensory nervous system function [11].

Centralized pain results from heightened nociceptive sensitivity in the absence of detectable peripheral stimulus and with negligible peripheral inflammatory pathology. The mechanism is poorly understood and is regarded as strictly pathologic as it lacks any evident adaptive function. Centralized pain syndromes include conditions such as fibromyalgia, tension headache, and irritable bowel syndrome [4; 13; 14].

PRIMARY PAIN PATHWAYS AND MECHANISMS OF PAIN

Whether pain originates from tissue injury, tissue infection, or peripheral nerve injury, similar mechanistic processes relay the nociceptive, inflammatory, or neuropathic pain impulse from the site of peripheral origin to the brain. This involves transduction, signaling, transmission, modulation, and perception of the pain impulse. These processes occur along a similar series of interconnected pathways, initially in the peripheral nervous system and spinal cord and then the mid-brain and cerebral cortex of the central nervous system (CNS).

Understanding the anatomy and physiology of normal pain perception is important, because altered structure and function of these mechanisms and pathways characterize chronic pain and represent therapeutic targets for a mechanism-based approach to pain treatment. Intercellular, cellular, and molecular contributions to pain impulse generation and propagation are highly complex, and the material presented in the following section is simplified.

NOCICEPTIVE PAIN

There are five stages of pain processing and location in the broader pain pathway. The first is transduction. Acute injury or damage to peripheral tissue initiates transduction (translation) by nociceptors of the physical stimulus into an electrical signal [4; 17]. This involves noxious or inflammatory stimuli activating peripheral terminals of nociceptors. The stimulus is transduced into an electrical impulse via voltage-gated sodium channels (NaVs) and transient receptor-potential channels (e.g., TRPV1, TRPA1). Nociceptive receptor activation initiates peripheral nerve depolarization that, if sufficient, activates NaVs to trigger a burst of action potentials. The frequency and duration of the action potentials are determined by the intensity of the noxious stimuli. Nociceptor transduction and depolarization are influenced by neurochemical contributions from tissues, inflammatory cells, and the neuron itself.

The second stage is signaling, during which the pain impulse is relayed along the neuron from peripheral nociceptor terminals to the dorsal horn of the spinal cord [4; 18]. Specifically, signaling involves the relay of action potentials along the nerve fiber, and the type of fiber carrying the signal influences pain quality. Sodium ions enter during depolarization, and then potassium ions leave to restore baseline negative charge.

In nociceptor neurons, signaling involves three types of primary afferents [17]:

- A-Beta fibers: Myelinated, large-diameter fibers that respond primarily to non-noxious stimuli such as touch or vibration
- A-Delta fibers: Myelinated, small-diameter fibers that rapidly carry sharp, well-localized pain signals
- C-fibers: Transmit delayed, long-lasting, dull, poorly localized pain from the injury area. Because they are unmyelinated, C-fibers are more easily damaged and bear the brunt of injury in herpes zoster (shingles) and painful diabetic neuropathy. Not surprisingly, the quality of pain in these conditions is often a burning allodynia.

Following signal entry into the dorsal horn of the spinal cord, transmission begins. This involves movement of the pain signal across the synaptic cleft (juncture) between the primary afferent neuron and the second-order ascending neuron for relay to the brain [10; 11]. To enhance movement across the synaptic cleft, transmitter chemicals are released from the presynaptic afferent neurons, including substance P, cholecystokinin, calcitonin gene-related peptide (CGRP), and glutamate, the most widespread excitatory amino acid in the CNS [16; 17; 19]. The signal is relayed postsynaptically by ascending spinal pathways to supra-spinal sites. Some ascending pathway axons synapse with thalamic nuclei, which project by relay neurons to various cortical regions. These cortical regions and their contribution to pain processing include [4; 20; 21]:

- Primary somatic sensory cortex (mediates perception of pain intensity and location)
- Insular cortex (perception and affective components of pain)
- Cingulate cortex (processes the emotional response to pain)
- Insular and anterior cortical regions (mediate behavioral, emotional, and autonomic response to pain)

Other axonal projections enter limbic system regions involved in emotional response to pain, including the insula, amygdala, and cingulate cortex.

Modulation is the process whereby the intensity of pain signaling is weakened or amplified [4; 21; 22; 23; 24]. Modulation can follow an ascending or descending pathway.

Within ascending pathways, modulation of sensory pain begins in the dorsal root ganglion and dorsal horn neurons of the spinal cord, and then subsequently occurs at numerous neuraxis levels through involvement of endorphins, neurokinins, prostaglandins, biogenic amines, gamma-aminobutyric acid (GABA), neurotensin, cannabinoids, and purines. Glutamate facilitates pain signaling in the spinal cord and throughout most of the CNS. Several receptors mediate the action of glutamate; these include the ionotropic receptors alpha-amino-3-hydroxy-5-methyl-4-izoxazolepropionic acid (AMPA), kainate, *N*-methyl-D-aspartate receptors (NMDA); and the metabotropic glutamate receptor.

Descending pathway modulation involves limbic, cortical, and thalamic structures projecting to excitatory glutamatergic neurons in the periaqueductal gray (PAG) matter [4; 16]. The glutamate neurons activate other neurons in the descending inhibitory pathway, which inhibit nociceptive transmission in the spinal cord through chemical signaling. Endogenous opioids activate pre- and post-synaptic opioid receptors in dorsal horn neurons. Noradrenergic inhibition originates in the locus coeruleus/subcoeruleus and travels to the spinal cord via the ventromedial funiculus. Norepinephrine released from these inhibitory terminals acts via presynaptic alpha-2 adrenergic receptors.

The dorsal horn neurons weaken pain transmission by regulating serotonergic neurons in the raphe nuclei and noradrenergic neurons in the reticular formation. This is achieved through:

- Release of endogenous opioids, norepinephrine, and serotonin in the dorsal spinal cord
- Recruitment of inhibitory interneurons that release GABA
- Direct inhibition of pain projection neurons

Input from cortical structures and the amygdala partially accounts for the influence of cognitive and emotional processes on pain intensity and experience [25].

In the non-pathologic state, only a small proportion of pain signals relayed to the spinal cord reach the thalamus, due to modulatory influences on synaptic transmission of sensory inputs in the dorsal horn, ascending, and descending pathway sites [4].

The final stage of pain processing is perception, the subjective pain experience resulting from interaction between transduction, transmission, and modulation with the psychologic state or traits of the individual [3; 26; 27; 28; 29; 30]. These states/traits include attention, anticipation, fear/anxiety, empathy, reward, placebo, and direct control. Brain regions that mediate cognitive and emotional pain processing include the prefrontal cortex and primary and secondary somatosensory cortices; limbic system structures; and the hypothalamus. This diverse brain region involvement in pain response is termed the "distributed network." Most importantly, these same brain regions can undergo neuroplastic change and functional alteration as the result of intense or prolonged nociceptive signal barrage.

INFLAMMATORY PAIN

The process of inflammatory pain generation and relay is similar to that described for nociceptive pain, but it also involves inflammatory mediators released at the injury site that trigger nociceptor activation [4; 11; 31; 32; 33; 34]. Peripheral tissue injury or infection releases the pro-inflammatory factors ATPase, potassium ions, chemokines, cytokines, prostaglandins, and nerve growth factors. The inflammatory mediators interleukin-1β and tumor necrosis factor (TNF)-α activate the release of cyclooxygenase (COX)-2, which generates prostaglandin PGE2, a vasodilator that produces pain and edema [18; 35]. TRPV1 and TRPA1 in peripheral nociceptor terminals are stimulated by signaling from pro-inflammatory molecules and activate nociceptors. Bradykinin, prostaglandins, and nerve growth factor activate C-fibers, normally unresponsive to non-inflammatory stimuli. C-fiber and nociceptor activation then facilitates afferent signal transmission to the spinal cord and initiates the changes that lead to peripheral sensitization.

ACUTE NEURAL INJURY AND NEUROPATHIC PAIN

Neuropathic pain has been defined as pain originating from a lesion or disease affecting the somatosensory system [36]. This definition emphasizes the sensory pathway as the pathophysiologic locus and reflects the progress made in elucidating neuropathic pain mechanisms [37].

Neuropathic pain conditions are diverse in etiology and mechanism and may originate from infection, metabolic disorders, surgery, nerve entrapment or compression, chemotherapy or radiation, and ischemic injury [38; 39]. Distinct mechanisms account for neuropathic pain but are nonspecific as to type of syndrome. Neuropathic pain may arise concurrently with nociceptive pain [40]. Neural damage is necessary but not sufficient for neuropathic pain to develop; the initiating condition must interact with the genotype, diet, and lifestyle of the individual [6].

Acute neural pain and neuropathic pain develop following neural damage that induces a neuroma (a regenerative nerve sprout) at the proximal nerve stump [6; 11; 38; 39; 40; 41]. Dysregulated voltage-gated sodium channel and non-selective cation channel TRPV1 expression at the damage site and in dorsal root ganglion A-Beta fibers lead to primary afferent hyperexcitability (e.g., lowered threshold and higher firing rate) and ectopic firing, respectively. Peripheral immune cells and microglia in the dorsal root ganglia of both injured and uninjured ipsilateral adjacent afferents release interleukin-1β, TNF, bradykinin, and nerve growth factor, which contribute to neuropathic pain by activating nociceptive neurons.

CENTRALIZED PAIN SYNDROMES

Patients with chronic, diffuse hyperalgesic pain in the absence of obvious peripheral origin have traditionally received diagnostic labels of idiopathic or functional pain, functional somatic syndrome, and somatization. A number of prevalent disorders, about which the general public is increasingly aware, fall into this category, including irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder, and myofascial pain syndrome [42]. Common underlying mechanisms in these conditions, now termed centralized pain syndromes or central sensitivity syndromes, have been identified and include heritable pain sensitivity combined with neuroplastic CNS alteration. This sensitivity and CNS alteration results in augmented pain transmission and amplified sensory inputs [42]. Although pain can be localized (as with temporomandibular joint disorder or generalized (as with fibromyalgia), differences in clinical presentation are now thought to reflect the manifestation of a shared disease state [4; 43]. This construct of a centralized pain sensitivity condition has moved beyond the narrow consideration in functional pain syndromes to broader recognition of its essential contribution to pain in many chronic peripheral pain conditions. Therapeutic targeting of central pain is necessary for pain control in these patients [42; 44; 45].

Overlapping or shared characteristics in centralized pain syndromes include [42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52]:

- Multifocal pain, fatigue, insomnia, cognitive or memory problems, and, in many cases, psychologic distress
- Broad variation in symptom presence and severity
- Strong familial predisposition and unambiguous evidence that these syndromes are separable from depression and other psychiatric conditions
- Initiation or exacerbation by a broad range of biologic and psychologic stressors
- Presence of diffuse hyperalgesia and/or allodynia and often hypersensitivity to non-pain sensory input
- Neurogenic inflammation, especially of mucosal surfaces, resulting in increased mast cells and the appearance of a mild inflammatory process, autonomic nervous system dysfunction, and hypothalamic pituitary dysfunction

- Lack of response to traditional pain treatments for nociceptive or inflammatory pain
- Effectiveness of the same drug and non-drug therapies among these conditions

In centralized pain syndromes, widespread musculoskeletal pain and hyperalgesia are induced by pH-dependent (acidity-sensing) ion channel-3 activation and suppressed by neurotrophin-3 inhibition [53]. Pain sensitivity and response is inhibited by the action of serotonin-norepinephrine and opioidergic descending pathway projections to the dorsal horn of the spinal cord. Alteration in descending inhibitory pathway function diminishes analgesia and promotes hyperalgesia and allodynia in patients with centralized pain syndromes. Central sensitization results from glutamate action on NMDA receptors, which increases intracellular calcium levels and kinase activation to initiate hyperalgesia and allodynia [54].

PSYCHOLOGIC PAIN MECHANISMS

Although the concept of central sensitization as a mechanism of chronic pain was first described in reference to the dorsal horn of the spinal cord, similar synaptic plasticity with functional and structural alteration has been found in regions of the brain that mediate pain-related emotion and memory, including sensorimotor, limbic, and prefrontal systems [55; 56; 57]. These may represent a substrate for chronic cognitive, emotional, and memory changes that are learned and retained—for example, conditioned fear and memory [11]. Pain is perceived via ascending nociceptive pain fibers that activate a complex system of pathways within diverse regions of the brain. Once activated, this system encodes nociceptive pain for location, intensity, quality, duration, and emotional association. The level of attention, distraction, and manipulation of mood also impact the degree of perceived pain, a reflection of the importance of psychologic factors in the chronic pain experience [15].

A 2019 narrative review, based on a neuroscience literature review to identify processes affecting pain chronification, examined the association between memory and the development of chronic pain, showing that chronic pain and memory interact closely on several levels [86]. Anatomically, the regions of the brain central to encoding and consolidation of memory are also implicated in experimental aspects of pain. Encoding of chronic pain and of memory is mediated by common neurotransmitters and involves similar mechanisms of neural plasticity, such as central sensitization. Serial imaging studies show that the transition to chronic pain is accompanied by spatiotemporal reorganization of brain activity, during which the representation of pain gradually shifts to emotional and limbic structures. The authors conclude that chronic pain can be seen, at least in part, as the persistence of the memory of pain and/or the inability to extinguish painful memories [86].

The relationship between emotion and pain perception is complex, and potentially reinforcing and potentiating. Pain involves active CNS regulation through excitatory and inhibitory modulation, primarily involving brainstem nuclei projections to the dorsal horn [15]. Forebrain centers and their products, including cognition, emotion, attention, and motivation, substantially influence brainstem nuclei and subjective pain experience. Specific cognitive styles and personality traits, such as somatization, catastrophizing, and hypervigilance, can amplify pain, sensitize dorsal horn spinal cord neurons and second-order pain pathway neurons, and prolong the development, amplification, and maintenance of persistent pain. Behavioral and cognitive therapies likely affect synaptic transmission in the spinal cord via descending pathways, and thus may prevent or reverse the long-term changes of synaptic strength in pain pathways [19; 58; 59; 60].

CENTRAL SENSITIZATION IN THE DEVELOPMENT AND MAINTENANCE OF CHRONIC PAIN

In recent decades, neuroscience has advanced understanding of the pathogenesis of chronic pain, specifically in relation the process of central sensitization within the neocortex of the brain, a process that has important implications for patient education and pain management [87]. The transformation of acute into chronic pain occurs with the development of central sensitization that is usually, but not always (as with centralized pain syndromes), preceded by peripheral sensitization. The persistence of pain beyond the period of tissue healing, whether from nociceptive, inflammatory, or neural injury, indicates that ongoing nociceptive activity has become dissociated from peripheral input and that a pathologic alteration in pain processing and perception has developed involving peripheral and central pain pathways. The pain feels as if the origin involves peripheral tissue, but it is actually a manifestation of abnormal sensory processing within the CNS [10].

Central sensitization is often preceded by peripheral sensitization, the result of alteration in the transduction proteins and ion channels that determine nociceptor terminal excitability. With peripheral sensitization, inflammatory mediators such as adenosine triphosphate (ATP) are released by tissue damage to activate peripheral nociceptor terminals, producing the sensation of pain. Inflammatory cells such as neutrophils become activated and produce other chemical mediators that generate COX-2, which generates prostaglandin PGE2. PGE2 alters pain sensitivity by amplifying response and dropping response threshold to stimuli in peripheral nociceptors.

In general, the development of central sensitization follows several overlapping neurologic events. Peripheral tissue damage generates intense or protracted nociceptive signaling to the dorsal spinal cord. Signaling and molecular barrage from pre-synaptic afferents across the synaptic juncture stresses post-synaptic terminals of second-order ascending neurons. This causes receptor membranes to depolarize and excitatory receptors to activate. A cascade of events is initiated that alters synaptic receptor density, threshold, kinetics, and activation and dramatically increases pain transmission [4; 25]. The resultant state of CNS stimulation and dysfunction is characterized by amplified pain signaling, nociceptor excitation, substantial drop in pain response threshold, pathologic loss of anti-nociceptive pain inhibition, and augmented descending pathway facilitation [11; 61]. This activity is enhanced by cognitive-emotional factors such as stress, anger, and catastrophic beliefs and fear concerning the future. These factors are known to facilitate pain, in part by inducing a state of cognitive-emotional sensitization within the CNS that results in more severe pain [87]. Pain hypersensitivity, allodynia, hyperalgesia, and enhanced temporal summation of pain perception with central sensitization underlie many chronic pain conditions.

There is evidence that neuroinflammation in the peripheral and central nervous systems plays an important role in promoting central sensitization and the perpetuation of chronic pain [88]. Central to this process is the activation of glial cells (microglia and astrocytes) within the spinal cord and brain that stimulates the release of proinflammatory cytokines and chemokines. Glial cells are part of the non-neuronal matrix within the nervous system that provides supportive physiologic functions. Peripheral nerve injury stimulates the local production of prostanoids, causing widespread induction of COX-2 and macrophage activation. The macrophages activate lymphocytes, which in turn release cytokines and chemokines. These activate microglia and astrocytes, which augment the inflammatory response via the signaling molecules ATP, fractalkine, monocyte chemotactic protein-1, proinflammatory cytokines, nitric oxide and glutamate. Studies show that cytokines and chemokines are powerful neuromodulators that play a role in inducing allodynia and hyperalgesia; their sustained release within the CNS also promotes chronic widespread pain affecting multiple body sites [62; 64; 88].

Activation of microglia is associated with several mechanisms that underlie central sensitization within the CNS. These include synthesis and release of neurotrophic factors that increase neuronal excitability, enhanced synaptic efficacy in patients with chronic pain, and activation of astrocytes, which is important in maintaining neural circuit and mediating inflammation via release of cytokines [87]. Increased glial activation and astrocyte-mediated neuroinflammatory markers have been demonstrated in patients with chronic non-specific low back pain, fibromyalgia, and lumbar radiculopathy [87]. Neuroinflammation is now recognized as possibly mediating the persistence and chronification of many human pain conditions [88].

Neuroplasticity is the cellular-level process whereby neuronal cytoarchitecture is physically remodeled. It accounts for the development of central sensitization and represents the core process by which acute pain transitions to a chronic pain syndrome. Intense or persistent acute pain generates peripheral nociceptive signal transmission to the dorsal root ganglia and thence to the relay neurons within the dorsal horn of the spinal cord. This input stimulates the release of glutamate and the neuropeptides substance P and CGRP from afferent neurons into the synaptic cleft between afferents and second-order dorsal horn neurons. With sufficient signaling barrage, post-synaptic NMDA receptor membranes depolarize, removing the Mg2+ ion that blocks the NMDA receptor channel. The NMDA channel complex is now primed and readily activated by the surge in presynaptic glutamate release, which induces cellular Ca2+ influx and initiates protein kinase C activity. Protein kinase C then activates nitric oxide synthase and production. From this second-order dorsal horn neuron, nitric oxide diffuses through the membrane and synaptic cleft into the nociceptor to close K+ channels by stimulating guanyl synthase. This enhancement in channel conductance and receptor membrane trafficking contributes to prolonged membrane depolarization [23; 61; 62].

Post-synaptic NMDA receptor activation in the spinal cord (and eventually in the thalamus, limbic system, and cerebral cortex) is the greatest contributor to the development of central sensitization. A far-reaching cascade is generated, resulting in altered balance between pro- and anti-nociceptive neurotransmitters [25; 54; 62; 63].

PAIN THERAPIES AND TARGET MECHANISMS

Strategies for managing chronic pain will increasingly rely on identification and targeting of the specific neurophysiologic mechanism(s) and molecular components responsible for pain generation and/or maintenance.

Peripheral tissue injury, damage, or inflammation initiates prostaglandin release at the injury site, where its precursor action helps propel the pain impulse from peripheral nociceptor terminals to the spinal cord. Prostaglandin PGE2 produces pain and edema and is highly active in arthritis and musculoskeletal injuries. NSAIDs inhibit the synthesis of PGE2 [18; 35].

Action potentials, produced by the exchange of ions along the inner and outer neuron membrane, relay the pain signal from peripheral injury site to the spinal level. Action potentials can be suppressed with local anesthetics and anticonvulsants by blocking membrane ion influx and efflux [18; 35].

Within the dorsal horn of the spinal cord, primary afferent neurons release transmitter molecules across the synaptic cleft to facilitate pain signal transmission to ascending neurons for relay to the brain. These neurotransmitters include substance P, cholecystokinin, CGRP, and glutamate. The presynaptic terminal is a major activity site of opioids and cannabinoids, and gabapentin and pregabalin act on the alpha-2-delta subunit of voltage-gated calcium channels to inhibit pain transmitter release here [18; 35].

The pain signal is transmitted by ascending spinal neurons and enters the brain via the PAG, the reticular formation, and thalamus. It is then distributed to the limbic system and cortical structures. The PAG contains a high density of opioid receptors and is a site of opioid binding to induce analgesia [35].

The descending pain pathway originates in higher brain centers and descends to the spinal cord, inhibiting pain signaling through the release of endogenous opiates, serotonin, and norepinephrine. At this site, TCAs and SNRIs reduce pain by blocking serotonin and norepinephrine reuptake [18; 35].

PHARMACOTHERAPIES

Topical Agents

Local Anesthetics

The local anesthetics lidocaine and bupivacaine block Na+ influx of voltage-gated ion channels in afferent neuron terminals, inhibiting depolarization and generation of action potentials, resulting in the transmission of fewer nociceptive impulses to the spinal cord. In clinical application, topical lidocaine is used for neuropathic pain to block hyperactive sodium ions in damaged peripheral nerves and inhibit transmission of ectopic impulses to the dorsal horn. This action interferes with peripheral and central sensitization and maladaptive neuroplasticity [66; 67].

Capsaicin

Capsaicin defunctionalizes nerve fiber terminals through multiple mechanisms to produce analgesia. The initial reduction in neuronal excitability and responsiveness result from inactivation of voltage-gated sodium channels and direct desensitization of plasma membrane TRPV1 receptors. This is followed by extracellular Ca2+ entry of TRPV1 and release from intracellular stores to overwhelm the TRPV1 receptor intracellular Ca2+ buffering capacity, subsequent activation of calcium-dependent proteases, and cytoskeleton breakdown [37; 61]. The persistent effect involves extracellular Ca2+ entry of TRPV1 and release from intracellular stores to overwhelm TRPV1 receptor intracellular Ca2+ buffering capacity, subsequent activation of calcium-dependent proteases, and cytoskeleton breakdown [37; 61]. Capsaicin is available as a high-potency (8%) patch and as a lower-concentration cream. A single 60-minute application may provide up to 12 weeks of analgesia [66]. Capsaicin may initially cause pain because substance P is released from nociceptive terminals to initiate nociceptive firing. The analgesic response follows as nociceptive terminals desensitize to elevate pain threshold [68].

NSAIDs and Acetaminophen

NSAIDs alleviate pain by inhibiting the conversion of arachidonic acid to prostaglandins catalyzed by COX isozymes. Nonselective NSAIDs inhibit COX-1 and COX-2 and include ibuprofen, aspirin, and naproxen. The nonselective action inhibits the formation of both gastroprotective-mediating prostaglandins and pain-promoting prostaglandins, increasing the risk of serious toxicities such as gastrointestinal (GI) ulceration and bleeding. This prompted the development of selective COX-2 inhibitors, which produce fewer GI side effects but are linked with an increased risk of cardio-renal morbidities [67]. To mitigate risk of GI adverse events, proton pump inhibitors are recommended for use in some patients using NSAIDs [69].

Acetaminophen is available over the counter and is also included in combination with many prescription opioids. Analgesia is achieved through central but not peripheral inhibition of prostaglandin. Although effective in mild pain, acetaminophen is not anti-inflammatory. The side-effect profile is relatively benign with intermittent use at recommended labeled dosing, but long-term or high-dose use can be hepatotoxic, and the daily dose should never exceed 4 g. Acetaminophen is recommended over NSAIDs as an analgesic in patients with GI, renal, or cardiovascular comorbidity [70].

Anticonvulsant Drugs

Gabapentinoids

Gabapentin and pregabalin are effective in a wide range of neuropathic pain conditions. Their mechanism of action involves selective binding to and blockade of the α2δ1 subunit of voltage-gated calcium channel in various brain regions and the superficial dorsal spine. This inhibits the release of glutamate, norepinephrine, and substance P to decrease spinal cord levels of neurotransmitters and neuropeptides [23; 66; 71]. The binding affinity of pregabalin for the calcium channel α2δ1 subunit is six times greater than gabapentin, which is reflected in the greater efficacy of pregabalin at lower doses. Because gabapentin possesses a shorter half-life and nonlinear absorption, pregabalin is easier to titrate and better tolerated [71].

Lacosamide

Lacosamide can produce antinociceptive effects through the modulation of collapsin-response mediator protein 2, which inhibits the NMDA receptor subunit NR2B. Several clinical trials have confirmed its efficacy in painful diabetic neuropathy, and a 2.5-year follow-up study confirmed its long-term safety profile and sustained efficacy [71].

Topiramate

Topiramate is used clinically in neuropathic pain syndromes and migraine headache prophylaxis. It is characterized by a complex mechanism of action involving suppression of action potentials with sodium-channel and calcium-channel blockade; GABA receptor; and AMPA receptor antagonism and kainate inhibition. Topiramate is also a glutamate antagonist, the only anticonvulsant drug for which this action is prominent [72].

Antidepressants

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are widely used in neuropathic pain. A TCA's mechanism involves blocking pre-synaptic reuptake of norepinephrine and serotonin; inhibition of neuronal membrane ion channels by reducing neuronal influx of calcium or sodium ions; and activity with adenosine and NMDA receptors [68]. A primary site of analgesic action is the descending modulatory pathway, where monoamine reuptake inhibition elevates norepinephrine and serotonin levels to enhance endogenous nociceptive inhibition. The secondary amines nortriptyline and desipramine are favored over the tertiary amines amitriptyline and imipramine due to more benign side effect profiles [11; 73]. Amitriptyline is often the treatment of choice for neuropathic pain [68].

Serotonin-Norepinephrine Reuptake Inhibitors

The dual serotonergic and noradrenergic re-uptake inhibitors (SNRIs) duloxetine, venlafaxine, and milnacipran are widely used in the treatment of neuropathic pain conditions. Duloxetine is used in painful diabetic neuropathy, with demonstrated efficacy at 60–120 mg/day. Venlafaxine behaves like a serotonin-specific re-uptake inhibitor (SSRI) at doses of ≤150 mg/day and like an SNRI at doses >150 mg/day. A dose ≥150 mg/day is often necessary to achieve pain control [66]. Of the three available SNRIs, milnacipran has the greatest affinity for norepinephrine, duloxetine has the greatest potency in blocking serotonin, and venlafaxine selectively binds to the serotonin but not the norepinephrine transporter [74]. SNRIs are better tolerated than TCAs because they lack affinity for cholinergic, histaminic, and adrenergic receptors [71]. The anti-nociceptive effect of the SNRIs duloxetine and milnacipran primarily involves increasing serotonin and norepinephrine concentrations in descending inhibitory pain pathways, which enhances the suppression of afferent spinal inputs and reduce pain [11].

Mirtazapine

Mirtazapine is an atypical tetracyclic antidepressant that acts through inhibition of 5HT-2, 5HT3, H1-a2-hetero, and alpha-2-adrenergic receptors. This accounts for its beneficial effect in the adjuvant treatment of migraine headache, anxiety, agitation, depression, insomnia, and low appetite. H1-receptor antagonism is most prominent at low doses (≤30 mg) [72].

Glutamate Antagonists

Dextromethorphan

Dextromethorphan is a commonly used oral cough suppressant and acts as an NMDA receptor antagonist, a sigma-1 receptor agonist, an N-type calcium channel antagonist, and a serotonin reuptake transporter antagonist. Rapid hepatic cytochrome P450-2D6 (CYP2D6) metabolism interferes with maintaining plasma concentrations sufficient for analgesia, reflected in poor clinical trial outcomes. Co-administration of the potent CYP2D6 inhibitor quinidine has been found to maintain therapeutic levels. The U.S. Food and Drug Administration (FDA) approved dextromethorphan for use in the treatment of pseudobulbar palsy. One trial found efficacy in using dextromethorphan for painful diabetic polyneuropathy [37].

Ketamine

Ketamine is a phencyclidine anesthetic given parenterally, neuraxially, nasally, transdermally or orally in subanesthetic doses to alleviate a variety of pain conditions, including severe acute pain, chronic or neuropathic pain, and opioid tolerance [68]. The mechanism of analgesic effect primarily involves NMDA receptor inhibition. Thus, patients with NMDA-mediated central sensitization are likely to realize significant benefit from treatment with ketamine. Ketamine also has activity on nicotinic, muscarinic, and opioid receptors and exerts both anti-nociceptive and anti-hyperalgesic effects, with the latter produced at lower dose ranges [75].

Ketamine is one of very few therapies demonstrating substantial and durable pain reduction of treatment-refractory chronic regional pain syndrome [65]. Potentially distressing adverse reactions (e.g., hallucinations, disturbing dreams, out-of-body experiences) and unwanted changes in mood, perception, and intellectual performance have limited its clinical use in pain control. However, trials have effectively controlled these side effects with high-dose co-administration of midazolam or lorazepam combined with either clonidine or ondansetron [76; 77].

Opioids

Morphine and Other Mu Opioid Receptor Agonists

The endorphinergic pathway is comprised of endogenous ligands and the mu, kappa, and delta opioid receptors. Endorphins, enkephalins, dynorphins, and their receptors are expressed in multiple CNS regions in peripheral nerves and the skin. Opioid analgesics bind to opioid receptors (primarily the mu opioid receptor), mimicking the action of endogenous ligands. In general, opioid drugs produce analgesia through opioid receptor binding on cell membranes, producing simultaneous activity at multiple presynaptic, postsynaptic, and nervous system sites. Presynaptic opioid receptor activation inhibits the release of nociceptive neurotransmitters such as substance P and glutamate. Postsynaptic activation inhibits pain transition by opening potassium or chloride channels to hyperpolarize and inhibit neuronal firing [78]. These actions inhibit pain signal transmission from peripheral afferents to ascending spinal cord neurons; activate descending pathway inhibition; and alter limbic activity, decreasing pain awareness [66].

Depending on receptor affinity, pharmacokinetics, mechanism of action, and other factors, each opioid produces a unique spectrum of pharmacologic effects. This includes analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished GI motility, altered circulatory dynamics, histamine release, physical dependence, and disease-specific utility [72]. As noted, the classical opioids, including morphine, codeine, hydrocodone, and oxymorphone, have greatest affinity for the mu opioid receptor and weak activity at kappa and delta opioid receptors [66].

Buprenorphine

Although opioids in general are less effective in reducing neuropathic pain than nociceptive pain, specific drugs vary in affinity for sodium channel types and thus in neuropathic pain efficacy. Buprenorphine is a partial mu opioid receptor agonist and a weak kappa and delta opioid receptor antagonist with efficacy in neuropathic pain due to its potent local anesthetic action and voltage-gated sodium channel blockade via the local anesthetic binding site. Buprenorphine efficacy in blocking sodium channels is superior to meperidine, lidocaine, tramadol, morphine, and bupivacaine [66].

Methadone

Methadone exerts modest NMDA antagonism and inhibition of 5-HT and norepinephrine reuptake. With nerve injury pain, it induces greater anti-allodynia action than morphine or oxycodone. Thus, methadone may be useful in neuropathic pain due to its cooperative actions as an NMDA receptor antagonist and mu-opioid receptor agonist [66].

Tramadol

Tramadol is a centrally acting, weak mu opioid receptor agonist and inhibits norepinephrine and serotonin reuptake to promote serotonin release [16]. About 30% of its analgesic effect is attributable to mu opioid receptor binding. Tramadol has shown some efficacy in fibromyalgia and neuropathic pain. Although tramadol is centrally acting, it has been associated with increased blood and intracranial pressure and should be used with caution [66].

Tapentadol

Tapentadol is a new opioid therapeutic for moderate-to-severe pain with a novel mechanism as a mu opioid receptor partial agonist and norepinephrine reuptake inhibitor [79]. Its potency is two to three times lower than morphine, and tolerance develops significantly slower than with morphine. Tapentadol has been approved by the FDA for relief of moderate-to-severe acute pain [37].

Cannabinoids

Cannabinoid receptors CB1 and CB2 are expressed in all peripheral and CNS nociceptive pathways, including spinal cord, dorsal root ganglion neurons, and peripheral nociceptors. Endogenous endocannabinoid ligands are derived from arachidonic acid, bind to cannabinoid receptors to decrease presynaptic Ca2+ concentration, and activate inward-rectifying K+ channels to inhibit presynaptic glutamate release and modulate neuronal excitability [61]. The cannabinoid receptor ligand mechanism involves retrograde synaptic inhibition and signaling that directly upregulates or downregulates presynaptic release of GABA, dopamine, norepinephrine, glutamate, and other neurotransmitters [80]. Numerous studies have found cannabinoid utility in pain management, demonstrated by reduced nociceptive pain and muscle spasticity; hyperalgesia and allodynia suppression in neuropathic pain; inflammatory modulation; and analgesic synergy between cannabinoid and opioid systems [61]. Cannabinoids have also displayed neuroprotection in ischemia and hypoxia [80]. Agonists include delta9-tetrahydrocannabinol (delta9-THC), cannabinol, and cannabidiol, all of which are found in the cannabis plant.

Alpha-2 Adrenoceptor Agonists

Antinociceptive activity of the α-2 adrenoceptor agonists clonidine and tizanidine includes modulating dorsal horn neuron function and norepinephrine and 5-HT release, potentiating mu-opioid receptors, and decreasing neuron excitability through calcium channel modulation [72]. Clonidine is available as a transdermal patch for use in neuropathic pain states. Local use enhances release of endogenous

enkephalin-like substances. Intrathecal or epidural administration with opioids and/or local anesthetics is favored in treating neuropathic pain because the synergistic effect improves pain control. Tizanidine is used as a muscle relaxant and antispasticity agent [66; 68].

Other Agents

Baclofen

Baclofen is a muscle relaxant that induces analgesia through agonist action on inhibitory GABA-B receptors. Baclofen is efficacious in patients with trigeminal neuralgia. Although efficacy has not been found in other neuropathic pain conditions, the anti-spasticity properties of baclofen may induce analgesia by relieving co-occurring muscle spasms [68].

Botulinum Toxin

Botulinum toxin is a neurotoxic protein synthesized by the bacterium *Clostridium botulinum* with broad clinical application. Botulinum toxin produces analgesia through blocking neurotransmitter release and TRPV1 receptor signaling in C-fibers, which inhibits substance P and CGRP release to reduce neurogenic inflammation and increase heat pain threshold. Trials have shown efficacy in focal painful neuropathies and mechanical allodynia and superior reduction in pain and opioid use versus lidocaine and placebo [37; 71]. A 2013 single-dose randomized controlled trial resulted in substantial improvements in pain and sleep outcomes in patients with postherpetic neuralgia [81].

Sulfasalazine

Tetrahydrobiopterin is an essential co-factor in producing nitric oxide and monoamines. Following peripheral nerve injury, tetrahydrobiopterin levels dramatically elevate and contribute to pain through excess production of neurotransmitters or signaling molecules. Sepiapterin reductase contributes to tetrahydrobiopterin biosynthesis and is upregulated in nerve injury; reducing tetrahydrobiopterin levels inhibits sepiapterin reductase, producing analgesia. Sulfasalazine is an FDA-approved anti-inflammatory agent that inhibits sepiapterin reductase. This mechanism in sulfasalazine may represent an effective, novel therapy for neuropathic pain [82].

Ondansetron

Ondansetron, a 5-HT3 receptor antagonist, has shown anti-nociceptive effects by blocking descending serotonergic facilitatory drive to the dorsal horn laminae. By this action, it may prevent neuroplastic changes in the dorsal horn [83]. Although gabapentin interacts with the auxiliary $\alpha 2\delta 1$ subunit of voltage-gated calcium channels, evidence suggests the actions of gabapentin also involve 5-HT3 receptors [61].

NONPHARMACOLOGIC THERAPIES AND A MULTIMODAL APPROACH

Centrally acting drugs, such as TCAs, SNRIs, and others, each target a particular mechanism that may be at play in a patient with chronic pain and may provide some degree of benefit. However, general practice and clinical trials over the years have not demonstrated satisfactory outcomes for most patients [87]. This is not surprising given that chronic pain and central sensitization consists of complex neuro-immunologic and psychologic interactions by multiple mechanisms. A 2019 review recommends a pain management strategy that takes into account central sensitization, and that clinicians design an individually tailored multimodal plan comprised of the following elements: pain neuroscience education of the patient, cognition-targeted exercise therapy, sleep management, stress management, and possibly dietary intervention [87].

Many patients with chronic pain receive multimodality treatment that includes pharmacology, cognitive-behavioral or other coping skills therapy, and a progressive strengthening or functional restoration modality. In addition to the greater benefit observed with this combined approach comes validation from neuroscience research showing that chronic pain is mediated by cortical structures.

Researchers have observed that patients with chronic low back pain achieve greater overall improvement with therapies addressing coping skills, functional ability, and activity tolerance (e.g., cognitive-behavioral therapy, progressive relaxation, yoga, meditation combined with progressive activity or exercise therapy) compared with therapies strictly targeting the lumbar spine (e.g., decompressive laminectomy) [84]. The latter approach can reduce pain but seldom improves physical function, a serious concern given the substantial correlation between physical performance and future disability [8; 85]. Diverse physiotherapies in chronic low back pain have been found effective in improving overall function unrelated to the original biomechanical focus [85]. The correlation between changes in brain structure and function suggests that structural and functional changes underlie or contribute to chronic low back pain and disability [8].

Learning- and memory-related neuroplastic changes that develop with chronic pain require therapies that facilitate extinction of aversive memories and restore body image and normal brain function. Successful approaches include brain stimulation, mirror training, therapeutic virtual reality, and behavioral extinction training [55].

According to the Institute for Clinical Systems Improvement, psychotherapy (e.g., cognitive-behavioral therapy, mindfulness-based stress reduction) is recommended for patients with a chronic pain diagnosis. (https://www.icsi.org/wp-content/uploads/2019/10/Pain-Interactive-7th-V2-Ed-8.17.pdf. Last accessed October 31, 2022.)

Strength of Recommendation: Expert Opinion/ Consensus Statement

CONCLUSION

The mechanism-based approach to pain management finds its greatest utility in the understanding and treatment of chronic pain. It is intended to augment, not replace, the traditional approach to the treatment of acute pain, which emphasizes the diagnosis and alleviation of the inciting injury or disease combined with the empiric application of analgesic medication. The aim of MBA is to identify and target the (potentially) multiple contributory mechanisms usually involved in any chronic pain syndrome. The strategy is to devise a therapeutic plan that addresses these mechanisms, often combining specific pharmacotherapies with psychotherapeutic approaches, physical rehabilitation, and behavior modification. Thus, MBA is consistent with the recommendations of numerous practice guidelines that suggest multidisciplinary modality treatment for many chronic pain conditions. It is also consistent with tailored treatment planning that considers the needs of the individual patient. The mechanism-based approach to pain management is now endorsed in a number of practice guidelines by leading organizations of pain professionals. The purpose of this course is to promote, among primary care clinicians and nurses, a broader understanding of the underlying neuroscience, pathophysiology, and treatment principles.

GLOSSARY

Terms associated with pain mechanisms and chronic pain [1; 39]:

Allodynia: Pain produced by a normally innocuous stimulus, such as light touch to the skin.

Central sensitization: Sustained pathologic excitability of neurons within the CNS that mediate pain perception, such that normal stimuli inputs produce abnormal responses.

Hyperalgesia: Exaggerated and prolonged pain response to noxious stimuli.

Nociceptive neuron: A central or peripheral neuron of the somatosensory nervous system capable of encoding noxious stimuli.

Nociceptive pain: Pain arising from damage to non-neural tissue, the result of nociceptor activation.

Nociceptive stimulus: A tissue-damaging event transduced and encoded by nociceptors.

Nociceptor: A high-threshold sensory receptor of the peripheral somatosensory nervous system capable of transducing and encoding noxious stimuli.

Noxious stimulus: A stimulus that is damaging or threatens damage to normal tissues.

Peripheral sensitization: Reduction in threshold and increase in responsiveness to stimuli of peripheral nociceptors.

Implicit Bias in Health Care

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

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

Works Cited

1. Pizzo PA, Clark NM. Alleviating suffering 101: pain relief in the United States. *N Engl J Med*. 2012;366(3):197-199.
2. Institute for Clinical Systems Improvement. Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management. Available at https://www.icsi.org/wp-content/uploads/2019/10/Pain-Interactive-7th-V2-Ed-8.17.pdf. Last accessed October 21, 2022.
3. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press; 2011.
4. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140:441-451.
5. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. *Trends Neurosci*. 2009;32(12):611-618.
6. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012;73(4):638-652.
7. Widerström-Noga EG, Finnerup NB, Siddall PJ. Biopsychosocial perspective on a mechanisms-based approach to assessment and treatment of pain following spinal cord injury. *J Rehabil Res Dev*. 2009;46(1):1-12.
8. Buckalew N, Haut MW, Aizenstein H, et al. Differences in brain structure and function in older adults with self-reported disabling and nondisabling chronic low back pain. *Pain Med*. 2010;11(8):1183-1197.
9. American Society of Anesthesiologists Task Force on Chronic Pain Management. Practice guidelines for chronic pain management. *Anesthesiology*. 2010;112(4):810-833.
10. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895-926.
11. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1-32.
12. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147(7):478-491.
13. National Comprehensive Cancer Network. Adult cancer pain. *J Natl Compr Canc Netw*. 2010;8:1046-1086.
14. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132(3):237-251.
15. Woolf CJ. What is this thing called pain? *J Clin Invest*. 2010;120:3742-3744.
16. Chen H, Lamer TJ, Rho RH, et al. Contemporary management of neuropathic pain for the primary care physician. *Mayo Clin Proc*. 2004;79(12):1533-1545.
17. Whitten CE, Donovan M, Cristobal K. Treating chronic pain: new knowledge, more choices. *Perm J*. 2005;9:9-19.
18. Charlton JE. *Core Curriculum for Professional Education in Pain*. 3rd ed. Seattle, WA: IASP Press; 2005.
19. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol*. 2007;26(4):465-473.
20. Willis WD. The somatosensory system, with emphasis on structures important for pain. *Brain Res Rev*. 2007;55(2):297-313.
21. Zhuo M. Neuronal mechanism for neuropathic pain. *Mol Pain*. 2007;3:14.
22. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-S15.
23. Cheng TH. Spinal cord mechanisms of chronic pain and clinical implications. *Curr Pain Headache Rep*. 2010;14(3):213-220.
24. Stein C, Clark JD, Oh U, et al. Peripheral mechanisms of pain and analgesia. *Brain Res Rev*. 2009;60:90-113.
25. Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: a review. *PM R*. 2011;3(12):1116-1125.
26. Younger J, Aron A, Parke S, Chatterjee N, Mackey S. Viewing pictures of a romantic partner reduces experimental pain: involvement of neural reward systems. *PLoS One*. 2010;5(10):e13309.
27. Borsook D, Becerra LR. Breaking down the barriers: fMRI applications in pain, analgesia, and analgesics. *Mol Pain*. 2006;2:30.
28. Koyama TM, Laurienti PJ, Coghill RC. The subjective experience of pain: where expectations become reality. *Proc Natl Acad Sci USA*. 2005;102(36):12950-12955.
29. Ohsner K, Ludlow D, Knierim K, et al. Neural correlates of individual differences in pain-related fear and anxiety. *Pain*. 2006;120:69-77.
30. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol*. 1999;82(4):1934-1943
31. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci*. 2012;15(8):1063-1067.
32. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. *Prim Care*. 2012;39(3):561-571.

33. Schaible HG, Ebersberger A, Natura G. Update on peripheral mechanisms of pain: beyond prostaglandins and cytokines. *Arthritis Res Ther*. 2011;13:210.
34. Michaud K, Bombardier C, Emery P. Quality of life in patients with rheumatoid arthritis: does abatacept make a difference? *Clin Exp Rheumatol*. 2007;25:S3-S45.
35. Helfand M, Freeman M. Assessment and Management of Acute Pain in Adult Medical Inpatients: A Systematic Review. Available at https://www.ncbi.nlm.nih.gov/books/NBK49074. Last accessed October 21, 2022.
36. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630-1635.
37. Kulkantrakorn K. Emerging concepts and treatment in neuropathic pain. *Neurology Asia*. 2012;17:265-271.
38. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol*. 2010;9:807-819.
39. Baron R. Mechanisms of disease: neuropathic pain—a clinical perspective. *Nat Clin Pract Neurol*. 2006;2:95-106.
40. Haanpää M, Hietaharju A. Central neuropathic pain. In: Kopf A, Patel NB (eds). *Guide to Pain Management in Low-Resource Settings*. Seattle, WA: IASP Press; 2010: 207-212.
41. Leone C, Biasiotta A, La Cesa S, et al. Pathophysiological mechanisms of neuropathic pain. *Future Neurology*. 2011;6(4):497-509.
42. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states: maybe it is all in their head. *Best Pract Res Clin Rheumatol*. 2011;25(2):141-154.
43. Clauw DJ. Fibromyalgia: update on mechanisms and management. *J Clin Rheumatol*. 2007;13:102-109
44. Kato K, Sullivan PF, Evengard B, Pedersen NL. A population-based twin study of functional somatic syndromes. *Psychol Med*. 2009;39:497-505.
45. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology*. 2006;130:1377-1390.
46. Fukuda K, Nisenbaum R, Stewart G, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA*. 1998;80:981-988.
47. Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. *Arthritis Rheum*. 2004;50(3):944-952.
48. Buskila D. Genetics of chronic pain states. *Best Pract Res Clin Rheumatol*. 2007;21:535-547.
49. Williams H. Making a difference in chronic pain management. *Nurs Times*. 2003;99:42-43.
50. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain*. 2009;10:777-791.
51. Raphael KG, Natelson BH, Janal MN, Nayak S. A community-based survey of fibromyalgia-like pain complaints following the World Trade Center terrorist attacks. *Pain*. 2002;100:131-139.
52. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation*. 1997;4(3):134-153.
53. DeSantana JM, Sluka KA. Central mechanisms in the maintenance of chronic widespread noninflammatory muscle pain. *Curr Pain Headache Rep*. 2008;12(5):338-343.
54. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther*. 2011;13(2):211.
55. Flor H. New developments in the understanding and management of persistent pain. *Curr Opin Psychiatry*. 2012;25(2):109-113.
56. Fu Y, Han J, Ishola T, et al. PKA and ERK, but not PKC, in the amygdala contribute to pain-related synaptic plasticity and behavior. *Mol Pain*. 2008;4:26.
57. Pedersen LH, Scheel-Kruger J, Blackburn-Munro G. Amygdala GABA-A receptor involvement in mediating sensory-discriminative and affective-motivational pain responses in a rat model of peripheral nerve injury. *Pain*. 2007;127:17-26.
58. Zusman M. Forebrain-mediated sensitization of central pain pathways: "nonspecific" pain and a new image for MT. *Man Ther*. 2002;7:80-88.
59. Rygh LJ, Tjølsen A, Hole K, Svendsen F. Cellular memory in spinal nociceptive circuitry. *Scand J Psychol*. 2002;43(2):153-159
60. Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. *Scand J Psychol*. 2002;43(2):113-121.
61. Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesth*. 2010;105(S1):i69-i85.
62. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev Neurother*. 2012;12(5):577-585.
63. Tam E, Furlan AD. Transdermal lidocaine and ketamine for neuropathic pain: a study of effectiveness and tolerability. *Open Neurol J*. 2012;6:58-64.
64. Staud R. Peripheral pain mechanisms in chronic widespread pain. *Best Pract Res Clin Rheumatol*. 2011;25(2):155-164.
65. Schwartzman RJ, Alexander GM, Grothusen JR. The use of ketamine in complex regional pain syndrome: possible mechanisms. *Expert Rev Neurother*. 2011;11(5):719-734.

66. Smith HS, Kara DK, Argoff CE. Management of neuropathic pain: current insights and future perspectives. *US Neurology*. 2012;8(1):57-61.
67. Raffa RB, Pergolizzi JV Jr, Tallarida RJ. The determination and application of fixed-dose analgesic combinations for treating multimodal pain. *J Pain*. 2010;11(8):701-709.
68. European Urological Association. Guidelines on Pain Management and Palliative Care. Available at https://d56bochluxqnz.cloudfront.net/media/Pocket-Pain-Management-Urology_LR.pdf. Last accessed October 21, 2022.
69. Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther.* 2013;15(Suppl 3):S5.
70. Whittle SL, Colebatch AN, Buchbinder R, et al. Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e Initiative. *Rheumatology*. 2012;51:1416-1425.
71. Xu B, Descalzi G, Ye HR, Zhuo M, Wang YW. Translational investigation and treatment of neuropathic pain. *Mol Pain.* 2012;8:15.
72. Barkin RL, Barkin SJ, Barkin DS. Pharmacotherapeutic management of pain with a focus directed at the geriatric patient. *Rheum Dis Clin North Am*. 2007;33(1):1-31.
73. Rahman W, D'Mello R, Dickenson AH. Peripheral nerve injury-induced changes in spinal alpha(2)-adrenoceptor-mediated modulation of mechanically evoked dorsal horn neuronal responses. *J Pain*. 2008;9:350-359.
74. Marks DM, Shah MJ, Patkar AA, et al. Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise.*Cur Neuropharmacology*. 2009;7(4):331-336.
75. Blonk MI, Koder BG, van den Bemt P, Huygen FJ. Use of oral ketamine in chronic pain management: a review. *Eur J Pain*. 2009;14(5):466-472.
76. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. *Pain Med*. 2012;13(2):263-269.
77. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo-controlled study. *Pain*. 2009;147(1-3):107-115.
78. Dinakar P. Pain management. In: Jankovic J, Mazziotta JC, Pomeroy SL, Newman NJ (eds). *Bradley and Daroff's Neurology in Clinical Practice*. 8th ed. Philadelphia, PA: Saunders; 2021.
79. Afilalo M, Morlion B. Efficacy of tapentadol ER for managing moderate to severe chronic pain. *Pain Physician*. 2013;16(1):27-40.
80. Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain*. 2013;29(2):162-171.
81. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. *Clin J Pain*. 2013;29(10):857-864.
82. Costigan M, Latremoliere A, Woolf CJ. Analgesia by inhibiting tetrahydrobiopterin synthesis. *Curr Opin Pharmacol*. 2012;12(1): 92-99.
83. McCleane GJ, Suzuki R, Dickenson AH. Does a single intravenous injection of the 5HT3 receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study. *Anesth Analg*. 2003;97(5):1474-1478.
84. Stevans JM, Saper RB. Chronic low back pain. In: Rakel D, Minichiello V (eds). *Integrative Medicine*. 5th ed. Philadelphia, PA: Saunders; 2022.
85. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Nonspecific low back pain. *Lancet*. 2012;379(9814):482-491.
86. McCarberg B, Peppin J. Pain pathways and nervous system plasticity: learning and memory in pain. *Pain Med*. 2019;20(12):2421-2437.
87. Nijs J, Leysen L, Vanlauwe, J, et al. Treatment of central sensitization in patients with chronic pain: time for change? *Expert Opin Pharmacother*. 2019;20(16):1961-1970.
88. Ji RR, Nackley A, Huh Y, et al. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology*. 2018;129(2):343-366.

Evidence-Based Recommendations Citation

Hooten WM, Thorson D, Hora J, et al. *Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management*. Bloomington, MN: Institute for Clinical Systems Improvement; 2017. Available at https://www.icsi.org/wp-content/uploads/2019/10/Pain-Interactive-7th-V2-Ed-8.17.pdf. Last accessed October 31, 2022.