

## REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

## Nonnarcotic Methods of Pain Management

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PAIN IS “AN UNPLEASANT SENSORY AND EMOTIONAL EXPERIENCE ASSOCIATED with actual or potential tissue damage, or [is] described in terms of such damage” when there is no physical derangement.<sup>1</sup> The function of pain is to protect the body by making the organism aware of damaging events and to promote healing by causing sensitivity to movement or other stimuli that may delay recovery. However, pain is not always related to tissue damage and does not always serve a protective function. This is the case with neuropathic pain, which is caused by a lesion or disease of the somatosensory parts of the nervous system, and with some other chronic pain conditions, such as fibromyalgia and migraine.<sup>2</sup> Acute and chronic pain may cause suffering and interfere with daily life, factors that influence the choice of treatment.

Acute pain is the most common reason for visiting an emergency department,<sup>3</sup> and surgical procedures are often associated with acute postoperative pain.<sup>4,5</sup> Chronic pain also causes suffering, as reflected by the finding in the Global Burden of Disease Study 2013 that chronic low back pain was the leading cause of years lived with disability.<sup>6</sup> In addition to the contribution of pain to disability, that study showed that the associated problem of opioid use disorders accounted for 5.8 million additional years lived with disability,<sup>6</sup> an observation that underpins attempts to treat pain with drugs other than opioids. Long-term opioid administration has minimal effects on chronic pain and can cause tolerance, drowsiness, and dependence, as well as impaired memory, concentration, and judgment.<sup>7</sup> For these reasons, the International Association for the Study of Pain recommends caution in prescribing opioids for chronic pain,<sup>8</sup> and there has been an increased emphasis on the use of nonopioid pain management.

The choice of treatment for pain depends on many factors, and the heterogeneity and large number of acute and chronic pain conditions preclude a general treatment algorithm. In cooperation with the World Health Organization, the International Association for the Study of Pain has developed a classification of chronic pain for the 11th revision of the *International Classification of Diseases*<sup>2</sup> (Table 1), and a similar classification has been proposed for acute pain,<sup>5</sup> providing the bases for facilitating treatment pathways.

## ASSESSMENT OF PAIN

A common way to assess pain is to ask the patient about the intensity of pain on an 11-point numerical scale (0 to 10), but an overemphasis on the effect of treatment on pain intensity and overdependence on the assessment of pain with the use of these scales can lead to unnecessary opioid use.<sup>9</sup> Furthermore, pain intensity does not reflect the entirety of the pain experience and is often not a measure of the suffering induced by pain.<sup>10</sup> If the pain is known to be short-lived or to serve a purpose such as healing, it may be accepted and tolerated by the patient. Also,

**Table 1. Factors to Consider in the Management of Pain.**

<b>Classification</b>
Primary pain (e.g., widespread pain)
Neuropathic pain
Postsurgical pain
Post-traumatic pain
Cancer-related pain
Visceral pain
Musculoskeletal pain
Headache, including migraine
<b>Temporal aspects</b>
Acute pain
Chronic pain
Ongoing pain
Intermittent or paroxysmal pain
<b>Assessment</b>
Pain intensity
Pain interference
Coexisting conditions
Psychological functioning
Physical functioning
Social aspects
Fear-avoidance behavior
Pain catastrophizing
Self-efficacy

if patients perceive pain as a threat, an explanation of the cause and physiological meaning of the pain may alter their perception.<sup>9</sup> Patients with chronic pain may have depression and anxiety, as well as “pain catastrophizing” (i.e., overly negative thoughts about pain in association with a tendency to feel helpless and magnify the threat of pain), which may increase the likelihood that pain will interfere with daily activities, whereas self-efficacy (the belief in one’s ability to meet challenges and achieve goals), coping strategies, and resilience have been linked to decreased interference with daily activities.<sup>11</sup> Depression, anxiety, emotional distress, and a perceived lack of social support also contribute negatively to the long-term outcome of chronic pain (Table 1).<sup>10</sup> These observations make it clear that the experience of pain is complex and subject to substantial individual variation, but they allow for the assessment and treatment of pain to be individualized on the basis of its severity and its interfer-

ence in daily life, as well as the degree of suffering that pain induces (Table 1).

#### PATIENT EDUCATION AND PSYCHOLOGICAL TREATMENT

The recent U.S. National Pain Strategy report emphasizes the need for self-management programs, which incorporate information about the nature of pain and the patient’s ability to prevent, cope with, and reduce pain through interdisciplinary pain treatment programs.<sup>12</sup> The American Pain Society recommends involving the patient in the pain management plan and choosing treatment that combines pharmacologic and nonpharmacologic methods for managing acute pain and pain from cancer.<sup>13</sup> Guidelines for the management of chronic low back pain, issued by the National Institute for Health and Care Excellence in the United Kingdom and the American College of Physicians, recommend educating patients and advising them to continue normal activities and to use self-management programs as first-line approaches, with supervised exercise therapy and cognitive behavioral or other psychological therapies or physical manipulation as second-line treatment.<sup>14,15</sup> Only in refractory cases are pharmacologic, interventional, and surgical treatments considered appropriate. Most guidelines acknowledge that the strength of the recommendations is based on evidence that is of low-to-moderate quality and on only a few randomized, controlled trials, which have the inherent difficulty of masking patients to treatment assignments. Moreover, the effect sizes of psychological and self-care interventions are small, with between-group differences in pain intensity of 0.5 to 1.0 on a rating scale of 0 to 10, and results between trials are often conflicting.<sup>14,15</sup>

Psychological treatments include cognitive behavioral therapy, hypnosis, mindfulness training, biofeedback, and stress management.<sup>16,17</sup> Cognitive behavioral therapy involves practical techniques to change physical activity, reduce distress and catastrophizing, and improve functioning and social engagement. These techniques include coping strategies, exposure to feared activities, activities that divert attention from pain, and relaxation training. There have been few studies of the benefits of psychological treatments in patients with chronic pain, and the available

evidence is of only low-to-moderate quality.<sup>16-18</sup> Multidisciplinary management of chronic pain, which addresses psychological, social, and occupational factors, is sometimes beneficial, but no specific components of the combined treatment approach have been identified that influence the success of treatment.<sup>19,20</sup> Hypnosis as a treatment for pain has been studied in a few randomized trials, with either uncertain evidence of an effect or small effect sizes on self-reported chronic pain; variable effect sizes on emotional stress resulting from pain during medical interventions have been noted.<sup>21</sup>

The lack of high-quality evidence supporting the long-term effects of self-management and psychological treatment,<sup>16</sup> in combination with patients or physicians who may not follow the recommended approaches, results in wide variations in practice.<sup>12</sup> Barriers to implementation of these approaches include resistance on the part of the patient, lack of resources, limitations of insurance coverage, and uncoordinated health care systems. Further studies are needed to determine when and how these strategies should be implemented.<sup>12</sup>

#### NONOPIOID ANALGESIC AGENTS

Several analgesic agents, developed primarily for conditions other than pain and with various biologic sites of action, are available (Fig. 1 and Table 2). These include nonsteroidal antiinflammatory drugs (NSAIDs), antidepressant agents, and antiepileptic drugs.

#### ACETAMINOPHEN, ASPIRIN, AND NSAIDS

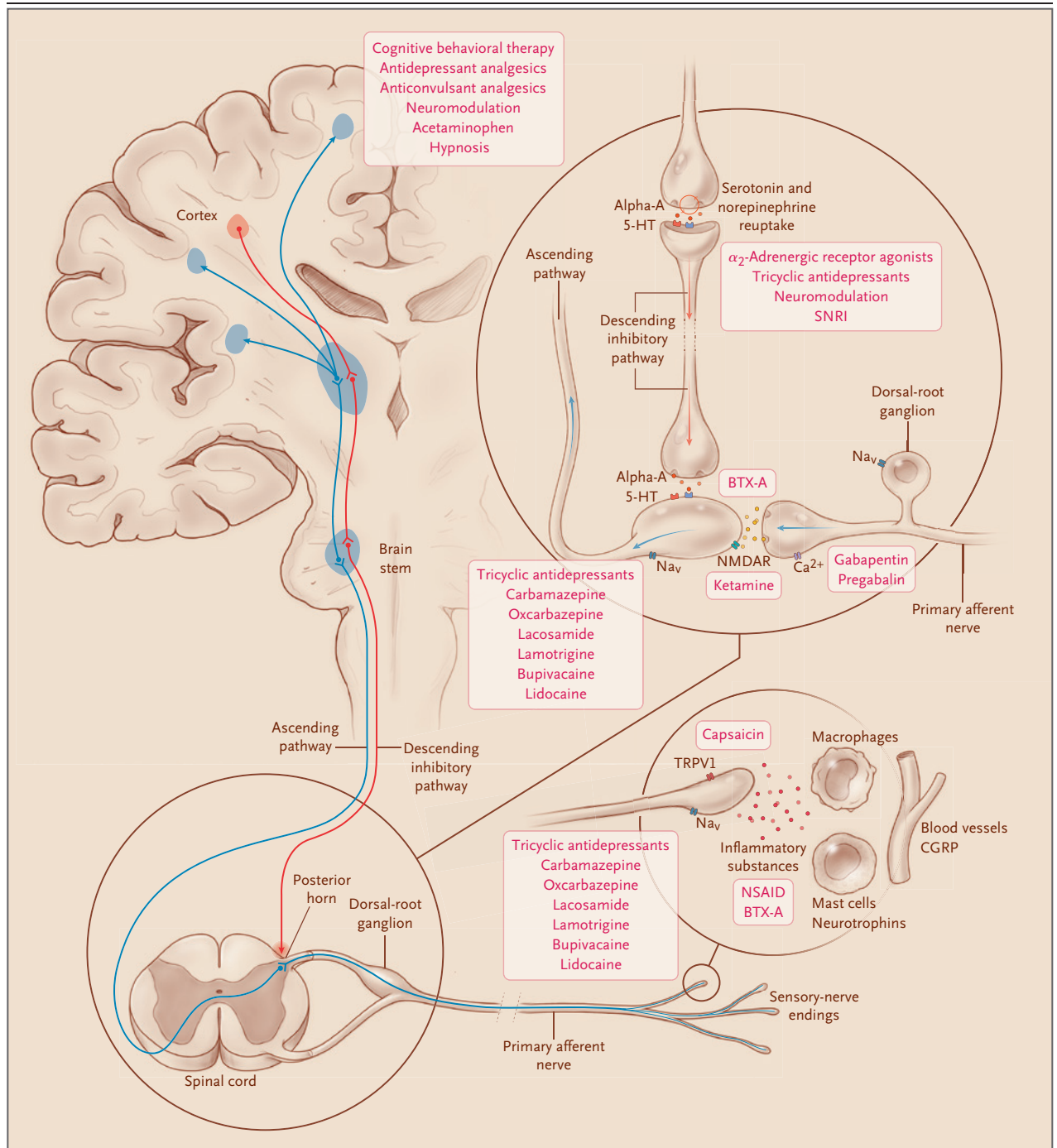
Acetaminophen (also known as paracetamol) has well-known analgesic and antipyretic effects. It is widely used as an over-the-counter and prescription analgesic, but its mechanisms of action are not known. There is a small risk of severe skin reactions and a risk of liver damage if this agent is used in large doses. Acetaminophen has been the leading cause of acute liver failure in the United States since 1998 and requires a warning about the hepatotoxic risks.<sup>22</sup> Although acetaminophen is still considered the safest analgesic, no high-quality studies have assessed chronic adverse effects, and the Food and Drug Administration (FDA) is monitoring the safety of its use during pregnancy.<sup>23</sup>

Aspirin (acetylsalicylic acid) and other NSAIDs, unlike acetaminophen, have antiinflammatory properties and inhibit platelet aggregation. Side effects of NSAIDs include nausea, gastrointestinal bleeding, and hypersensitivity reactions. NSAIDs, with the exception of aspirin, are associated with a risk, albeit low, of heart attack or stroke. The magnitude of the risk is not known with certainty, suggesting that the lowest doses should be used for the shortest time possible.<sup>24</sup> NSAIDs are used for slight-to-moderate pain such as muscle and joint pain, toothache, menstrual pain, certain types of visceral pain, and postoperative pain and are first-line treatment for conditions such as migraine and single episodes of tension-type headache.<sup>25</sup>

#### ANTIDEPRESSANT AGENTS

Several drugs initially developed for the treatment of depression have been used for chronic pain. Tricyclic antidepressants and serotonin–norepinephrine (noradrenaline) reuptake inhibitors (SNRIs) reduce the intensity of pain in patients who have depression and in those who do not.<sup>26</sup> One randomized, controlled trial estimated that less than 12% of the effect of duloxetine at a dose of 60 mg or 120 mg was attributable to improvement in mood or anxiety.<sup>27</sup> However, antidepressants may be more effective in patients with both pain and depressive symptoms than in those with pain alone.<sup>28</sup> The reason for the analgesic effect is not known but may be related in part to presynaptic inhibition of the reuptake of serotonin and norepinephrine in pain inhibitory pathways, as well as peripheral mechanisms involving  $\beta_2$ -adrenergic receptors and the opioid system.<sup>29,30</sup>

Tricyclic antidepressants and SNRIs have been used as first-line treatments for neuropathic pain, defined as pain due to a lesion or disease of the peripheral or central somatosensory nervous system.<sup>31</sup> In a systematic review of trials of these agents as compared with placebo, the number of patients who would need to be treated (number needed to treat) in order to achieve at least a 50% reduction in neuropathic pain in one patient was 3.6 for tricyclic antidepressants and 6.4 for SNRIs.<sup>31</sup> Antidepressants have also been recommended for prophylactic treatment of migraine and tension-type headache.<sup>32</sup> There is some evidence of an analgesic effect of these



**Figure 1. Sites of Action of Various Methods of Pain Management.**

Shown are pain treatments that act on the brain, multiple drug targets along the pain pathway in the spinal cord (including facilitation of descending pain inhibitory pathways and blockade of pre- and postsynaptic receptors and neurotransmitter release), and drug targets at the level of the peripheral nociceptor. Alpha-A denotes  $\alpha$ -adrenergic receptor, BTX-A botulinum toxin type A, CGRP calcitonin gene-related peptide, 5-HT 5-hydroxytryptamine,  $Na_v$  voltage-gated sodium channel, NMDAR *N*-methyl-D-aspartate receptor, NSAID non-steroidal antiinflammatory drug, SNRI serotonin-norepinephrine reuptake inhibitor, and TRPV1 transient receptor potential cation channel subfamily vanilloid member 1.

**Table 2. Nonopioid Analgesic Agents for Acute and Chronic Pain.\***

Drug	Dose†	Indication	Side Effects and Risks‡	Other Information
Acetaminophen	650 mg orally every 4 to 6 hr; maximum dose, 4000 mg/day; also available as injection	Mild-to-moderate pain	Overdose can cause liver damage	No evidence of an effect on neuropathic pain
Aspirin	350–650 mg orally every 4 hr; maximum dose, 3600 mg/day; individual doses for rheumatic diseases	Mild pain (temporary use), inflammatory rheumatic diseases	Nausea, dyspepsia, abdominal pain, bleeding tendency, tinnitus, headache, dizziness, insomnia, hypersensitivity reactions; risk of gastrointestinal bleeding	Contraindicated in patients with known hypersensitivity; should not be used in children under 16 yr of age (risk of Reye's syndrome); no evidence of an effect on neuropathic pain
NSAIDs	Dose depends on the specific drug	Mild-to-moderate pain, pain associated with inflammation	Nausea, dyspepsia, diarrhea, constipation, headache, dizziness, somnolence, hypersensitivity reactions; risks of gastrointestinal bleeding, myocardial infarction, stroke	Contraindicated in patients with known hypersensitivity; recommended dose is the lowest effective dose for the shortest period; no evidence of an effect on neuropathic pain
Amitriptyline§	25–150 mg orally once daily or in two divided doses;¶ maximum single dose, 75 mg; daily doses above 75 mg/day should be used with caution in patients >65 yr of age	Neuropathic pain (first-line therapy), fibromyalgia, prevention of tension-type headache or migraine	Somnolence, tremor, dizziness, headache, drowsiness, tachycardia, orthostatic hypotension, dry mouth, constipation, nausea, micturition disorder, weight gain, hyperhidrosis, decreased libido; increased risk of suicidal thoughts	Patients with poor metabolism of CYP2D6 require lower doses; abrupt discontinuation should be avoided; contraindicated in patients with recent myocardial infarction or cardiac rhythm disorders; caution required if used with other serotonergic agents
Duloxetine	60–120 mg orally once daily or in two divided doses¶	Neuropathic pain (first-line therapy), chronic musculoskeletal pain, fibromyalgia	Nausea, headache, dry mouth, somnolence, dizziness, increased blood pressure; increased risk of suicidal thoughts	Abrupt discontinuation should be avoided; caution required if used with other serotonergic agents
Gabapentin	900–3600 mg/day orally in three divided doses¶	First-line therapy for neuropathic pain	Dizziness, somnolence, peripheral edema, fever, infection, nausea, lack of coordination, blurred vision; increased risk of suicidal thoughts	Dose adjustment required in patients with compromised renal function; misuse, abuse, and dependence have been reported
Pregabalin	300–600 mg/day orally in two divided doses¶	Neuropathic pain (first-line therapy), fibromyalgia	Dizziness, somnolence, headache, peripheral edema, nausea, weight gain, disorientation, blurred vision; increased risk of suicidal thoughts	Dose adjustment required in patients with compromised renal function; misuse, abuse, and dependence have been reported
Lidocaine, 1.8% or 5% patch	1–3 Patches applied to intact skin for up to 12 hr/day	Peripheral neuropathic pain	Application-site pain, pruritus, erythema, and skin irritation	Approved by FDA and EMA for postherpetic neuralgia only
Capsaicin, 8% patch	1–4 Patches applied to intact skin for 30 or 60 min every 3 mo	Peripheral neuropathic pain	Application-site pain and erythema; transient increase in blood pressure; risk of reduced sensation	Applied by a health care professional wearing nitrile gloves

\* The drugs listed are those commonly used, but the list does not include all analgesics used for all pain conditions. CYP2D6 denotes cytochrome P-450 2D6, EMA European Medicines Agency, FDA Food and Drug Administration, and NSAID nonsteroidal antiinflammatory drug.  
 † Doses are given for adults.  
 ‡ For a comprehensive list of side effects, risks, contraindications, and warnings, refer to the product information for each drug.  
 § Other tricyclic antidepressants (imipramine, desipramine, and nortriptyline) have not been evaluated as extensively for the treatment of pain but may be associated with more acceptable side-effects profiles.  
 ¶ The starting dose is lower.



drugs on pain from fibromyalgia, although it has been suggested that the benefits are outweighed by side effects in most patients.<sup>33</sup> Systematic review of studies involving patients with low back pain suggests no overall effect of antidepressants on pain intensity or function, except for a small effect of duloxetine (a reduction in pain of <1 point on a scale of 0 to 10).<sup>34</sup> The question of whether certain antidepressants have advantages over others is not settled. Amitriptyline is the tricyclic antidepressant with the best-documented analgesic effects, but desipramine, nortriptyline, and imipramine are likely to have less pronounced anticholinergic and sedative side effects and are associated with a lower risk of falls.<sup>30</sup>

#### ANTIPILEPTIC MEDICATIONS

Several drugs used for the treatment of epilepsy have apparent analgesic properties through their putative effects of lowering neurotransmitter release or reducing neuronal firing. Gabapentin and pregabalin are ligands of the  $\alpha_2\delta$  subunit of neuronal voltage-gated calcium channels. They cause reduced calcium-dependent release of excitatory neurotransmitters, thereby decreasing neuronal excitability. Gabapentin and pregabalin are recommended in guidelines for the treatment of neuropathic pain,<sup>31</sup> and pregabalin has also been shown to be effective in trials for pain from fibromyalgia, with modest adverse events.<sup>35</sup> In a systematic review of trials evaluating antiepileptic medications as compared with placebo for the treatment of neuropathic pain conditions, the number needed to treat in order to achieve 50% pain reduction in one patient was 7.7 for pregabalin and 7.2 for gabapentin.<sup>31</sup> Not all trials show the superiority of antiepileptic agents over placebo, and a recent trial failed to show an effect of pregabalin in patients with sciatica.<sup>36</sup> Perioperative use of pregabalin has an opioid-sparing effect on acute postoperative pain but an increased risk of serious adverse events and is therefore not recommended as routine postoperative treatment for pain.<sup>37</sup> Side effects such as sedation and dizziness are common with both gabapentin and pregabalin, and there is increasing evidence of misuse and abuse of these drugs.<sup>38</sup> Pregabalin is approved by the FDA only for neuropathic pain and pain from fibromyalgia; evidence of an effect on pain from other conditions is lacking, and concern has been expressed about increasing off-label use.<sup>38</sup>

Oxcarbazepine, carbamazepine, lamotrigine, and lacosamide reduce neuronal excitability in the central and peripheral nervous systems by acting on voltage-gated sodium channels. Oxcarbazepine and carbamazepine are first-line treatments for trigeminal neuralgia,<sup>39</sup> and the rate of success with these agents in treating this disorder has been considered to be good. On the basis of a few small, short-duration studies for conditions such as trigeminal neuralgia, the number needed to treat in order to achieve pain control in one patient is approximately 1.7.<sup>39</sup> For other types of neuropathic pain, there is inconclusive evidence for the use of these drugs.<sup>31</sup>

#### LOCAL TREATMENT OF PAIN

An advantage of topical treatment of pain is the absence of effects on the central nervous system and other systemic side effects. Among the most commonly used agents in this class is the lidocaine patch, at a dose of 1.8% or 5%, which is approved by the FDA for postherpetic neuralgia and is recommended for peripheral neuropathic pain.<sup>31</sup> The patches are applied over the sites of pain for up to 12 consecutive hours per day. They have few side effects but may cause skin irritation. Too few trials have been conducted to provide a dependable estimate of effect sizes. Capsaicin, which is the active pungent ingredient in chili peppers, activates the transient receptor potential vanilloid channel of small peripheral sensory nerves. The effect of repeated applications or of a single high-dose application is thought to occur through desensitization and a temporary reduction in the number of pain fibers in the skin. The capsaicin 8% patch is a second-line treatment for peripheral neuropathic pain such as postherpetic neuralgia and painful polyneuropathy, but there is no evidence of effectiveness in other pain conditions.<sup>31</sup> On the basis of an analysis of seven trials, the combined number needed to treat is 10.6.<sup>31</sup> Local side effects include skin reactions and discomfort on initial application. Because of precautions required to avoid contact with mucous membranes, the capsaicin 8% patch is applied by a health care professional. Up to four patches are applied once for 30 or 60 minutes, and the treatment can be repeated every 3 months. There is no good evidence that the weaker, over-the-counter preparations of menthol, methyl salicylate, or capsaicin have an effect on pain. Botulinum toxin type A

given subcutaneously in the region of pain is a third-line treatment for peripheral neuropathic pain.<sup>31</sup>

#### INTERVENTIONAL PAIN MANAGEMENT

Surgery is indicated for the treatment of pain if the underlying cause can be addressed safely and with a net clinical benefit. Examples that fulfill these conditions include removal of a tumor or herniated disk adjacent to neural tissue. Devices designed to modulate abnormal activity in the nervous system by stimulating neuronal pathways are used for symptomatic pain treatment. There is weak evidence for a benefit of spinal cord stimulation in patients with painful diabetic polyneuropathy, postsurgical chronic back and leg pain, or complex regional pain syndrome, and the evidence is similarly weak for a benefit of repetitive transcranial magnetic stimulation in the treatment of neuropathic pain and pain from fibromyalgia; in various other conditions, the effect of these devices is absent or unclear.<sup>40</sup> The effect of spinal cord stimulation has been compared with the effect of conventional care or reoperation for low back pain, and most studies have been of short duration, making it difficult to estimate effect sizes over the long term.<sup>40</sup>

Interventional treatments are available for pain conditions such as microvascular decompression or percutaneous radiofrequency rhizotomy for trigeminal neuralgia and occipital-nerve stimulation for cluster headache. Epidural analgesia or intrathecal treatment with ziconotide (a selective N-type voltage-gated calcium channel blocker), clonidine (a central  $\alpha_2$ -adrenergic receptor agonist), bupivacaine, or a combination of these agents may be used for uncontrolled pain associated with cancer.

#### COMPLEMENTARY THERAPIES

Many patients with chronic pain use complementary therapies, which include meditation, yoga, acupuncture, music therapy, heat therapy, massage, chiropractic, guided imagery, and biofeedback.<sup>41,42</sup> Complementary therapies such as acupuncture and massage are recommended by the American College of Physicians for chronic low back pain.<sup>15</sup> These therapies may support

active self-care, and meditation and yoga are recommended to improve psychological well-being.<sup>41</sup> However, the quality of evidence supporting the recommendations for complementary therapies is low, and there is controversy about the clinical relevance of the effects of these therapies, the role of placebo responses, and trial design, particularly in the case of acupuncture.<sup>43</sup>

#### FUTURE DIRECTIONS

Pharmacologic and interventional treatments for chronic pain often provide no reduction or only a small reduction in pain and are often judged by the patient to be inadequate.<sup>34</sup> Each approach may have side effects that are associated with a decreased quality of life and interference with daily activities.<sup>44</sup> Education and training of health care professionals to ensure cost-effective and safe evidence-based treatments are therefore considered essential for pain management.<sup>12,25</sup>

Recent advances in our understanding of the mechanisms underlying pain have led to the development of new approaches. Several drugs are under investigation, such as calcitonin gene-related peptide antagonists and serotonin (5-hydroxytryptamine) type 1F (5-HT<sub>1F</sub>) agonists for migraine and angiotensin II type 2 receptor antagonists, selective sodium-channel blockers (e.g., voltage-gated sodium channel Na<sub>v</sub>1.7), and vanilloid receptor antagonists for neuropathic pain.<sup>45,46</sup> New but not rigorously tested interventional treatments include high-frequency spinal cord stimulation and dorsal-root ganglion stimulation. Well-known drugs such as the anesthetics ketamine (an N-methyl-D-aspartate [NMDA] receptor antagonist) and nitrous oxide are also being considered as alternatives to opioids for acute pain in the emergency department or as part of analgesic regimens for postoperative pain.<sup>45,47,48</sup>

Attempts are being made to identify biomarkers that predict the likelihood that a treatment will be effective<sup>49</sup> by targeting the pain mechanism in each patient. For example, one study showed that refined testing of somatosensory function in patients with neuropathic pain could identify patients who would have a response to the sodium-channel blocker oxcarbazepine.<sup>50</sup> Other possible methods that could individualize the approach to pain treatment include molecular profiling in rare pain conditions caused by gene variants that code for specific sodium

channels, brain imaging to assess brain networks involved in pain and its emotional effects, and assessment of psychological functioning that may suggest a benefit from the use of specific psychological treatments.<sup>49</sup>

## CONCLUSIONS

For the management of acute pain, the use of multiple approaches that do not include opioids and the establishment of acute pain services for postoperative pain management can reduce

opioid-related adverse effects and dependence.<sup>4,25,48</sup> Patient education, psychological treatments, and avoidance of opioids may be useful for the management of chronic pain.<sup>12</sup>

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