Alternatives and Adjuncts to Opioids for the Treatment of Chronic Pain

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The use of opioids to treat chronic noncancer pain is controversial because of concerns about safety, efficacy, and the potential for addiction and abuse. Clinicians must therefore continue to seek out alternatives to opioids, such as nonsteroidal anti-inflammatory drugs, acetaminophen, muscle relaxants, benzodiazepines, and antidepressants.

The use of opioid analgesia has long been the standard of care for treatment of moderate to severe acute pain and chronic cancer pain [1]. In recent years, however, opioid medications are also being more commonly used to treat chronic noncancer pain. Although this paradigm shift has afforded many patients more complete pain control, physicians must maintain some degree of reservation when prescribing long-term opioid therapy. Diversion and abuse of narcotic pain medications are ever-growing problems; thus careful patient selection and monitoring throughout the course of therapy are required. Patients who have been on opioid therapy for months to years will develop tolerance and a physical dependence on their medications even in the absence of addictive behaviors [1]. In addition, side effects such as nausea, constipation, pruritus (itching), sedation, and respiratory depression can limit the potential for effective therapy, especially at escalating doses.

These issues make the careful consideration of nonopioid medications increasingly important. Whether they are used in lieu of opioid management or as adjuncts to opioid therapy in order to reduce opioid-related side effects, nonopioid therapy plays an integral role in the treatment of chronic pain.

There are currently many different classes of nonopioid medications that can be used in the treatment of chronic pain, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, benzodiazepines, antispasmodics, calcium channel blockers, corticosteroids, alpha-2 agonists, local anesthetics, N-methyl d-aspartate (NMDA) receptor antagonists, and topical agents [1]. Professionals involved in treating unresolved pain have a responsibility to utilize these medications in the best possible manner, either alone or in conjunction with opioid therapy, to lessen pain and to improve function and quality of life for their patients.

Acetaminophen

Acetaminophen and NSAIDs are by far the most commonly used nonopioid analgesics, but they are often significantly underrated and are often unnecessarily omitted from the treatment regimen for patients with moderate to severe chronic pain [2]. Acetaminophen is a widely serviceable analgesic, since it is effective either alone or in combination with opioids. It is a nonsalicylate that may have analgesic and antipyretic effects similar to those of aspirin, but it does not have aspirin's antiplatelet effects or its peripheral anti-inflammatory effects, and acetaminophen does not compromise the gastric mucosa. In 2009, the US Food and Drug Administration (FDA) recommended that the maximum daily dose of acetaminophen be lowered from 4,000 mg per day to 3,250 mg per day. Although the FDA did not require this change, the manufacturer of Tylenol voluntarily lowered the maximum recommended dose of its 500-mg tablets to 6 doses per day (for a total of 3,000 mg) [3]. Acetaminophen is well tolerated at these levels, but an overdose can cause potentially fatal hepatic necrosis [4]. Also, use of acetaminophen must be monitored in alcoholic patients and in patients with underlying liver disease, as they can develop severe hepatotoxicity even at standard doses. The risk of gastrointestinal irritation is lower with acetaminophen than with NSAIDs, and acetaminophen is rarely associated with renal toxicity.

NSAIDs

Like acetaminophen, NSAIDs are useful for treating chronic pain resulting from trauma, arthritis, surgery, or cancer. There is a ceiling effect to the dose-response curve of NSAIDs, meaning that after a therapeutic ceiling is achieved, increasing the dose increases the side effects but produces no additional analgesia [2]. NSAIDs do not produce physical or psychological dependence and are also antipyretic. Their mechanism of action involves inhibiting the enzyme cyclo-

Electronically published June 18, 2013.

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N C Med J. 2013;74(3):209-214. ©2013 by the North Carolina Institute of Medicine and The Duke Endowment. All rights reserved.
0029-2559/2013/74305

Medical Marijuana for Chronic Pain

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In 1970, the Controlled Substances Act classified cannabis as a Schedule I drug; this category is reserved for drugs that are defined as having "a high potential for abuse," "no currently accepted medical use in treatment in the United States," and "a lack of accepted safety for use of the drug or other substance under medical supervision" [1]. Interest in the medicinal potential of cannabis has persisted, however, fueled by the isolation of the active compounds in marijuana, starting with tetrahydrocannabinol (THC) in 1964. This research continued in the 1990s with the discovery of the endocannabinoid system, a network of receptors that bind both compounds in marijuana and endogenous ligands produced by the human body. There are 2 types of cannabinoid receptors: CB1 receptors and CB2 receptors. CB1 receptors are present in areas of the brain that modulate pain, in the nociceptive pathways of the spinal cord, and on peripheral nerves; these receptors may help modulate pain signals in multiple areas. CB2 receptors are found primarily in the cells of the immune system and may help to down-regulate inflammation [2].

The prevalence of cannabinoid receptors in pain pathways suggests that marijuana or its components may have significant pharmaceutical potential for analgesia. There are currently 2 synthetic analogs of THC: dronabinol and nabilone, both of which have been approved by the US Food and Drug Administration for treatment of chemotherapy-induced nausea and vomiting and for AIDS-related anorexia and wasting. A third cannabinoid, nabiximols, is available in Canada for treatment of cancer pain and for treatment of neuropathic pain in multiple sclerosis. A recent systematic review and meta-analysis concluded that cannabinoids have moderate efficacy for the treatment of chronic pain but that side effects limit their use [3].

The term *medical marijuana* refers, not to the purified and regulated compounds described above, but to botanical cannabis, which contains at least 60 active compounds and is usually smoked. Eighteen states and the District of Columbia have now passed legislation permitting the use of marijuana for medical purposes [4]; North Carolina is not currently among these states. In October 2009, the US Department of Justice issued a directive stating that people who follow state laws that allow them to possess and use marijuana for medical purposes would not face federal prosecution. However, those who use, sell, and grow medical marijuana are still doing so in violation of federal law, and there continue to be federal raids on dispensaries and on marijuana growing operations in states that permit the use of marijuana for medical purposes. In the absence of federal oversight, the clinical conditions for which use of marijuana is permitted, the way in which permission for medical use is granted, and the amount of marijuana that a person may possess for medical use vary widely from state to state [5]. Chronic pain is an approved indication for use of medical marijuana in 15 states [4].

There are few studies of smoked marijuana because its Schedule I status means that strict limitations curtail research regarding its medical effects [1]. However, 5 randomized, placebo-controlled trials have evaluated the benefits of smoked marijuana for pain; the placebo in these studies was a marijuana cigarette that contained no cannabinoids (0% THC) [6-10]. One study of neuropathic pain [6] and 2 studies of HIV-associated sensory neuropathy [7, 8] found that use of marijuana led to significantly more individuals achieving a 30% reduction in pain. However, another study of neuropathic pain [9] showed a mean reduction of only 0.7 points on a 10-point pain scale in patients with refractory pain. Finally, a study of experimentally induced neuropathic pain [10] showed significant improvement in analgesia among individuals who smoked marijuana cigarettes containing 4% THC. Interestingly, there was no pain reduction when the marijuana in the cigarette contained only 2% THC, and there was an increase in pain when it contained 8% THC, suggesting that marijuana may have an optimal dosing window. These

oxygenase (COX), which results in inhibition of prostaglandin synthesis.

Currently there are 3 classes of NSAIDs: aspirin, which irreversibly inhibits COX; drugs that reversibly inhibit COX, such as ibuprofen and naproxen; and drugs that selectively and reversibly inhibit COX-2, such as celecoxib [1].

Although NSAIDs are generally safe and have great efficacy, practitioners must be careful in prescribing these drugs because of their common and potentially serious side effects. Elderly patients and individuals with certain medical comorbidities are particularly at risk of side effects. Gastrointestinal symptoms—including anorexia, dyspepsia, nausea, abdominal pain, and diarrhea—are the most common side effects related to these drugs [2]. The risk of mucosal injury and ulceration is thought to increase when NSAIDs are used in the presence of the bacteria *Helicobacter pylori*, with concomitant use of glucocorticoids, or in patients who consume significant amounts of alcohol. COX-2 inhibitors have been found to have a lower incidence of gastric ulcers compared with nonselective NSAIDs taken in equally effective doses [2]. Adding misoprostol or a proton pump inhibitor to the treatment regimen can be effective in preventing duodenal and gastric ulceration [5].

Traditional NSAIDs and COX-2 inhibitors are generally well tolerated but have been shown to have detrimental effects on renal function and blood pressure in patients with congestive heart failure, chronic renal insufficiency, hypovolemia, or hepatic cirrhosis [2]. Long-term use of high doses of NSAIDs in patients with concomitant recurrent urinary tract infections poses a risk of slowly progressive renal

studies are difficult to generalize to patients with chronic pain because of the short duration of these studies, the small numbers of subjects enrolled (between 15 and 50), the varying THC content of the plant material smoked, and the difficulty of blinding participants regarding which treatment they have been selected to receive [11].

Marijuana does not pose a risk of fatal overdose, and the public health burden of marijuana is estimated to be less than that of alcohol, tobacco, or other illicit substances [12]. However, use of marijuana has significant adverse effects. Acutely, marijuana increases the risk of motor vehicle accidents and can cause anxiety and panic; at high doses, it can even cause psychotic symptoms. Long-term users have a 9% risk of dependence and show signs of subtle cognitive impairment [13]. Adolescent users have decreased educational attainment and are more than twice as likely to develop schizophrenia. Finally, smoking marijuana has the advantage of delivering THC and other active components to the bloodstream much more efficiently than oral administration, but smoking carries with it an increased risk of chronic bronchitis, an increased risk of impaired respiratory function, and possibly an increased risk of lung cancer [12].

There are physiologic reasons to believe that marijuana may have analgesic properties, and trials of purified cannabinoids and of smoked marijuana furnish some preliminary support for this idea, particularly in the case of neuropathic pain. However, the current evidence is based on small trials whose results are difficult to generalize to widespread use of medical marijuana. We need more high-quality studies to determine whether the benefits of medical marijuana outweigh its risks. NCMJ

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Acknowledgment

Potential conflicts of interest. E.K. has no relevant conflicts of interest.

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Electronically published June 18, 2013.

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0029-2559/2013/74306

failure and decreased concentrating capacity at the renal tubule [2]. In comparison with other NSAIDs, COX-2 inhibitors have also been shown to increase the risk of myocardial infarction and stroke in patients who are at risk for thrombosis [6-10]. Topical application of NSAIDs results in lower systemic drug levels, however, and thus fewer side effects.

It should also be noted that hypersensitivity to NSAIDs is a known phenomenon that can result in angioedema, urticaria, exacerbation of asthma, laryngeal edema, and shock. Patients with hypersensitivity to aspirin should avoid all other NSAIDs, as cross-sensitivity can cause a life-threatening reaction [2].

Antidepressants

Tricyclic antidepressants (TCAs) have long been known to enhance analgesia when administered with opioids. Early studies of various opioids showed a reduction in the amount of drug used after cholecystectomy or cesarean section when the opioid was administered with intramuscular amitriptyline [11-15]. Today TCAs are more commonly used when neuropathic pain is suspected. Disease processes such as diabetic and nondiabetic peripheral neuropathy [16, 17], postherpetic neuralgia [18], and fibromyalgia [19, 20] have all shown significant pain reduction when treated with TCAs. The analgesic action of TCAs seems to be independent of the drugs' antidepressant properties, as analgesia has been established within 24 hours of use, whereas the antidepressant effects take more than 1 week to develop. The mechanism of action is thought to be related to blocking of serotonin reuptake, blocking of norepinephrine, and stabilizing of nerve membranes.

Different studies have examined the use of selective

serotonin reuptake inhibitors (SSRIs) for treatment of pain. Although SSRIs can produce some pain relief in conditions such as diabetic peripheral neuropathy, the degree of pain relief is believed to be considerably less than that produced by TCAs [21]. However, SSRIs have been found to have fewer side effects than TCAs [22, 23].

Serotonin-norepinephrine reuptake inhibitors (SNRIs) selectively block the reuptake of serotonin and norepinephrine. Duloxetine, an SNRI, is the first antidepressant to have been approved by the FDA with a specific indication for pain. The prescribing information for duloxetine [24] states that it is now indicated for the management of neuropathic pain (diabetic peripheral neuropathy) [25], fibromyalgia, and chronic musculoskeletal pain.

When prescribing antidepressants for the management of chronic pain, clinicians need to consider the potential side effects associated with these medications both when they are taken at normal doses and in the event of an overdose. TCAs are more likely to cause weight gain, cholinergic side effects, driving impairment, and falls than are SSRIs [21]. TCAs are also the class of antidepressants most commonly used in suicide attempts [26], which is an important consideration in this patient population.

Anticonvulsants

The main actions of anticonvulsants involve the modulation of voltage-gated calcium or sodium channels, antagonism of glutamate, enhancement of the gamma-aminobutyric acid (GABA) inhibitory system, or a combination of these effects [27]. These mechanisms, which are thought to reduce neuronal hyperexcitability, can be successful in treating pain when opioids have little efficacy, such as for cases of diabetic neuropathy and trigeminal neuralgia [27].

Gabapentin is probably the anticonvulsant most widely used for neuropathic pain in the United States. In 1998, a double-blind, placebo-controlled clinical trial showed gabapentin to be effective in the treatment of postherpetic neuralgia [28], and the drug is now approved by the FDA for this indication. In that same clinical trial, gabapentin was also found to have a synergistic relationship with morphine [28]. Unlike many of the older antiepileptic agents, gabapentin does not induce hepatic enzymes, and it is known for its lack of drug-drug interactions. The most common side effects are somnolence (drowsiness), dizziness, and fatigue; it can also cause weight gain. It is thought to be relatively safe even in the event of an overdose [27].

Pregabalin has a mechanism of action similar to that of gabapentin, and its properties are also very similar. Pregabalin has been shown to be effective in the treatment of postherpetic neuralgia, fibromyalgia, and generalized anxiety disorder [29-33].

Topiramate is yet another anticonvulsant with analgesic properties. It has multiple mechanisms of action and is a mild inducer of hepatic enzymes. Common side effects include paresthesias, drowsiness, fatigue, and cognitive complaints [27]. Kidney stones occurred in 1.5% of patients treated with topiramate in clinical trials [34], and mild weight loss is often noted (which may be a desirable side effect in overweight patients). Topiramate has received FDA approval for migraine prophylaxis. When topiramate was tested as a treatment for diabetic peripheral neuropathy, however, 3 placebo-controlled trials did not show significant analgesic effects [34].

Older anticonvulsants such as phenobarbital, phenytoin, valproic acid, and carbamazepine can be beneficial in the treatment of neuropathic pain but are now used less often because of side effects, drug-drug interactions, and the risk of toxicity. Newer agents continue to be introduced, and their utility in the treatment of neuropathic pain continues to be investigated.

Benzodiazepines

Benzodiazepines are most commonly prescribed for their antianxiety effects and for the emergent management of seizures and status epilepticus. However, evidence shows that benzodiazepines also have intrinsic analgesic properties. Benzodiazepines bind to the GABA-A receptor, which facilitates the actions of GABA in the central nervous system (CNS) [27]. An early study showed that alprazolam produced substantial analgesia in cancer patients who had malignancies and an associated causalgic pain syndrome [35]. Patients who received an oral narcotic and a benzodiazepine before undergoing a bone marrow biopsy had less pain than usual for this type of procedure [36]. Finally, clonazepam has been shown in small clinical trials to reduce chronic facial pain [37].

Patients who suffer from chronic pain may have concomitant anxiety and mood disorders, as well as some degree of sleep disturbance, so adding a benzodiazepine to their treatment regimen can be beneficial. These drugs also serve as clinically effective muscle relaxants, and there is evidence that they hasten recovery from acute back pain [38]. However, the side effects of drowsiness, ataxia, and tolerance can limit the utility of benzodiazepines for long-term use. Adding benzodiazepines to opioids can also potentiate respiratory depression, leading to serious consequences. The potential for misuse and addiction must also be considered during patient selection.

Skeletal Muscle Relaxants

Despite their common use, very little is known about the role of skeletal muscle relaxants in the treatment of chronic back pain. Although none of the regularly used muscle relaxants carries an indication for chronic back pain, at least 1 survey showed that they are commonly prescribed on a long-term basis for that indication [38]. In choosing a specific muscle relaxant, a prescriber must consider side effects, patient tolerability, and contraindications. For example, cli-

nicians often avoid carisoprodol because of its high potential for addiction; cyclobenzaprine is often avoided because its similarities to TCAs cause concern that it might produce arrhythmias, and it can potentiate seizures when administered with tramadol; and metaxalone is often selected over its counterparts because it is thought to be less sedating [38]. No current data show any of these agents to be more efficacious than the others [38]. Most muscle relaxants are CNS depressants, and this fact should be considered when prescribing these drugs for patients using alcohol, anxiolytics, opioids, or other sedatives.

Other Therapeutic Agents

Although it would be impossible to provide an exhaustive list of nonopioid analgesics in this commentary, there are several additional agents to consider.

Corticosteroids are very effective in their ability to reduce inflammation, edema, and neuronal excitability. They are often used to treat back pain, headaches, bone pain, and neuropathic pain [2]. However, serious side effects limit their long-term use.

Pentoxifylline increases blood flow and tissue oxygenation by decreasing blood viscosity and erythrocyte flexibility. It has been used to treat Peyronie's disease, neuropathic injury, and sickle cell disease [2].

The alpha-2 agonist clonidine has been widely used to improve postoperative analgesia. Due to its effects on the CNS when it is administered through transdermal, intrathecal, or oral routes, clonidine is also effective in the management of burn pain, cancer pain, and complex regional pain syndrome [2].

Topical local anesthetics, specifically lidocaine, have been effective in the treatment of postherpetic neuralgia and other neuropathic conditions. These agents have very minimal risk of systemic toxicity [2].

Finally, 2 NMDA receptor antagonists, dextromethorphan and ketamine, may have pain reduction and opioid-sparing effects [2].

Conclusion

Medication management continues to be the mainstay of chronic pain management. As the use of opioid medications becomes more widely accepted in the treatment of noncancer pain, it remains extremely important for clinicians to keep in mind the importance of nonopioid therapies. Not only can these medications synergistically reduce pain levels when administered in conjunction with opioids, but they also allow for opioid sparing, thus decreasing the overall side effect profile of opioid medications. Nonopioid medications can be utilized when opioids should be avoided—such as in cases of severe respiratory disease, ileus, or substance abuse—and in certain pain conditions nonopioid medications can be even more efficacious than their opioid counterparts. In order to best manage patients with chronic pain conditions, clinicians must understand not only the indications for these important alternatives to opioids but also their related side effects. NCMJ

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Acknowledgment

Potential conflicts of interest. P.J.L. has no relevant conflicts of interest.

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