01 - 9 Chronic Pain and Its Treatment

9 Chronic Pain and Its Treatment

Chronic Pain and

Its Treatment What is Pain? 379 “Normal” Pain and the Activation of Nociceptive Nerve Fibers 381 Nociceptive Pathway to the Spinal Cord 381 Nociceptive Pathway from the Spinal Cord to the Brain 382 Neuropathic Pain 382 Peripheral Mechanisms in Neuropathic Pain 382 Central Mechanisms in Neuropathic Pain 382 The Spectrum of Mood and Anxiety Disorders with Pain Disorders 387 This chapter will provide a brief overview of chronic pain conditions associated with different psychiatric disorders and treated with psychotropic drugs. Included here are discussions of the symptomatic and pathophysiological overlap between disorders with pain and many other disorders treated in psychopharmacology, especially depression and anxiety. Clinical descriptions and formal criteria for how to diagnose painful conditions are only mentioned here in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize how discoveries about the functioning of various brain circuits and neurotransmitters – especially those acting upon the central processing of pain – have impacted our understanding of the pathophysiology and treatment of many painful conditions that may occur with or without various psychiatric disorders. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of the symptom of pain, how it can hypothetically be caused by alterations of pain processing within the central nervous system, how it can be associated with many of the symptoms of depression and anxiety, and finally, how it can be treated with several of the same agents that can treat depression and anxiety. The discussion in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as Stahl’s Essential Psychopharmacology: the Prescriber’s Guide) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice. Fibromyalgia 387 Decreased Gray Matter in Chronic Pain Syndromes? 387 Descending Spinal Synapses in the Dorsal Horn and the Treatment of Chronic Pain 390 Targeting Sensitized Circuits in Chronic Pain Conditions 395 Targeting Ancillary Symptoms in Fibromyalgia 399 Summary 400 WHAT IS PAIN? No experience rivals pain for its ability to capture our attention, focus our actions, and cause suffering (see Table 9-1 for some useful definitions regarding pain). The powerful

experience of pain, especially acute pain, can serve a vital function – to make us aware of damage to our bodies, and to rest the injured part until it has healed. When acute pain is peripheral in origin (i.e., originating outside of the central nervous system) but continues as chronic pain, it can cause changes in central nervous system pain mechanisms that enhance or perpetuate the original peripheral pain. For example, osteoarthritis, low back pain, and diabetic peripheral neuropathic pain all begin as peripheral pain, but over time these conditions can trigger central pain mechanisms that amplify peripheral pain and generate additional pain centrally. This may explain why research has recently shown that chronic pain conditions of peripheral origin can be successfully targeted for relief by psychotropic drugs that work on central pain mechanisms. Many other chronic pain conditions may start centrally and never have a peripheral causation to the pain, especially conditions associated with multiple unexplained painful physical symptoms such as depression, anxiety, and fibromyalgia. Because these centrally mediated pain conditions are associated with emotional symptoms, that type of pain has until recently often not been considered "real" but rather a nonspecific outcome of unresolved psychological 379

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY conflicts that would improve when the associated psychiatric condition improved, and therefore that this type of pain did not need to be targeted specifically for treatment. Today, however, many painful conditions without identifiable peripheral lesions that were once linked only to psychiatric disorders are now hypothesized to be forms of chronic neuropathic pain syndromes and can be treated with the same agents that successfully treat neuropathic pain syndromes that are not associated with psychiatric disorders. These treatments include the SNRIs (serotonin–norepinephrine reuptake inhibitors, discussed in Chapter 7 on treatment for mood disorders [Figures 7-28 through 7-33]) and the α2δ ligands (anticonvulsants that block voltage-gated calcium channels or VSCCs, discussed in Chapter 8 on anxiety disorders [Figures 8-17 and 8-18]). Additional psychotropic agents acting centrally at various other sites are also used to treat a variety of chronic pain conditions and will be mentioned below. Many additional drugs are being tested as potential novel pain treatments as well. Table 9-1 Pain: some useful definitions Pain An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage Acute pain Pain that is of short duration and resolves; usually directly related to the resolution or healing of tissue damage Chronic pain Pain that persists for longer than would be expected; an artificial threshold for chronicity (e.g., 1 month) is not appropriate Neuropathic pain Pain that arises from damage to, or dysfunction of, any part of the peripheral or central nervous system Nociception The process by which noxious stimuli produce activity in the sensory pathways that convey "painful" information Allodynia Pain caused by a stimulus that does not normally provoke pain Hyperalgesia An increased response to a stimulus that is not normally painful Analgesia Any process that reduces the sensation of pain, while not affecting normal touch Local anesthesia Blockade of all sensation (innocuous and painful) from a local area Noxious stimulus Stimulus that inflicts damage, or would potentially inflict damage, on tissues of the body Primary afferent neuron (PAN) The first neuron in the somatosensory pathway; detects mechanical, thermal, or chemical stimuli at its peripheral terminals and transmits action potentials to its central terminals in the spinal cord; all PANs have a cell body in the dorsal root ganglion Nociceptor A primary afferent (sensory) neuron that is only activated by a noxious stimulus Nociception The process by which a nociceptor detects a noxious stimulus and generates a signal (action potentials) that is propagated towards higher centers in the nociceptive pathway Dorsal root ganglion (DRG) Contains the cell bodies of PANs; proteins, including transmitters, receptors, and structural proteins, are synthesized here and transported to

peripheral and central terminals Interneuron Neuron with its cell body, axon, and dendrites within the spinal cord; can be excitatory (e.g., containing glutamate) or inhibitory (e.g., containing GABA) Projection neurons Neuron in the dorsal horn that receives input from PANs and/or interneurons, and projects up the spinal cord to higher processing centers Spinothalamic tract Tract of neurons that project from the spinal cord to the thalmus Spinobulbar tracts Several different tracts of neurons that project from the spinal cord to brainstem nuclei Somatosensory cortex Region of the cerebral cortex that receives input mainly from cutaneous sensory nerves; the cortex is topographically arranged, with adjacent areas receiving input from adjacent body areas; stimulation of the somatosensory cortex creates sensations from the body part that projects to it

Since pain is clearly associated with some psychiatric disorders, and psychotropic drugs that treat various psychiatric conditions are also effective for a wide variety of pain conditions, the detection, quantification, and treatment of pain are rapidly becoming standardized parts of a psychiatric evaluation. Modern psychopharmacologists increasingly consider pain to be a psychiatric “vital sign,” thus requiring routine evaluation and symptomatic treatment. In fact, elimination of pain is increasingly recognized as necessary in order to have full symptomatic remission not only of chronic pain conditions, but also of many psychiatric disorders. “Normal” Pain and the Activation of Nociceptive Nerve Fibers The nociceptive pain pathway is the series of neurons that begins with detection of a noxious stimulus and ends with the subjective perception of pain. This so-called “nociceptive pathway” starts from the periphery, enters the spinal cord, and projects to the brain (Figure 9-1). It is important to understand the processes by which incoming information can be modulated to increase or decrease the perception of pain associated with a given stimulus because these processes can explain not only why maladaptive pain states arise but also why drugs that work in psychiatric conditions such as depression and anxiety can also be effective in reducing pain. Nociceptive Pathway to the Spinal Cord Primary afferent neurons detect sensory inputs including pain (Figure 9-1). They have their cell bodies in the dorsal root ganglion located along the spinal column outside the central nervous system and thus are considered peripheral and not central neurons primary afferent dorsal root periphery neurons ganglion non-noxious mechanical stimulus Aß fiber noxious mechanical stimulus PN dorsal root projection neurons noxious heat and chemical stimuli C fiber gray matter white matter Chapter 9: Chronic Pain and Its Treatment (Figure 9-1). Nociception begins with transduction – the process by which specialized membrane proteins located on the peripheral projections of these neurons detect a stimulus and generate a voltage change at their peripheral neuronal membranes. A sufficiently strong stimulus will lower the voltage at the membrane (i.e., depolarize the membrane) enough to activate voltage-sensitive sodium channels (VSSCs) and trigger an action potential that will be propagated along the length of the axon to the central terminals of the neuron in the spinal cord (Figure 9-1). VSSCs are introduced in Chapter 3 and illustrated in Figures 3-19 and 3-20. Nociceptive impulse flow from primary afferent neurons into the central nervous system can be reduced or stopped when VSSCs are blocked by peripherally administered local anesthetics such as lidocaine. The specific response characteristics of primary afferent neurons are determined by the specific receptors and channels expressed by that neuron in the periphery (Figure 9-1). For example, primary afferent neurons that express a stretch-activated ion channel are mechanosensitive; those that express the vanillinoid receptor 1 (VR1) ion channel are activated by capsaicin, the pungent ingredient in chili peppers, and also by noxious heat, leading to the burning sensation that both these stimuli evoke. These functional response properties are used to classify primary afferent neurons into three types: Aβ-, Aδ-, and C-fiber neurons (Figure 9-1). Aβ fibers detect small movements, light touch, hair

movement, and vibrations; C-fiber peripheral terminals are bare nerve endings that are only activated by noxious mechanical, thermal, or chemical stimuli; Aδ fibers fall somewhere in between, sensing noxious mechanical stimuli and sub-noxious thermal stimuli (Figure 9-1). Figure 9-1 Activation of nociceptive nerve fibers. Detection of a noxious stimulus occurs at the peripheral terminals of primary afferent neurons and leads to generation of action potentials that propagate along the axon to the central terminals. Aβ fibers respond only to non-noxious stimuli, Aδ fibers respond to noxious mechanical stimuli and subnoxious thermal stimuli, and C fibers respond only to noxious mechanical, heat, and chemical stimuli. Primary afferent neurons have their cell bodies in the dorsal root ganglion and send terminals into that spinal cord segment as well as sending less dense collaterals up the spinal cord for a short distance. Primary afferent neurons synapse onto several different classes of dorsal horn projection neurons (PN), which project via different tracts to higher centers. spinal cord to higher centers dorsal horn 381

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Nociceptive input and pain can thus be caused by activating primary afferent neurons peripherally, such as from a sprained ankle or a tooth extraction. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce painful input from these primary afferent neurons, presumably via their peripheral actions. Opiates can also reduce such pain, but from central actions as explained below. Nociceptive Pathway from the Spinal Cord to the Brain The central terminals of peripheral nociceptive neurons synapse in the dorsal horn of the spinal cord onto the next cells in the pathway – dorsal horn neurons, which receive input from many primary afferent neurons and then project to higher centers (Figures 9-2 and 9-3). For this reason, they are sometimes also called dorsal horn projection neurons (PN in Figures 9-1 through 9-3). Dorsal horn neurons are thus the first neurons of the nociceptive pathway that are located entirely within the central nervous system and thus a key site for modulation of nociceptive neuronal activity as it comes into the central nervous system. A vast number of neurotransmitters have been identified in the dorsal horn, some of which are shown in Figure 9-2. Neurotransmitters in the dorsal horn are synthesized not only by primary afferent neurons, but also by the other neurons in the dorsal horn, including descending neurons and various interneurons (Figure 9-2). Some neurotransmitter systems in the dorsal horn are successfully targeted by known pain-relieving drugs, especially opiates, serotonin and norepinephrine boosting SNRIs, and α2δ ligands acting at VSCCs. All of the neurotransmitter systems acting in the dorsal horn are potential targets for novel pain-relieving drugs (Figure 9-2) and a plethora of such novel agents is currently in clinical and preclinical development. There are several classes of dorsal horn neurons: some receive input directly from primary sensory neurons, some are interneurons, and some project up the spinal cord to higher centers (Figure 9-3). There are several different tracts in which these projection neurons can ascend, which can be crudely divided into two functions: the sensory/discriminatory pathway and the emotional/ motivational pathway (Figure 9-3). In the sensory/discriminatory pathway, dorsal horn neurons ascend in the spinothalamic tract; then, thalamic neurons project to the primary somatosensory cortex (Figure 9-3). This particular pain pathway is thought to convey the precise location of the nociceptive stimulus and its intensity. In the emotional/motivational pathway, other dorsal horn neurons project to brainstem nuclei, and from there to limbic regions (Figure 9-3). This second pain pathway is thought to convey the affective component that nociceptive stimuli evoke. Only when these two aspects of sensory discrimination and emotions come together and the final, subjective perception of pain is created, can we use the word "pain" to describe the modality (see "ouch" in Figure 9-3). Before this point, we are simply discussing activity in neural pathways, which should be described as noxious-evoked

or nociceptive neuronal activity but not necessarily as pain. NEUROPATHIC PAIN The term neuropathic pain describes pain that arises from damage to, or dysfunction of, any part of the peripheral or central nervous system, whereas “normal” pain (so-called nociceptive pain just discussed in the section above) is caused by activation of nociceptive nerve fibers. Peripheral Mechanisms in Neuropathic Pain Normal transduction and conduction in peripheral afferent neurons can be hijacked in certain neuropathic pain states to maintain nociceptive signaling in the absence of a relevant noxious stimulus. Neuronal damage by disease or trauma can alter electrical activity of neurons, allow cross-talk between neurons, and initiate inflammatory processes to cause “peripheral sensitization.” In this chapter, we will not emphasize peripheral sensitization disorders and mechanisms, but rather central sensitization disorders and mechanisms. Central Mechanisms in Neuropathic Pain At each major relay point in the pain pathway (Figure 9-3), the nociceptive pain signal is susceptible to modulation by endogenous processes to either dampen down the signal or to amplify it. This happens not only peripherally at primary afferent neurons, as has just been discussed, but also at central neurons in the dorsal horn of the spinal cord as well as in numerous brain regions. The events in the dorsal horn of the spinal cord are better understood than those in brain regions of nociceptive pathways, but pain processing in the brain may be the key to understanding the generation and amplification of pain centrally in disorders of chronic peripheral pain, such as osteoarthritis, low back pain, and diabetic peripheral neuropathic pain, as well as painful physical symptoms in affective and anxiety disorders and in fibromyalgia.

Chapter 9: Chronic Pain and Its Treatment to higher centers dorsal horn projection neuron descending neurons Multiple Neurotransmitters Modulate Pain Processing in the Spinal Cord 5HT 5HT opioid opioid VIP CGRP GABA glu Sub P NKA NKB somato statin NE VIPR SR CGRP-R AMPA-R NMDA-R NK1,2,3 GABAA,B GABAA,B CCK-A,B 5HT3 5HT3 5HT 1/B/D interneuron primary afferent neuron 2 opioid glycine CCK NO GABA PN Figure 9-2 Multiple neurotransmitters modulate pain processing in the spinal cord. There are many neurotransmitters and their corresponding receptors in the dorsal horn. Neurotransmitters in the dorsal horn may be released by primary afferent neurons, by descending regulatory neurons, by dorsal horn projection neurons (PN), and by interneurons. Neurotransmitters present in the dorsal horn that have been best studied in terms of pain transmission include substance P (NK1, 2, and 3 receptors), endorphins (μ-opioid receptors), norepinephrine (α2 adrenoceptors), and serotonin (5HT1B/D and 5HT3 receptors). Several other neurotransmitters are also represented, including vasopressin inhibitory protein (VIP) and its receptor VIPR; somatostatin and its receptor SR; calcitonin G-related peptide (CGRP) and its receptors CGRP-R; GABA and its receptors GABAA and GABAB; glutamate and its receptors AMPA-R (α-amino-3hydroxy-5-methyl-4-isoxazole propionic acid receptor) and NMDA-R (N-methyl-D-aspartate receptor); nitric oxide (NO); cholecystokinin (CCK) and its receptors CCK-A and CCK-B; and glycine and its receptor NMDA-R.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY somatosensory cortex somatosensory cortex thalamus thalamus PN PN limbic structures limbic structures spinothalamic tract spinothalamic tract brainstem brainstem spinobulbar tract spinobulbar tract “Segmental” central sensitization is a process thought to be caused when plastic changes occur in the dorsal horn, classically in conditions such as phantom pain after limb amputation. Specifically, this type of neuronal plasticity in the dorsal horn is called activity-dependent or use-dependent because it requires constant firing of the pain pathway in the dorsal horn. The consequence of this constant input of pain is eventually to cause exaggerated (hyperalgesic) or prolonged responses to any noxious input – a phenomenon

sometimes called “wind-up” – as well as painful responses to normally innocuous inputs (called allodynia). Phosphorylation of key membrane receptors and channels in the dorsal horn appears to increase synaptic efficiency and thus to trip a master switch opening the gate to the pain pathway and turning on central sensitization, which acts to amplify or create the perception of pain even if there is no pain input actually coming from the periphery. The gate can also close, as conceptualized in the classic “gate theory” of pain, in order to explain how innocuous stimulation (e.g., acupuncture, vibration, rubbing) away from the site of an injury can close the pain gate and reduce the perception of the injury pain. In segmental central sensitization, a definite peripheral injury (Figure 9-4A) is combined with central sensitization at the spinal cord segment receiving nociceptive input from the damaged area of the body (Figure 9-4B). Segmental central sensitization syndromes are thus “mixed” states where the insult of central segmental changes (Figure 9-4B) are added to peripheral injuries such as low back pain, diabetic peripheral Figure 9-3 From nociception to pain. Dorsal horn neurons in the spinothalamic tract project to the thalamus and then to the primary somatosensory cortex. This pathway carries information about the intensity and location of the painful stimuli and is termed the sensory/discriminatory pathway. Neurons ascending in the spinobulbar tract project to brainstem nuclei and then to both the thalamus and limbic structures. These pathways convey the emotional and motivational aspects of the pain experience. Only when information from the sensory/ discriminatory (thalamocortical) and emotional/motivational (limbic) pathways combine is the human subjective experience of pain formed (“ouch”). subjective experience of pain subjective experience of pain OUCH! OUCH! neuropathic pain, and painful cutaneous eruptions of herpes zoster (shingles) (Figure 9-4A). “Suprasegmental” central sensitization is hypothesized to be linked to plastic changes that occur in brain sites within the nociceptive pathway, especially the thalamus and cortex, in the presence of known peripheral causes (Figure 9-5A) or even in the absence of identifiable triggering events (Figure 9-5B). In the case of peripherally activated suprasegmental central sensitization, it is as though the brain “learns” from its experience of pain, and decides not only to keep the process going, but also to enhance it and make it permanent. In the case of pain that originates centrally without peripheral input, it is as though the brain has figured out how to spontaneously activate its pain pathways. Interrupting this process of sensitized brain pathways for pain and getting the central nervous system to “forget” its molecular memories may be one of the greatest therapeutic opportunities in psychopharmacology today, not only because this may be a therapeutic strategy for various chronic neuropathic pain conditions as discussed here, but also because it may be a viable approach to treating the hypothesized molecular changes that may underlie disease progression in a wide variety of disorders, from schizophrenia, to stress-induced anxiety and affective disorders, to addictive disorders. Conditions hypothesized to be caused by suprasegmental central sensitization syndromes of pain originating in the brain without peripheral pain input include fibromyalgia, the syndrome of chronic widespread pain, and painful physical symptoms of depression and anxiety disorders, especially posttraumatic stress disorder (PTSD) (Figure 9-5B).

Onset of Acute Pain from Painful Peripheral Conditions OUCH! A Development of Segmental Central Sensitization and Increased Pain OUCH! segmental central sensitization low back pain B Chapter 9: Chronic Pain and Its Treatment Figure 9-4 Acute pain and development of segmental central sensitization. (A) When peripheral injury occurs, nociceptive impulse flow from primary afferent neurons is transmitted via dorsal horn neurons to higher brain centers, where it can ultimately be interpreted as pain (represented by the “ouch”). (B) In some cases, injury or disease directly

affecting the nervous system may result in plastic changes that lead to sensitization within the central nervous system, such that the experience of pain continues even after tissue damage is resolved. Impulses may be generated at abnormal locations either spontaneously or via mechanical forces. At the level of the spinal cord, this process is termed segmental central sensitization. This mechanism underlies conditions such as diabetic peripheral neuropathic pain and shingles. joint affected by osteoarthritis diabetic peripheral neuropathic pain low back pain shingles joint affected by osteoarthritis diabetic peripheral neuropathic pain shingles 385

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 9-5 Suprasegmental central sensitization. Plastic changes in brain sites within the nociceptive pathway, especially the thalamus and cortex, can cause sensitization. This process within the brain is termed suprasegmental central sensitization. This can occur following peripheral injury (A) or even in the absence of identifiable triggering events (B). This mechanism is believed to underlie conditions such as fibromyalgia, chronic widespread pain, and painful symptoms in depression and anxiety disorders. OUCH! joint affected by osteoarthritis diabetic peripheral neuropathic pain low back pain shingles OUCH! fibromyalgia chronic widespread pain painful physical symptoms of depression/anxiety Chronic Pain with Suprasegmental Central Sensitization from Peripheral Injury Suprasegmental Central Sensitization Originating in the Brain suprasegmental central sensitization A B

Chapter 9: Chronic Pain and Its Treatment Fibromyalgia Fibromyalgia has emerged as a diagnosable and treatable pain syndrome, with tenderness but no structural pathology in muscles, ligaments, or joints. Fibromyalgia is recognized as a chronic, widespread pain syndrome associated with fatigue and nonrestorative sleep. It is diagnosed based on the number of body areas in which the patient experiences pain (widespread pain index, or WPI) combined with the severity of associated symptoms (fatigue, waking unrefreshed, cognitive symptoms, and other somatic symptoms) (Figure 9-7). It is the second most common diagnosis in rheumatology clinics, and may affect 2–4% of the general population. Although symptoms of fibromyalgia are chronic and debilitating, they are not necessarily progressive. There is no known cause and there is no known pathology identifiable in the muscles or joints. This syndrome can be deconstructed into its component symptoms (Figure 9-8), and then matched with hypothetically malfunctioning brain circuits (Figure 9-9). Decreased Gray Matter in Chronic Pain Syndromes? Some very troubling preliminary reports suggest that chronic pain may even "shrink the brain" in the DLPFC (dorsolateral prefrontal cortex) (Figure 9-9) and thereby The Spectrum of Mood and Anxiety Disorders with Pain Disorders A large group of overlapping disorders can have emotional symptoms, painful physical symptoms, or both (Figure 9-6). Although pain in the absence of emotional symptoms has long been seen as a neurological disorder, and pain in the presence of emotional symptoms as a psychiatric disorder, it is now clear that pain is a symptom that can be mapped onto inefficient information processing within the pain circuit, and is largely considered the same symptom with the same treatments, whether occurring by itself or as part of any number of syndromes (Figure 9-6). Thus, pain (Figure 9-6, right) can occur not only by itself, but also concomitantly with the emotional symptoms of depressed mood and anxiety (Figure 9-6, left), and with the physical symptoms of fatigue, insomnia, and problems concentrating (Figure 9-6, middle). No matter whether pain occurs by itself or with additional concomitant emotional or physical symptoms, or in the presence of full syndromal psychiatric disorders such as major depressive disorder, generalized anxiety disorder, or PTSD (Figure 9-6, left), it must be treated and the treatments are the same across the spectrum (Figure 9-6), namely SNRIs and α2δ ligands as will be

explained below. Figure 9-6 The spectrum from mood and anxiety disorders to chronic neuropathic pain syndromes. Pain, though not a formal diagnostic feature of depression or anxiety disorders, is nonetheless frequently present in patients with these disorders. Similarly, depressed mood, anxiety, and other symptoms identified as part of depression and anxiety disorders are now recognized as being common in pain disorders. The Spectrum from Mood and Anxiety Disorders to Chronic Neuropathic Pain Syndromes major depressive disorder general anxiety disorder PTSD anxiety disorder subtypes fatigue sleep cognition anxiety and mood disorders mood/anxiety pain chronic neuropathic pain syndromes mixed shingles fibromyalgia Z Z Z worry $ chronic widespread pain painful physical symptoms of depression/anxiety diabetic peripheral neuropathic pain osteoarthritis low back pain

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Widespread Pain Index (WPI) for Diagnosis of Fibromyalgia neck shoulder girdle chest upper back upper arm lower arm lower back upper leg hip (buttock) lower leg fibromyalgia fatigue concentration pain sleep depression contribute to cognitive dysfunction in certain pain states such as fibromyalgia (Figure 9-8) and low back pain. Brain atrophy is discussed in relationship to stress and anxiety disorders in Chapter 6 and illustrated in Figure 6-30. It would not be surprising if stressful conditions that cause pain, as well as pain that causes distress, may Figure 9-7 Widespread pain index (WPI). Fibromyalgia is a chronic widespread pain syndrome, formerly diagnosed based on the number of body areas in which the patient experiences pain (widespread pain index, or WPI) combined with the severity of associated symptoms (fatigue, waking unrefreshed, cognitive symptoms, and other somatic symptoms. jaw abdomen Figure 9-8 Symptoms of fibromyalgia. In addition to pain as a central feature of fibromyalgia, many patients experience fatigue, anxiety, depression, disturbed sleep, and problems concentrating. anxiety all be involved in causing brain atrophy and/or cognitive dysfunction in fibromyalgia and other chronic pain states. Chronic back pain, for example, has also been reported to be associated with decreased prefrontal and thalamic gray-matter density (Figure 9-10). Some experts have hypothesized that in fibromyalgia and other chronic

Match Each Symptom of Fibromyalgia to Hypothetically Malfunctioning Brain Circuits psychomotor fatigue (physical) pleasure interests fatigue/ energy -"fibro-fog"

- problems concentrating
- lack of interest/pleasure psychomotor fatigue (mental) pain PFC S NA BF T Hy NT A H mood depressed mood anxiety sleep appetite Gray-matter loss in chronic pain DLPFC thalamus temporal cortex neuropathic pain syndromes, the persistent perception of pain could lead to overuse of DLPFC neurons, excitotoxic cell death in this brain region, and reduction Chapter 9: Chronic Pain and Its Treatment Figure 9-9 Symptom-based algorithm for fibromyalgia. A symptom-based approach to treatment selection for fibromyalgia follows the theory that each of a patient's symptoms can be matched with malfunctioning brain circuits and neurotransmitters that hypothetically mediate those symptoms; this information is then used to select a corresponding pharmacological mechanism for treatment. Pain is linked to transmission of information via the thalamus (T), while physical fatigue is linked to the striatum (S) and spinal cord (SC). Problems concentrating and lack of interest (termed "fibro-fog") as well as mental fatigue are linked to the prefrontal cortex (PFC), specifically the dorsolateral PFC. Fatigue, low energy, and lack of interest may all also be related to the nucleus accumbens (NA). Disturbances in sleep and

appetite are associated with the hypothalamus (Hy), depressed mood with the amygdala (A) and orbital frontal cortex, and anxiety with the amygdala. pain C SC fatigue (physical) pain Figure 9-10 Gray-matter loss in chronic pain. Research suggests that chronic pain, like anxiety and stress-related disorders, may lead to brain atrophy. Specifically, there are data showing gray-matter loss in the dorsolateral prefrontal cortex (DLPFC), the thalamus, and the temporal cortex in patients with chronic pain conditions. of the cortico-thalamic "brake" on nociceptive pathways. Such an outcome could cause not only increased pain perception, but diminished executive functioning, 389

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY sometimes called "fibro-fog" in fibromyalgia. In Chapter 6 we discussed how stress-related HPA (hypothalamicpituitary-adrenal) axis abnormalities in CRF–ACTH– cortisol regulation may be linked to hippocampal atrophy (see Figure 6-32), possibly linked to reduced availability of growth factors (Figures 6-27 and 6-29). Alterations in growth factors may be linked to the reports of reduction in gray-matter volume in chronic pain syndromes (fibromyalgia and low back pain), but in different brain regions (DLPFC, temporal cortex, and thalamus) (Figure 9-10) than reported for depression (Figure 6-30). Gray matter may actually be increased in other brain regions in chronic pain. Although still preliminary, these findings suggest a possible structural consequence to suprasegmental central sensitization (Figure 9-10), not unlike that suspected for depression and stress (Figure 6-30). Abnormal pain processing, exaggerated pain responses, and perpetual pain could hypothetically be linked to deficiencies in the DLPFC circuit and its regulation by dopamine, and provide a potential explanation for the cognitive difficulties associated with chronic pain, especially fibro-fog in fibromyalgia (Figure 9-8). Thalamic abnormalities could hypothetically be linked to problems sleeping as well as nonrestorative sleep seen in chronic pain syndromes (Figure 9-8). Thus, chronic pain syndromes not only cause pain, but also problems with fatigue, mental concentration, sleep, depression, and anxiety (Figure 9-8). Structural brain abnormalities associated with inefficient information processing in brain areas that mediate these symptoms (Figure 9-9) may explain why these various symptoms (Figure 9-8) are frequently associated with chronic pain syndromes. DESCENDING SPINAL SYNAPSES IN THE DORSAL HORN AND THE TREATMENT OF CHRONIC PAIN The periaqueductal gray is the site of origin and regulation of much of the descending inhibition that projects down the spinal cord to the dorsal horn (Figure 9-2). The periaqueductal gray is discussed in relationship to its connections with the amygdala and the motor component of the fear response in Chapter 8 and illustrated in Figure 8-9. The periaqueductal gray also integrates inputs from nociceptive pathways and limbic structures such as the amygdala and limbic cortex, and sends outputs to brainstem nuclei and the rostroventromedial medulla to drive descending inhibitory pathways. Some of these descending pathways release endorphins, which act via mostly presynaptic μ-opioid receptors to inhibit neurotransmission from nociceptive primary afferent neurons (Figure 9-2). Spinal μ-opioid receptors are one target of opioid analgesics; so are μ-opioid receptors in the periaqueductal gray itself (Figure 9-11). Interestingly, since Aβ fibers (Figure 9-1) do not express μ-opioid receptors, this may explain why opioid analgesics spare normal sensory input. Enkephalins, which also act via δ-opioid receptors, are also antinociceptive, whereas dynorphins, acting at κ-opioid receptors, can be either anti- or pronociceptive. It is also interesting that opiates in general are no more effective for chronic neuropathic pain states than SNRIs or α2δ ligands, but in many cases, such as in fibromyalgia, opiates are not proven to be effective at all. Two other important descending inhibitory pathways are also shown in Figure 9-2. One is the descending spinal norepinephrine pathway (Figure 9-12A), which originates in the locus coeruleus, and especially from noradrenergic

cell bodies in the lower (caudal) parts of the brainstem neurotransmitter center (lateral tegmental norepinephrine cell system). The other important descending pathway is the descending spinal serotonergic pathway (Figure 9-13A), which originates in the nucleus raphe magnus of the rostroventromedial medulla and especially the lower (caudal) serotonin nuclei (raphe magnus, raphe pallidus, and raphe obscuris). Descending noradrenergic neurons inhibit neurotransmitter release from primary afferents directly via inhibitory α2 adrenoceptors (Figure 9-2), explaining why direct-acting α2 agonists such as clonidine can be useful in relieving pain in some patients. Serotonin inhibits primary afferent terminals via postsynaptic 5HT1B/D receptors (Figure 9-2). These inhibitory receptors are G-protein-coupled, and indirectly influence ion channels to hyperpolarize the nerve terminal and inhibit nociceptive neurotransmitter release. However, serotonin is also a major transmitter in descending facilitation pathways to the spinal cord. Serotonin released onto some primary afferent neuron terminals in certain areas of the dorsal horn acts predominantly via excitatory 5HT3 receptors to enhance neurotransmitter release from these primary afferent neurons (Figure 9-2). The combination of both inhibitory and facilitatory actions of serotonin may explain why SSRIs (selective serotonin reuptake inhibitors), with actions that increase only serotonin levels, are not consistently useful in the treatment of pain, whereas SNRIs, with actions on both serotonin and norepinephrine, are now proven to be effective in various neuropathic pain states, including diabetic peripheral neuropathic pain and fibromyalgia.

Chapter 9: Chronic Pain and Its Treatment Figure 9-11 Acute nociceptive pain and opioids. The periaqueductal gray integrates inputs from nociceptive pathways and limbic structures and sends outputs to drive descending inhibitory pathways, including descending opioid projections. (A) Shown here is nociceptive input from a peripheral injury being transmitted to the brain and interpreted as pain. The descending opioid projection is not activated and thus is not inhibiting the nociceptive input. (B) Endogenous opioid release in the descending opioid projection, or exogenous administration of an opioid, can cause inhibition of nociceptive neurotransmission in the dorsal horn or in the periaqueductal gray and thus prevent or reduce the experience of pain. A B OUCH! OUCH! Acute Nociceptive Pain descending opioid projections periaqueductal gray sprain broken bone dental extraction sprain broken bone dental extraction opioid opioid Anatomic Site of Action of Opioids

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY back pain stomach pain muscle/ joint pain back pain stomach pain muscle/ joint pain A B Descending NE Inhibition of Pain descending NE projections normal NE release deficient NE release Deficient NE Inhibition Leads to Pain digestion digestion back posture muscle/joint movement back posture muscle/joint movement Figure 9-12A, B Descending noradrenergic neurons and pain. (A) The descending spinal norepinephrine (NE) pathway originates in the locus coeruleus. Descending NE neurons inhibit neurotransmitter release from primary afferent neurons via presynaptic α2 adrenoceptors, and inhibit activity of dorsal horn neurons via postsynaptic α2 adrenoceptors. This suppresses bodily input (e.g., regarding muscles/joints or digestion) from reaching the brain and thus prevents it from being interpreted as painful. (B) If descending NE inhibition is deficient, then it may not be sufficient to mask irrelevant nociceptive input, potentially leading to perception of pain from input that is normally ignored. This may be a contributing factor for painful somatic symptoms in fibromyalgia, depression, irritable bowel syndrome, and anxiety disorders.

Chapter 9: Chronic Pain and Its Treatment Descending inhibition is also activated during severe injury by incoming nociceptive input, and in dangerous “conflict” situations via limbic structures, causing the release of endogenous opioid peptides (Figure 9-11B), serotonin (Figure 9-13A), and norepinephrine (Figure 9-12A). When this happens, this reduces not only the release of nociceptive neurotransmitters in the dorsal horn (Figure 9-2) but also the transmission of nociceptive impulses up the spinal cord into the brain (Figure 9-3), thereby reducing the perception of pain, dulling it to allow escape from the situation without the injury compromising physical performance in the short run (reduction of “ouch” in Figure 9-3). On return to safety, descending facilitation replaces the inhibition to redress the balance, increase awareness of the injury, and force rest of the injured part (lots of “ouch” in Figure 9-3). The power of this system can be seen in humans persevering through severe injury on the sports field and on the battle field. The placebo effect may also involve endogenous opioid release from these descending inhibitory neurons (Figure 9-11B), since activation of a placebo response to pain is reversible by the μ-opioid antagonist naloxone. These are adaptive Descending inhibition, mostly via serotonin and noradrenergic pathways, is normally active at rest and is thought to act physiologically to mask perception of irrelevant nociceptive input (e.g., from digestion, joint movement, etc.) (Figures 9-12A and 9-13A). One hypothesis for why patients with depression or fibromyalgia or related chronic pain disorders perceive pain when there is no obvious sign of peripheral trauma is that descending inhibition may not be acting adequately to mask irrelevant nociceptive input. This leads to the perception of pain from what is actually normal input that is ordinarily ignored (Figures 9-12B and 9-13B). If this descending monoaminergic inhibition is enhanced with an SNRI, irrelevant nociceptive inputs from joints, muscles, and the back in fibromyalgia and depression, and from digestion and the gastrointestinal tract in irritable bowel syndrome, depression, and anxiety disorders, are hypothetically once again ignored and thus are no longer perceived as painful (Figures 9-12C and 9-13C). SNRIs include duloxetine, milnacipran, levomilnacipran, venlafaxine, desvenlafaxine, and some tricyclic antidepressants (TCAs). SNRIs and TCAs are discussed extensively in Chapter 7. Figure 9-12C Enhancement of descending noradrenergic inhibition. A serotonin–norepinephrine reuptake inhibitor (SNRI) can increase noradrenergic neurotransmission in the descending spinal pathway to the dorsal horn, and thus may enhance inhibition of bodily input so that it does not reach the brain and get interpreted as pain. C SNRI Action Boosts NE Inhibition of Pain descending NE projections SNRI boosts NE back pain stomach pain digestion = SNRI muscle/ joint pain back posture muscle/joint movement

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 9-13A, B Descending serotonergic neurons and pain. (A) The descending spinal serotonin (5HT) pathway originates in the raphe nucleus. Descending serotonergic (5HT) neurons directly inhibit activity of dorsal horn neurons, predominantly via 5HT1B/D receptors. This suppresses bodily input (e.g., regarding muscles/joints or digestion) from reaching the brain and thus prevents it from being interpreted as painful. (B) If descending 5HT inhibition is deficient, it may not be sufficient to mask irrelevant nociceptive input, potentially leading to perception of pain from input that is normally ignored. This may be a contributing factor for painful somatic symptoms in fibromyalgia, depression, irritable bowel syndrome, and anxiety disorders. A B Descending 5HT Inhibition of Pain descending 5HT projections normal 5HT release deficient 5HT release Deficient 5HT Inhibition Leads to Pain back pain stomach pain muscle/ joint pain back pain stomach pain digestion muscle/ joint pain digestion back posture muscle/joint movement back posture muscle/joint movement

Chapter 9: Chronic Pain and Its Treatment voltage-sensitive calcium channels (VSCCs; Figure 9-14), which is often coupled to the release of glutamate, but also to aspartate, substance P (SP), calcitonin-gene-related peptide (CGRP), and other neurotransmitters (Figure 9-2). When this occurs at suprasegmental levels in the thalamus and cortex, it is likely linked to release mostly of glutamate via the same N-type and P/Q-type VSCCs (Figures 9-14 and 9-15). The idea is that low release of neurotransmitter creates no pain response because there is insufficient neurotransmitter release to stimulate the postsynaptic receptors (Figure 9-14A). However, normal amounts of neurotransmitter release cause a full nociceptive pain response and acute pain (Figure 9-14B). Hypothetically, in states of central sensitization, there is excessive and unnecessary ongoing nociceptive activity causing neuropathic pain (Figure 9-15A). Blocking VSCCs with the α2δ ligands gabapentin or pregabalin (Figures 9-15B and 9-16) inhibits release of various neurotransmitters in the dorsal horn (Figures 9-2, 9-15B, and 9-17A) or in thalamus and cortex (Figures 9-15B and 9-17B) and has indeed proven to be an effective treatment for various disorders causing neuropathic pain. Gabapentin and pregabalin changes within the pain pathways that facilitate survival and enhance function for the individual. However, maladaptive changes can also hijack these same mechanisms to inappropriately maintain pain without relevant tissue injury, as may occur in various forms of neuropathic pain, ranging from diabetes to fibromyalgia and beyond. TARGETING SENSITIZED CIRCUITS IN CHRONIC PAIN CONDITIONS Chronic pain perpetuated as a marker of an irreversible sensitization process within the central nervous system has already been discussed as a disorder triggered by progressive molecular changes due to abnormal neuronal activity within the pain pathway, sometimes called central sensitization. When this occurs at the spinal or segmental level, it is likely linked to the multiple different neurotransmitters released there, with each neurotransmitter’s release mechanism requiring presynaptic depolarization and activation of N-type and P/Q-type Figure 9-13C Enhancement of descending serotonergic inhibition. A serotonin–norepinephrine reuptake inhibitor (SNRI) can increase serotonergic neurotransmission in the descending spinal pathway to the dorsal horn, and thus may enhance inhibition of bodily input so that it does not reach the brain and get interpreted as pain. However, the noradrenergic effects of SNRIs may be more relevant to suppression of nociceptive input. C SNRI Action Boosts 5HT Inhibition of Pain descending 5HT projections SNRI boosts 5HT back pain stomach pain digestion = SNRI muscle/ joint pain back posture muscle/joint movement

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 9-14 Activity-dependent nociception in pain pathways, part 1: acute pain. The degree of nociceptive neuronal activity in pain pathways determines whether one experiences acute pain. An action potential on a presynaptic neuron triggers sodium influx, which in turn leads to calcium influx, and ultimately release of neurotransmitter. (A) In some cases, the action potential generated at the presynaptic neuron causes minimal neurotransmitter release; thus the postsynaptic neuron is not notably stimulated and the nociceptive input does not reach the brain (in other words, there is no pain). (B) In other cases, a stronger action potential at the presynaptic neuron may cause voltage-sensitive calcium channels (VSCCs) to remain open longer, allowing more neurotransmitter release and more stimulation of the postsynaptic neuron. Thus, the nociceptive input is transmitted to the brain and acute pain occurs. A no pain Subthreshold Pain Response Full Nociceptive Activity B acute pain N P/Q N P/Q N P/Q N P/Q

Chapter 9: Chronic Pain and Its Treatment Figure 9-15 Activity-dependent nociception in pain pathways, part 2: neuropathic pain. The degree of nociceptive neuronal activity in pain pathways

determines whether one experiences acute pain. An action potential on a presynaptic neuron triggers sodium influx, which in turn leads to calcium influx, and ultimately release of neurotransmitter. (A) Strong or repetitive action potentials can cause prolonged opening of calcium channels, which may lead to excessive release of neurotransmitter into the synaptic cleft, and consequently to excessive stimulation of postsynaptic neurons. Ultimately this may induce molecular, synaptic, and structural changes, including sprouting, which are the theoretical substrates for central sensitization syndromes. In other words, this can lead to neuropathic pain. (B) Alpha-2-delta ligands such as gabapentin or pregabalin bind to the α2δ subunit of voltage-sensitive calcium channels (VSCCs), changing their conformation to reduce calcium influx and therefore reduce excessive stimulation of postsynaptic receptors. A dorsal horn, thalamus, or cortex neuropathic pain B neuropathic pain Central Sensitization and Excessive Nociceptive Activity Relief of Painful Excessive Nociceptive Activity in Central Sensitization = alpha-2delta ligand N P/Q N P/Q N P/Q N P/Q

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY gabapentin pregabalin VSCC 2 site VSCC 2 site OUCH! OUCH! (Figure 9-16) may more selectively bind the "open-channel" conformation of VSCCs (Figures 9-17 and 9-18), and thus be particularly effective in blocking those channels that are the most active, with a "use-dependent" form of inhibition Figure 9-16 Gabapentin and pregabalin. Shown here are icons of the pharmacological actions of gabapentin and pregabalin. These agents bind to the α2δ subunit of voltage-sensitive calcium channels (VSCCs). Figure 9-17 Anatomic actions of α2δ ligands. (A) Alpha-2-delta ligands may bind to voltage-sensitive calcium channels in the dorsal horn to reduce excitatory neurotransmission and alleviate pain. (B) Alpha-2-delta ligands may also bind to voltage-sensitive calcium channels in the thalamus and cortex to reduce excitatory neurotransmission and alleviate pain. (Figures 9-17B and 9-18B). This molecular action predicts more affinity for centrally sensitized VSCCs that are actively conducting neuronal impulses within the pain pathway. Thus, they have a selective action on those VSCCs causing

Molecular Action of Alpha-2-Delta Ligands A. Open conformation of VSCC inside the cell ß N P/Q outside the cell Ca++ B. Alpha-2-delta ligand binding to open conformation and inhibiting VSCC ß N P/Q C. Closed conformation of VSCC ß N P/Q Figure 9-18 Binding of α2δ ligands. (A) Calcium influx occurs when voltage-sensitive calcium channels (VSCCs) are in the open-channel conformation. (B) Alpha-2-delta ligands such as gabapentin and pregabalin have greatest affinity for the openchannel conformation and thus block those channels that are most active. (C) When VSCCs are in the closed conformation α2δ ligands do not bind and thus do not disrupt normal neurotransmission. neuropathic pain, ignoring other VSCCs that are not open, and thus not interfering with normal neurotransmission in central neurons uninvolved in mediating the pathological pain state. Treatment of pain, including neuropathic pain conditions, may be less costly when you "pay" for it Chapter 9: Chronic Pain and Its Treatment in advance, or at least early in the game. The hope is that early treatment of pain could interfere with the development of chronic persistent painful conditions by blocking the ability of painful experiences to imprint themselves upon the central nervous system by not allowing triggering of central sensitization. Thus, the mechanisms whereby symptomatic suffering of chronic neuropathic pain is relieved, such as with SNRIs or α2δ ligands, may also be the same mechanisms that could prevent disease progression to chronic persistent pain states. This notion calls for aggressive treatment of painful symptoms in these conditions that theoretically have their origin within the central nervous system, thus "intercepting" the central sensitization process before it is durably imprinted into angry circuits. Thus, major depression and

anxiety disorders and fibromyalgia can all be treated with SNRIs and/or α2δ ligands to eliminate painful physical symptoms and thereby improve the chances of reaching full symptomatic remission. The opportunity to prevent permanent pain syndromes or progressive worsening of pain is one reason why pain is increasingly being considered a psychiatric “vital sign” that must be assessed routinely in the evaluation and treatment of psychiatric disorders by psychopharmacologists. Future testing of agents capable of reducing pain should be done to determine whether eliminating painful symptoms early in the course of psychiatric and functional somatic illnesses will improve outcomes, including preventing symptomatic relapses, the development of treatment resistance or even brain atrophy from stress in pain states (Figure 9-9), and hippocampal atrophy from stress in anxiety and affective disorders (Figure 6-30). Pre-emptively treating pain before it occurs, or at least rescuing centrally mediated and sensitizing pain by intercepting such pain before it becomes permanent, may be some of the most promising therapeutic applications of dual reuptake inhibitors and α2δ ligands and deserves careful clinical evaluation. TARGETING ANCILLARY SYMPTOMS IN FIBROMYALGIA We have repeatedly mentioned the proven usefulness of the α2δ ligands gabapentin and pregabalin and the SNRIs duloxetine, milnacipran, venlafaxine, and desvenlafaxine for treating the painful symptoms of fibromyalgia, yet these two classes have not been studied extensively in combination. Nevertheless, they are frequently used together in clinical practice on an empiric basis and anecdotally have been shown to give additive 399

 improvement in relieving pain. Each class of drug may also help different ancillary symptoms in fibromyalgia, so the combination of α2δ ligands with SNRIs may lead to broader symptom relief than using either alone, although both are effective for pain in fibromyalgia. That is, α2δ ligands may reduce symptoms of anxiety in fibromyalgia (see discussion of α2δ ligands in anxiety in Chapter 8 and illustrated in Figures 8-17C and 8-18C) and for improving the slow-wave sleep disorder of fibromyalgia (sleep disorders and their treatment are discussed in further detail in Chapter 10). SNRIs can be useful in reducing symptoms of depression and anxiety in fibromyalgia (see Chapter 7 on treatment for mood disorders) and for treating fatigue as well as the cognitive symptoms associated with fibromyalgia, sometimes also called fibrofog (see Figures 9-8 and 9-9). Problems with executive functioning in a wide variety of clinical conditions are generally linked to inefficient information processing in the dorsolateral prefrontal cortex (DLPFC) where dopamine neurotransmission is important in regulating brain circuits (see Chapter 4 on cognition in schizophrenia and Figure 4-17). This concept of dopaminergic regulation of cognition in the DLPFC and the role of boosting dopamine neurotransmission to improve executive dysfunction is also discussed in Chapter 11 on attention deficit hyperactivity disorder. Since SNRIs increase dopamine concentrations in the DLPFC (see Figure 7-33C), SNRI agents can also potentially improve symptoms of fibro-fog in fibromyalgia patients. This may be particularly so for the SNRIs milnacipran and levomilnacipran, which have potent norepinephrine reuptake binding properties at all clinically effective doses (Figures 7-30 and 7-31), or for higher doses of the SNRIs duloxetine (Figure 7-29), venlafaxine, and desvenlafaxine (Figure 7-28), which act to increase norepinephrine reuptake blocking properties of these agents and thus act to increase concentrations of dopamine in the DLPFC (Figure 7-33C). Other strategies for improving fibro-fog in fibromyalgia patients include the same ones used to treat cognitive dysfunction in depression, and include modafinil, armodafinil, selective norepinephrine reuptake inhibitors (NRIs) such as atomoxetine, norepinephrine– dopamine reuptake inhibitors (NDRIs) such as bupropion, and with caution, stimulants. SNRIs, sometimes augmented with modafinil, stimulants, or bupropion can also be useful for symptoms of physical fatigue as well as mental fatigue in fibromyalgia patients.

Second-line treatments for pain in fibromyalgia can include sedating drugs for depression including mirtazapine and tricyclic antidepressants, as well as the tricyclic muscle relaxant cyclobenzapine. Other sleep aids such as benzodiazepines, hypnotics, and trazodone can be helpful in relieving sleep disturbance in fibromyalgia. Evidence is also accumulating for the efficacy of γ-hydroxybutyrate (GHB or sodium oxybate) in fibromyalgia (use with extreme caution because of diversion and abuse potential). GHB is approved for narcolepsy, enhances slow-wave sleep, and is discussed in Chapter 10 on sleep (see Figures 10-67 and 10-68). In heroic cases the use of GHB by experts for the treatment of severe and treatment-resistant cases of fibromyalgia may be justified. A number of anticonvulsants other than the α2δ ligands (Figure 9-16) are also used second-line for chronic neuropathic pain states, including fibromyalgia. These agents are thought to target voltage-gated sodium channels rather than voltage-gated calcium channels and thus seem to have a different mechanism of action than α2δ ligands and may be effective in patients with inadequate response to α2δ ligands. SUMMARY This chapter has defined pain, and has explained the processing of nociceptive neuronal activity into the perception of pain by pathways that lead to the spinal cord, and then up the spinal cord to the brain. Neuropathic pain is discussed extensively, including both peripheral and central mechanisms, and the concept of central sensitization. The key role of descending inhibitory pathways that reduce the activity of nociceptive pain neurons with the release of serotonin and norepinephrine is explained, and shown to be the basis for the actions of serotonin–norepinephrine reuptake inhibitors (SNRIs) as agents that reduce the perception of pain in conditions ranging from major depression to fibromyalgia to diabetic peripheral neuropathic pain, low back pain, osteoarthritis, and related conditions. The critical role of voltage-sensitive calcium channels (VSCCs) is also explained, providing the basis for the actions of α2δ ligands as agents that also reduce the perception of pain in diabetic peripheral neuropathic pain, fibromyalgia, painful physical symptoms of depression and anxiety disorders, shingles, and other neuropathic pain conditions. Finally, the spectrum of conditions from affective disorders to chronic neuropathic pain disorders is introduced, with emphasis on the condition of fibromyalgia and its newly evolving psychopharmacological treatments.

Revision #1
Created 2026-01-04 20:07:56 UTC by Omar Ayman
Updated 2026-01-04 20:07:56 UTC by Omar Ayman