Pain is associated with myriad medical conditions and affects millions of Americans. Chronic pain is one of the most common reasons prompting visits to healthcare providers; collectively, it possibly disables more people annually than heart disease and cancer combined. Primary goals of treating patients with chronic pain are to reduce pain as much as possible and facilitate functional restoration. When chronic pain becomes a disease state, it can be controlled, but, at present, it cannot be cured. Better understanding of the pathophysiology of acute and chronic pain has led to numerous advances in pharmacologic management of painful disorders, including low back pain, migraine headache, fibromyalgia, postherpetic neuralgia, osteoarthritis, rheumatoid arthritis, and cancer-related neuropathic pain. This presentation reviews the available agents and how to use them rationally, either singly or in combination, so practitioners can treat patients with chronic pain as effectively as possible.

(Key words: α-adrenergic agonists, antidepressants, anticonvulsants, botulinum toxin, chronic pain, local anesthetics, muscle relaxants, NMDA receptor antagonists, nonopioid analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs], opioid analgesics, topical analgesics)
ally than heart disease and cancer combined! Attempts primarily by health insurance companies to define acute and chronic pain based on duration (acute: less than 3 months; chronic: more than 3 months) do not accurately nor appropriately respect scientific advances regarding known mechanisms of these states. Certainly, we can all appreciate what an acute painful event is; however, pain can be considered chronic much before the “magic” 3-month waiting period has elapsed; chronic pain truly is that which exists beyond the time of normal healing and as such may be present even within weeks of an acute injury. Because chronicity results in functional disability, it therefore has become increasingly important to manage acute pain as if it might become chronic and, wherever possible, prevent development of chronic pain. This, in my opinion, is one of the greatest challenges of modern medical care.

Chronic headache (migraine, tension-type, chronic daily, mixed), chronic neuropathic pain (postherpetic neuralgia [PHN], diabetic neuropathy, complex regional pain syndrome, “neuropathic” low back pain, cancer-associated neuropathic pain), pain secondary to degenerative spinal disorders, pain secondary to nonspinal degenerative joint disease, fibromyalgia, soft tissue pain disorders (eg, chronic myofascial pain), and others are among the many chronic painful states that clinicians regularly encounter.

Evaluation of chronic pain may be quite challenging for a multitude of reasons, including lack of a specific pain measurement tool that can prove or disprove the presence and/or intensity of pain as well as limitations in interpretation of available test results (eg, imaging and electrophysiologic tests). For example, though it is well known that the degree of abnormality seen on a magnetic resonance image (MRI) of the lumbar spine does not routinely correlate with the degree of pain an individual has—and that asymptomatic individuals may be noted to have disk herniations or other obvious structural problems with such imaging tools—is it as equally well accepted that patients with severe low back pain may have little or no structural abnormalities seen by MRI?

Electrophysiologic tests such as electromyography and nerve conduction evaluations do not measure the fiber types (C and A-delta) responsible for transmission of pain; therefore, the presence of normal nerve conductions for a patient with severe chronic neuropathic pain does not—as some practitioners and many insurance companies interpret these findings—indicate the absence of pain or that the patient is malingering. Psychosocial and other factors may often play a role in the chronic pain experience.

Despite these challenges, advances in our understanding of the pathophysiology of various chronic pain problems have been made which in turn have led to new pharmacotherapeutic options for managing chronic pain. Different types of agents have been developed and hold great promise for reducing the amount of pain that an individual has to endure, hopefully leading to functional restoration whenever possible.

Success with pharmacologic management of chronic pain may be enhanced by recognition of differences between nociceptive and neuropathic pain. Nociceptors are specialized nerve endings that are able to respond to typical normal pain-producing stimuli such as thermal, chemical, mechanical, and other potential causes of tissue damage. An activated nociceptor, through C and A-delta nerve fibers, transmits its pain-producing information from the peripheral nervous system (PNS) to the central nervous system (CNS), where it is processed further at spinal cord and brain levels. At each level of the nervous system, processes exist to either facilitate or to dampen transmission of painful stimuli. Nociceptive input does not become experienced as pain unless nociceptive information reaches appropriate regions of the brain.

Nociception may be augmented by release of proinflammatory agents such as cytokines, adenosine, bradykinin, serotonin, and prostaglandins that can alter or sensitize neural transmission and temporally create a neuropathic pain state. In the absence of nociceptive input, a normal nervous system does not experience pain. In contrast, chronic neuropathic pain results from injury to the PNS and/or CNS and represents abnormalities in transmission that have developed from an injury. Ongoing injury is not required for these abnormalities to be expressed. Clear evidence exists that chronic neuropathic pain appears to result from the manner in which the nervous system is reorganized after injury.

One result of this reorganization is a lowered threshold to nociceptive processing. Stimuli that may normally not be painful are now, in chronic neuropathic pain states, experienced as painful (allodynia). Stimuli that are normally painful may be more painful than usual (hyperalgesia). Any sensory stimuli, painful or otherwise, may be perceived in a more exaggerated manner (hyperesthesia). These clinical findings are the hallmark of chronic neuropathic pain and reflect a nervous system that is now able to facilitate pain production because it is more easily excited than in a normal state. It must be emphasized that neuropathic pain may therefore be experienced even when the affected individual is not subjected to a tissue-damaging stimulus.

It is also important to recognize that a nociceptive pain state may have associated clinical features of a neuropathic pain state, at least initially. It is also possible for an acute nociceptive pain state over time to transform into a chronic neuropathic pain state, eg, for some individuals with soft tissue pain disorders or chronic radicular low back pain. Factors underlying this transformation are being actively studied and hold the key to treatment and, it is hoped, prevention of many different chronic pain states including postherpetic neuralgia, complex regional pain syndrome, chronic headache, chronic pain related to degenerative joint disease, chronic low back pain, and fibromyalgia.

Excitatory neurotransmission through the N-methyl-d-aspartate (NMDA) receptor appears to play a significant role in development of a chronic painful state and tolerance to opioids (and perhaps to other analgesics). Pharmacologic agents that block the NMDA receptor (dextromethorphan hydrobromide, ketamine hydrochloride, amantadine hydrochloride, and d-methadone) stabilize neuronal excitability and suppress central sensitization.

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It must be noted that all chronic pain syndromes have in common some degree of facilitation by the CNS. Various analgesics have in common the ability to dampen this facilitation and therefore act on either peripheral or central neural mechanisms of pain transmission or both, holding great promise in the treatment of patients with chronic pain. For each patient, the development of a chronic pain treatment plan should include both medical and nonmedical options. Therapeutic exercise, formal physical therapy, stress reduction, relaxation therapy, biofeedback, other lifestyle modifications, and acupuncture among other nonpharmacologic approaches have the clear potential to help patients with chronic pain.

Pharmacotherapy plays a key role in the management of chronic pain, as drug therapy may help to turn off noxious stimuli or dampen the underlying neuropathic disturbance, thereby reducing the pain. Intervventional modes of therapy for chronic pain may also be explored, and these modes are often used as part of a comprehensive treatment program. Perhaps the most important role of pharmacotherapy in the management of chronic pain is to help facilitate functional restoration through the provision of sufficient analgesia to break the pain cycle and then to help keep the pain at an acceptable level. It is therefore critical for effective treatment and comfort for both prescriber and patient that the prescriber be comfortable with the wide range of pharmacologic options currently available for management of chronic pain. Although this may seem obvious for the patient with chronic pain who has been refractory to multiple modes of therapy, the truth is that each patient needs to be treated individually as even naive patients may respond quite differently and these modes are often used as part of a comprehensive treatment program.

One must balance the evidence for efficacy of a particular agent with its safety and ease of use. In some instances, the underlying pathophysiology of a specific syndrome, if known, may help to guide the prescriber. For example, although benzodiazepines may be potentially helpful for a number of chronic painful states associated with muscle spasm, use of these agents may result in significant sedation and physical as well as psychological dependence. Opioids have also been found to be helpful for a variety of chronic pain problems, but they can also be sedating, and their use is frequently associated with constipation and other gastrointestinal (GI) side effects. Contrarily, pure opioids do not produce significant organ toxicity and, although their use may be associated with a high incidence of withdrawal symptoms upon sudden cessation of use, they rarely produce psychological dependence (addiction) on their own.

Nonsteroidal anti-inflammatory drugs
NSAIDs are known to have multiple actions within the CNS and PNS. Many of these effects seem to be related to their inhibition of the synthesis of prostaglandins, in large part through the inhibition of the enzyme cyclooxygenase (COX). Beneficial as well as many of the adverse effects of many of the NSAIDs are the result of this COX inhibition. At least two different isoforms of COX are known. COX-1 is needed for normal homeostasis in the endothelium, the kidney, and the gut. COX-2 is considered the “inducible” enzyme, and it helps to produce prostaglandins during an inflammatory process.

Other activities of COX-2, including its inhibition of activity at the NMDA receptor, have been demonstrated in animal studies and are under active intense investigation. This division of activity between the two isoforms is not absolute. Known pharmacologic effects of NSAIDs include analgesia, anti-inflammation, antipyresis, the production of sodium retention and hyponatremia, the development of renal failure, potential changes in vascular tone, gastric irritation, platelet inhibition, hepatic dysfunction, and CNS effects such as dizziness, sedation, and confusion.9–13

NSAIDs have traditionally been used both on a short-term and on a long-term basis for the management of a wide variety of musculoskeletal pain syndromes including low back pain, osteoarthritis, ankylosing spondylitis, rheumatoid arthritis, as well as in a number of other pain syndromes including dental pain, and acute and chronic headache.

Salicylate group of NSAIDs—The salicylate group of NSAIDs includes aspirin, choline magnesium trisalicylate, and difunisal. Aspirin, perhaps the most widely used analgesic, is commonly used not only as an anti-inflammatory agent and antipyretic, but also for platelet-inhibiting effects in prevention of cerebrovascular accidents and myocardial infarctions. COX is inhibited irreversibly, an action that may be effective for mild to moderate pain. Common side effects of aspirin include dyspepsia, nausea, and emesis; aspirin can also produce GI hemorrhage, peptic ulcer, gastritis, and liver function abnormalities. Its use in children and adolescents has been associated with Reye’s syndrome, and aspirin is believed to be the most nephrotoxic of the NSAIDs.14

Choline magnesium trisalicylate is similar to aspirin with respect to the anti-inflammatory, antipyretic, and analgesic effects but different because it has less GI irritability, a longer half-life, and no significant platelet inhibition; it is often better tolerated. Difunisal, another salicylic acid derivative, also has less GI irritability and less platelet-inhibiting effects than aspirin.15,16

Indoleacetic acid derivatives—Indomethacin, sulindac, and etodolac are indoleacetic acid derivatives. Indomethacin has been used in management of various types of arthritis, other forms of musculoskeletal pain, “indomethacin-responsive” headache syndromes, metastatic bone disease, and gout (promotes urinary excretion of uric acid). This is not a well-tolerated medicine as GI side effects are quite common; other adverse effects include psychosis, headache production, depression, hypertension, and fluid retention.

Sulindac has often been used to treat various musculoskeletal pain conditions.
and it produces fewer toxic side effects than indomethacin; however, a causal relationship to liver disease has been suggested. Etodolac appears to be a mixed COX-1 and COX-2 inhibitor and is used in management of osteoarthritis, bursitis, rheumatoid arthritis, and other musculoskeletal pain conditions.\textsuperscript{17,18} Although diclofenac, one of two commonly used pyrrolocetic acid derivatives, has both COX-1– and COX-2–inhibiting activities, it appears to have more COX-2 than COX-1 activity and therefore seems to have less toxicity.\textsuperscript{19}

**Pyrrlactic acid derivatives**— Diclofenac is used in the management of gout, low back and neck pain associated with degenerative joint disease, osteoarthritis, and rheumatoid arthritis. In addition to GI side effects, there is a small risk of hepatic inflammation, so liver function tests must be done within 8 weeks of administration.\textsuperscript{20}

Ketorolac, another pyrrolocetic acid derivative, is perhaps more of an analgesic than an anti-inflammatory agent; its analgesic effect may be related to promotion of release of endogenous opioids. Potential and actual GI and renal toxicities, however, limit overall effectiveness; to avoid such toxicity, short-term use (<5 days orally and <48 hours parenterally) is practically mandated. For acute, short-term treatment, however, ketorolac is still considered an effective agent for the management of acute low back pain, postoperative pain, and acute headache.\textsuperscript{21}

**Propionic acid derivatives**—Propionic acid derivatives include ibuprofen, naproxen, ketoprofen, and oxaprozin. Ibuprofen, a widely prescribed NSAID, is also available as an over-the-counter (OTC) agent. Naproxen is recognized as having more GI side effects than ibuprofen. Ketoprofen may also cause GI side effects. Each may be used in a variety of chronic painful states and each is widely prescribed. The long half-life of oxaprozin (55 hours), allows this drug to be prescribed on a once-daily basis.\textsuperscript{22}

**Benzothiazine derivatives**—Benzothiazine derivatives, or oxicams, include piroxicam and meloxicam. Meloxicam is considered to be a mixed COX-1/COX-2 inhibitor, but it is, in fact, primarily a COX-2 selective agent. Piroxicam has been demonstrated to be an effective anti-inflammatory agent in management of osteoarthritis and acute musculoskeletal injuries; its use is more frequently associated with serious GI side effects than other agents.\textsuperscript{23–25} Alkanones, a newer class of NSAIDs, include the drug nabumetone; its GI side effects are reported to be milder than those of other NSAIDs.\textsuperscript{26}

Selective COX-2 inhibitors that are currently available in the United States include rofecoxib, celecoxib, and valdecoxib. Rofecoxib is useful for the management of pain associated with osteoarthritis as well as rheumatoid arthritis, acute postprocedural pain, and dysmenorrhea. Both celecoxib and valdecoxib have been used for the treatment of pain and inflammation associated with osteoarthritis and rheumatoid arthritis. There is much current debate in the medical literature regarding true side effect profiles of this class of NSAIDs and whether they offer superior efficacy to other older, less COX-2-selective agents.\textsuperscript{27}

**Nonopioid analgesics**

Acetaminophen, often combined with opioids, has analgesic and antipyretic properties; it inhibits prostaglandin synthesis more in central than in peripheral regions and therefore is considered not effective as an anti-inflammatory agent. Overuse of acetaminophen has been associated with nephrotoxicity, hepatotoxicity, and thrombocytopenia; therefore, doses greater than 4 g/d are not recommended. Even if prescribers of combination agents follow this guideline, widespread use of OTC medications with acetaminophen often inadvertently leads to its overuse.\textsuperscript{28}

Tramadol hydrochloride, a synthetic centrally-acting analgesic, has multiple mechanisms of action: activation of opioid receptors and inhibition of presynaptic reuptake of serotonin and norepinephrine. It has been used in management of cancer-related pain and a wide variety of musculoskeletal pain syndromes. Doses greater than 400 mg/d as well as rapid withdrawal of this medication has been reported to cause seizures in some patients. Other adverse effects, including dizziness and nausea, are not uncommon and appear to be dose related.\textsuperscript{29,30}

**Topical analgesics**

Topical analgesics are peripherally acting agents, i.e., the site of activity is directly under the site of application in soft tissues. Because clinically significant serum drug levels are not produced, the potential for systemic side effects and drug interactions is minimized. This fact may be especially relevant in a patient having difficulty with oral medications or using multiple oral medications for other medical problems.

Applied topically as a gel or as a cream, NSAIDs have been widely studied as topical agents for sports injury pain, osteoarthritis, postoperative pain, and eye pain; these agents include diclofenac (patch/gel), ibuprofen (cream), ketoprofen (gel), piroxicam (gel), etenac (gel), and aspirin.\textsuperscript{31–33}

Two topical local anesthetic preparations are currently commercially available in the United States. One of these, the lidocaine patch, is a 5% topical lidocaine preparation. Controlled clinical trials demonstrating its efficacy in PHN led to the Food and Drug Administration’s approval for such treatment. Up to three patches are applied to the affected area 12 hours daily.\textsuperscript{34,35} This patch has been shown in an open-label study to be effective in management of other neuropathic painful conditions such as stump pain, complex regional pain syndrome type I (RSD), diabetic neuropathy, and human immunodeficiency virus neuropathy.\textsuperscript{36} There is now evidence that the 5% lidocaine patch may be useful in treatment of chronic myofascial pain.\textsuperscript{37,38} Another local anesthetic topical agent (2.5% lidocaine/2.5% prilocaine) has not been shown to be superior to placebo in PHN studies.\textsuperscript{39}

Capsaicin and clonidine have also been studied and/or used as topical agents. Capsaicin is available commercially as an OTC preparation, but, for all currently available preparations, the formal and practical results have been largely disappointing in my assessment.\textsuperscript{40} Currently, no commercial clonidine preparation is available.

**Opioid analgesics**

It is beyond the scope of this article to discuss in detail many other issues concerning long-term opioid use such as tol-
erance, physical dependence, and psychological dependence (addiction). However, development of tolerance and physical dependence in pharmacotherapy of many medical conditions is not unique to opioids. Furthermore, it should be noted that although there are in fact many addicts of various types in the United States, there is clear evidence that a nonaddict who is using an opioid for a medical condition is extremely unlikely to become an addict. Opioids are commonly used in the management of various acute and chronic pain states; they have been shown to be effective for a variety of cancer pain states as well as for noncancer-related pain states such as neuropathic pain.41

In fact, contrary to the belief that opioid analgesics are not useful in the management of neuropathic pain, several studies indicate otherwise. A double-blind, crossover, controlled trial comparing controlled-release oxycodone with placebo in patients with PHN demonstrated significant pain reduction in the treated group only.42 An open-label study of long-acting oral opioids and a placebo-controlled study of intravenous morphine use have each demonstrated that opioids can be effective in the management of neuropathic pain.43,44 There are few randomized controlled data to suggest the benefit of opioids in the long-term management of chronic musculoskeletal pain; however, noncontrolled studies and clinical experience have suggested that opioids may be very effective in reducing pain for patients with chronic musculoskeletal pain. Short-acting agents should be exclusively used on a short-term basis. Whenever possible, single (not combination) agents should be considered, especially for patients with chronic pain; for example, any toxicity associated with an opioid and acetaminophen or an NSAID is primarily related to the latter two agents—the acetaminophen or the ibuprofen. A more defined role of opioid use in management of chronic musculoskeletal pain may be available after further study; although commonly used successfully, they are often used as last-choice agents. This approach may not be entirely appropriate, but further studies are required to determine which patients with chronic musculoskeletal pain are most likely to benefit and how opioids agents should be best used.45,46

**Anticonvulsants**

Although commonly used as first-line agents in management of painful neuropathic states and chronic headache, there is currently no clear evidence that used alone, anticonvulsants are effective for management of chronic musculoskeletal pain. In contrast, many chronic musculoskeletal pain states are actually mixed-pain states with both neuropathic and nonneuropathic aspects. Therefore, further study is needed to assess responsiveness of certain types of musculoskeletal pain disorders such as fibromyalgia or neuropathic low back pain to these medications. Newer anticonvulsants such as gabapentin, lamotrigine, topiramate, zonisamide, and oxcarbazepine are often used in management of chronic pain; compared with older agents such as carbamazepine and valproic acid, they are easier to use owing to lack of organ toxicity and lesser need to monitor therapy with blood tests. At this time, they can be recommended when neuropathic pain is present or if the prescriber believes this type of medication is likely to benefit the patient.47-52

**Antidepressants**

Tricyclic antidepressants (TCAs) have proven efficacy for a number of different chronic pain states such as headache and neuropathic pain and are widely prescribed for such; however, it has been difficult to determine conclusively how effective TCAs are in chronic low back pain or other chronic musculoskeletal pain syndromes. Serotonin specific receptor inhibitors in general appear to be less effective as analgesics in neuropathic pain and headache syndromes compared with TCAs, but some reports suggest that these agents may be effective in management of various soft tissue pain problems.53-56 Recently, bupropion sustained-release has been shown to be effective in a randomized trial involving patients with neuropathic pain.57

**α-Adrenergic agents**

As described earlier, all medications effective in management of chronic pain have a common action to dampen or modify nociceptive information processed by the CNS at various levels. Certain such agents may also reduce muscle tone as well as pain perception; those associated with this effect include the α-adrenergic agonists tizanidine hydrochloride and clonidine.58-63 Whereas clonidine as an analgesic is used primarily through an epidural or intrathecal route, tizanidine is used as an oral agent and is associated with a much lower incidence of hypotension than clonidine. Since the 1980s, tizanidine has been shown to be effective in managing low back pain; its role in managing chronic headache and neuropathic pain have also been recently documented. Tizanidine appears to have a significant role in treatment of fibromyalgia and chronic myofascial pain, as several recent studies have suggested.59 A new and emerging role of tizanidine is as an aid in the withdrawal of other agents such as opioids. Although this withdrawal traditionally has been accomplished with clonidine, tizanidine appears to be potentially comparable in preventing withdrawal symptoms during analgesic reorganization but, at the same time, appears to be more effective as an analgesic during this process. Two recent studies have suggested this benefit, one in chronic headache62 and the other in patients undergoing detoxification63; its usefulness for management of spasticity has been documented.59

**Muscle relaxants**

Despite their classification as such, very little is known about how muscle relaxants actually produce their effects; they are a widely prescribed group of medications. As a rule, use of benzodiazepines is limited to short-term use because of the potential for tolerance, and physical and psychological dependence, as well as for other function-impairing adverse effects. Other commonly prescribed skeletal muscle relaxants include mexatone, methocarbamol, cyclobenzaprine hydrochloride, carisoprodol, orphenadrine citrate, and chlorzoxazone. Structurally similar to TCAs, cyclobenzaprine has a similar adverse effect profile, including sedation, seizures, anticholinergic actions, and cardiac effects. Carisoprodol is actually metabolized in part to...
meprobamate, a schedule IV substance approved for use as an anxiolytic agent in the United States but frequently abused during the 1970s. Meprobamate remains an often misused medication; thus, significant caution needs to be followed when prescribing carisoprodol. The mechanism of action of orphenadrine is similar to that of the antihistamine diphenhydramine; it is contraindicated in patients with glaucoma, bladder dysfunction, and peptic ulcer disease. Metaxalone and methocarbamol are agents with the least likelihood of causing sedation and may be part of an effective pharmacotherapeutic program.

Local anesthetics

The use of lidocaine hydrochloride and similar agents for pain reduction can result in significant analgesia for some patients. The use of lidocaine in topical preparations has already been described. For acute states, the use of intravenous lidocaine can be quite effective; however, its use in chronic pain is less clear. Although some patients with chronic pain report long-lasting benefit from intravenous lidocaine, this benefit is uncommon. Yet, even temporary responsiveness to intravenous lidocaine does predict success with other local anesthetic agents given orally, such as mexiletine hydrochloride. Several studies have documented the benefit of mexiletine in chronic pain; a dose of 450 mg/d appears to be optimal.

N-methyl-D-aspartate receptor antagonists

The use of NMDA receptor antagonists as analgesics is one of the most promising areas of current clinical pain research.

Chronic pain is associated with the development of increased sensitivity in the CNS to pain transmission (wind-up-like pain and central sensitization). Activation of NMDA receptors is believed to contribute to this effect as well as to the development of analgesic tolerance to opioids (and possibly other agents). Ketamine and dextromethorphan hydrochloride have been investigated as single agents or in combination with opioids; they have been used successfully to reduce neuropathic pain associated with allodynia and hyperalgesia. Dextromethorphan has been shown to reduce pain associated with diabetic neuropathy in several studies, but patients with PHN curiously did not report the same benefit. In a double-blind trial evaluating potential benefits of a product containing dextromethorphan plus morphine, patients with chronic pain who were using the combination required 50% less opioid to achieve satisfactory pain control than those receiving opioid alone. Oral, parenteral, and topical formulations of ketamine have been studied in chronic painful states with mixed results; intolerable side effects such as cognitive impairment and hallucinations were reported. When administered intravenously, amantadine hydrochloride, another NMDA receptor antagonist, has provided analgesia, but larger trials have yet to be completed. The racemate of methadone is known to act as an NMDA receptor antagonist, which may be clinically relevant. Several important clinical trials involving NMDA receptor antagonists are near completion.

Botulinum toxin

Two commercially available botulinum toxins are currently available in the United States, botulinum toxin type A and botulinum toxin type B. Recent data from a randomized controlled trial suggest that botulinum toxin type A may be helpful in managing chronic low back pain. Several studies suggest a potentially significant role of these agents in treatment of chronic myofascial pain disorders and chronic headache.

Comment

Pain affects millions of Americans and is associated with a variety of medical conditions. As the pathophysiology of acute and chronic pain has become better understood, numerous advances have been made in pharmacologic management of painful disorders. Healthcare providers must be aware of these available agents and how to use them rationally, either singly or in combination, so that patients with chronic pain can be treated as effectively as possible.

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