

# Opioid Adjuvants for Multimodal Pain Management

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Chronic pain has become a significant diagnostic and therapeutic concern for many practitioners. With the cost of treatment estimated at more than \$100 billion in the United States alone,<sup>1</sup> along with attendant decreases in quality of life and productivity, physicians must be familiar with chronic pain as both major public health and economic issues. The origins of chronic pain are manifold, and include trauma, degenerative disorders, and other causes. Increasing evidence shows that uncontrolled pain after surgery is a significant risk factor for the development of chronic pain. Efforts to manage pain in the perioperative period therefore may be effective in reducing the burden of chronic pain, both for patients and as a public health problem.

**Table 1. Nonopioid Medications With Efficacy for Treating Perioperative Pain**

<b>Nonsteroidal Anti-inflammatory Drugs</b>		<i>SSRIs</i>	Citalopram
<i>Salicylates</i>	Aspirin		Fluoxetine
	Diflunisal		Fluvoxamine
	Salsalate		Paroxetine
<i>Propionic acid derivatives</i>	Fenoprofen		Sertraline
	Flurbiprofen	<i>Serotonin and norepinephrine reuptake inhibitors (SNRIs)</i>	Desvenlafaxine
	Ibuprofen		Duloxetine
	Ketoprofen		Venlafaxine
	Naproxen	<b>Anticonvulsants</b>	
	Oxaprozin		Carbamazepine
<i>Fenamates</i>	Diclofenac		Lamotrigine
	Ketorolac		Oxcarbazepine
	Meclofenamate		Phenytoin
	Mefenamic acid		Valproic acid
	Tolmetin		Topiramate
<i>Enolic acid derivatives (oxicams)</i>	Meloxicam	<i>α<sub>2</sub>δ-subunit calcium channel</i>	Baclofen
	Nabumetone		Pregabalin
	Piroxicam		Gabapentin
<i>Acetic acid derivatives</i>	Etodolac	<b>Muscle relaxants</b>	
	Indomethacin		Cyclobenzaprine
	Sulindac		Tizanidine
<i>COX-2 selective (coxibs)</i>	Celecoxib	<b>Topical agents</b>	
<b>Antidepressants</b>			Capsaicin
<i>TCAs</i>	Amitriptyline		Diclofenac
	Clomipramine		Lidocaine
	Desipramine	<b>Other analgesics</b>	
	Imipramine	<i>Para-aminophenol derivative</i>	Acetaminophen
	Maprotiline		
	Nortriptyline		
<i>MAOIs</i>	Selegiline		
	Tranylcypromine		

COX, cyclooxygenase; MAOI, monoamine oxidase inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin receptor inhibitor; TCA, tricyclic antidepressant

Treatment options for patients with chronic pain include pharmacologic, psychological, surgical, nerve blocks, and rehabilitative strategies. Among the pharmacologic approaches, the use of opioids for the treatment of noncancer pain is particularly controversial. The potential for adverse effects (AEs) of these drugs,

along with the risk for misuse and diversion and the well-publicized potential for opioid-related AEs, have prompted increased discussion of the utility of alternative analgesic and opioid-sparing medications.

This review focuses on so-called opioid adjuvant analgesics (Table 1). These medications traditionally are

defined as a diverse group of drugs originally developed for a primary indication other than pain but that nonetheless have analgesic properties.<sup>2</sup> Many of these medications are being used to enhance analgesia under specific circumstances. Broadening their application could ease or eliminate the concerning dependence on opioids as monotherapy for pain relief.

The major therapeutic principle underlying the use of opioid adjuvants is to achieve a balance between increasing analgesic efficacy while minimizing AEs. Adjuvant analgesics have been recommended when the toxic limit of a primary analgesic is reached or the therapeutic benefit of a primary analgesic has plateaued. These drugs also can be beneficial in the presence of disabling nonpainful complaints such as insomnia, depression, anxiety, and fatigue that may cause deterioration of the patient's quality of life and function.<sup>3</sup>

## Types of Opioid Adjuvants

### *NONSTEROIDAL ANTI-INFLAMMATORY DRUGS*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed and consumed medications in the world.<sup>4</sup> These drugs have analgesic, antipyretic, and anti-inflammatory activity through the inhibition of prostaglandin synthesis. Selective cyclooxygenase-2 (COX-2) inhibitors have the additional benefit of the reduction of the incidence of gastrointestinal (GI) side effects. The SUCCESS-I study compared the safety and efficacy of COX-2 inhibitors versus nonselective NSAIDs in 13,274 patients with osteoarthritis. Celecoxib (Celebrex, Pfizer) was found to be as effective as the nonselective NSAIDs as measured by patients' assessment of arthritis pain, as well as joint stiffness and function.<sup>5</sup> GI-related complications were significantly less common among patients taking celecoxib than among those receiving traditional NSAIDs. Cardiothromboembolic events were infrequent and comparable for the 2 arms of the study.<sup>5</sup>

A Cochrane review of 65 trials showed that nonselective NSAIDs were slightly effective for short-term symptomatic relief in the treatment of patients with acute and chronic low back pain without radicular symptoms and that patients treated with COX-2 agents, although not getting superior pain relief, reported fewer side effects.<sup>6</sup> Related to COX-2 agents is the drug meloxicam, an oxicam derivative thought to be relatively COX-2 preferential at low therapeutic doses.<sup>7</sup> A recent study demonstrated that NSAIDs reduce the morphine requirement in patient-controlled analgesia after major surgery with a concomitant reduction in morphine-related side effects such as postoperative nausea, vomiting, and sedation.<sup>8</sup> Both celecoxib and ibuprofen (an IV form of ibuprofen [Caldolor, Cumberland Pharmaceuticals] approved by the FDA in 2009) have been reported to diminish pain after ambulatory surgery, enhancing both the quality of recovery and patient satisfaction.<sup>9</sup> NSAIDs have been included in practice guidelines for acute pain management in the perioperative setting.<sup>10</sup>

### *NON-NSAID ANALGESICS*

The platelet-sparing properties of the non-NSAID acetaminophen, which has recently become available in an IV preparation in the United States (Ofirmev, Cadence Pharmaceuticals), and selective COX-2 inhibitors make them appropriate for most patients as part of multimodal analgesia in the perioperative setting.<sup>11</sup>

### *ANTIDEPRESSANTS*

Antidepressants have several mechanisms of action including inhibition of the reuptake of norepinephrine and serotonin, calcium channel blockade, sodium channel blockade, *N*-methyl-D-aspartate receptor antagonism, and activation of opioid receptors.<sup>12</sup> They have been widely used for the treatment of neuropathic pain, a group of disorders characterized by damage or dysfunction of the central or peripheral nervous systems. They have been classified based on their mode

## Case 1

A 52-year-old woman complained of severe pain on day 1 following a right radical mastectomy and lymph node dissection. She was receiving morphine by self-administration pump in escalating dosages but without relief, and began experiencing nausea and vomiting. She described her pain as aching, stabbing, and burning.

In response to her complaints, IV administration of 1,000 mg of IV acetaminophen (Ofirmev, Cadence Pharmaceuticals) and 400 mg of IV ibuprofen (Caldolor, Cumberland Pharmaceuticals) every 6 hours was initiated. The patient was treated with antiemetics and her morphine dose was decreased. When the patient's nausea abated, she was started on oral

gabapentin, at a dose of 100 mg twice daily.

By postoperative day 2, the patient's pain complaints had greatly diminished. Her morphine was discontinued and she was converted to 5 mg of oral oxycodone with 325 mg of acetaminophen orally every 4 hours as needed. She was converted to 100 mg of celecoxib (Celebrex, Pfizer) twice daily, and her gabapentin was maintained at 100 mg 3 times per day. She was discharged that afternoon.

In this case, opioid monotherapy not only produced inadequate analgesia for the patient but also resulted in unpleasant, poorly tolerated side effects. Instituting multimodal therapy with opioid adjuvant analgesics led to rapid, marked improvement.

## Case 2

A 57-year-old man is scheduled to undergo left knee replacement. His medical history is significant for hypertension and chronic obstructive pulmonary disease. He is a nonsmoker and drinks alcohol socially. The patient has had chronic pain in his left knee, for which he has been taking ibuprofen (800 mg twice daily) chronically. For periodic episodes of breakthrough pain, he has taken 5 mg oxycodone with 325 mg of acetaminophen once or twice a day. He requested that the use of opioids postoperatively be limited as much as possible.

On the day of his surgery he is given 400 mg celecoxib (Celebrex, Pfizer), along with 150 mg pregabalin (Lyrica, Pfizer), both orally, with a sip of water

before entering the operating room. The surgery is performed under spinal anesthesia augmented by a single shot femoral block with ropivacaine. Approximately 30 minutes before the end of surgery, the patient is given 1 g IV acetaminophen (Ofirmev, Cadence Pharmaceuticals).

Twelve hours after surgery, the patient receives another dose of celecoxib (200 mg) and 150 mg of pregabalin. He also receives 650 mg of acetaminophen orally for primary pain control every 6 hours. IV morphine is used sparingly to control moderate to severe breakthrough pain in the first 24 hours after surgery. The patient reports good pain control and minimal opioid-related side effects.

of action and include traditional tricyclic antidepressants (TCAs), reversible inhibitors of monoamine oxidase inhibitors type A, selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs).<sup>13</sup>

A 2007 Cochrane review assessed the effectiveness and safety of antidepressant drugs in the treatment of neuropathic pain.<sup>14</sup> Sixty-one trials of 20 antidepressants were considered eligible for inclusion. TCAs and SSRIs had a number needed to treat (NNT) of approximately 3. No study of SNRIs was included. Meta-analyses evaluating the effectiveness of TCAs and SSRIs in the treatment of fibromyalgia have shown that both types of medications improve a patient's sense of well-being, sleep pattern, fatigue, and pain.<sup>15</sup>

A 2009 study explored antidepressant dose- or concentration-response relationships in achieving optimal analgesia for the treatment of chronic pain and affirmed that TCAs produce analgesia in much lower doses than those required for an antidepressant effect.<sup>16</sup>

Failure to respond to treatment with these agents might indicate low drug concentrations owing to poor compliance or absorption. It has been suggested that monitoring drug concentrations might prove useful in cases of treatment failure, noncompliance, drug-drug interaction, and severe adverse reactions.<sup>16</sup>

### ANTICONVULSANTS

Anticonvulsants are another commonly used family of adjuvant analgesics. The basis for the effectiveness of anticonvulsants for the treatment of neuropathic pain appears to be related to a shared pathophysiology with epilepsy<sup>17</sup>; both conditions are characterized by neuronal hyperexcitability. The hyperexcitable state of neuropathic pain is marked by reduced thresholds (sensitization) and ectopic discharges at the spinal dorsal horn or dorsal root ganglion.<sup>18</sup>

Among the mechanisms of action of anticonvulsants are the modulation of voltage-gated sodium and calcium (specifically, the  $\alpha_2\delta$ -subunit) channels and

inhibition of  $\gamma$ -aminobutyric acid (GABA).<sup>19</sup> Anticonvulsants that have received FDA approval for neuropathic pain include carbamazepine for trigeminal neuralgia; gabapentin for postherpetic neuralgia (PHN); and pregabalin (Lyrica, Pfizer) for PHN, diabetic peripheral neuropathy, and fibromyalgia. Multiple studies have demonstrated their efficacy. Both gabapentin and pregabalin have few drug-drug interactions, and their route of renal excretion may offer an advantage for patients with hepatic compromise.<sup>20-23</sup> Pregabalin provides the potential benefits of relatively rapid titration, linear pharmacokinetics, and an early onset of analgesia.<sup>24</sup> Dose-dependent AEs include somnolence, dry mouth, dizziness, and edema. Gabapentin demonstrates nonlinear pharmacokinetics; its adverse reactions are similar to those of pregabalin.<sup>25</sup>

Carbamazepine has been demonstrated to be of potential value in the treatment of trigeminal neuralgia. Its analgesic properties derive from its ability to block voltage-dependent sodium channels, resulting in membrane stabilization and decreased discharges from ectopic nerves.<sup>26</sup> Common side effects of carbamazepine include dizziness, nausea, drowsiness, blurred vision, and ataxia. More serious reactions may include leukopenia, liver dysfunction, and hyponatremia.<sup>26</sup>

Oxcarbazepine is a ketoanalog of carbamazepine. It binds to sodium channels in their inactive state, increases potassium channel conductance, and modulates high-voltage-activated calcium channels.<sup>27</sup> Oxcarbazepine is used as a second-line agent in trigeminal neuralgia for patients who fail to respond to carbamazepine.<sup>28</sup> It also may be effective in the treatment of painful diabetic neuropathy.<sup>29</sup>

Phenytoin is one of the oldest adjuvant analgesics. It inhibits the presynaptic release of glutamate and blocks sodium channels.<sup>30</sup> The NNT of phenytoin for effectiveness in the treatment of painful diabetic neuropathy has been reported as 2.1 (95% confidence interval, 1.5-3.6).<sup>31</sup> Potential AEs include nystagmus, ataxia, slurred speech, decreased coordination, mental confusion, nausea,

vomiting, constipation, hepatic compromise, thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without suppression of bone marrow.<sup>32</sup>

Lamotrigine has shown some efficacy for trigeminal neuralgia that is resistant to carbamazepine.<sup>33</sup> The analgesic effect of lamotrigine appears to result from its blockade of tetrodotoxin-resistant sodium channels and from an inhibition of glutamate release from presynaptic neurons.<sup>34</sup> Lamotrigine has been studied in both animals and humans and may reduce pain associated with a variety of conditions including diabetic neuropathy, multiple sclerosis, spinal cord injury, central poststroke pain, polyneuropathy, complex regional pain syndrome, and trigeminal neuralgia.<sup>35</sup>

Other anticonvulsants include valproic acid, sodium valproate, and topiramate. Although several small-scale, randomized controlled trials have evaluated their efficacy in the treatment of neuropathic pain, the evidence regarding their routine clinical use as adjuvant analgesics has been equivocal.<sup>36</sup>

### MUSCLE RELAXANTS

Skeletal muscle relaxants encompasses several medications with multiple modes of action. Cyclobenzaprine is widely used for the treatment of musculoskeletal disorders. It also has been reported to be effective in the treatment of fibromyalgia.<sup>38</sup> Animal studies have suggested that cyclobenzaprine activates the locus ceruleus in the brain stem, increases release of norepinephrine in the ventral horn of the spinal cord, and inhibits  $\alpha$ -motor neurons.<sup>39</sup> The drug is structurally related to TCAs and has a similar AE profile. Concomitant use with tramadol may precipitate seizures, and caution should be used when prescribing cyclobenzaprine to patients with arrhythmias, congestive heart failure, hyperthyroidism, and during the acute recovery phase following a myocardial infarction.<sup>40</sup>

Tizanidine is a centrally acting skeletal muscle relaxant. An  $\alpha_2$ -receptor agonist, tizanidine inhibits the release of excitatory amino acids from spinal interneurons. It is chemically related to clonidine but has significantly less antihypertensive effect.<sup>41</sup> A 2008 review reported that tizanidine was helpful not only for patients with spasticity from spinal cord injury, traumatic brain injury, and multiple sclerosis but also for those with chronic low back and neck pain associated with myofascia.<sup>42</sup> Tizanidine should be used with caution in patients with impaired renal function, as clearance is decreased by 50% when creatinine clearance falls below 25 mL per minute.<sup>43</sup>

Baclofen is a GABA analog that acts on GABA<sub>B</sub> receptors, which are abundant throughout the central nervous system.<sup>44</sup> Baclofen reduces hyperreflexia, a feature of phasic spasticity, but typically is less beneficial in patients with supraspinal spasticity.<sup>45</sup> A 1994 study showed the drug to be more effective for muscle relaxation than diazepam.<sup>46</sup> It is FDA-approved to be given intrathecally in patients with severe spasticity

**Table 2. First-Tier Adjuvants for Neuropathic Pain**

Medication	Daily Dose Range	Major Side Effects
Duloxetine	30-120 mg	Nausea
Gabapentin	100-3,600 mg	Sedation, dizziness, peripheral edema
Pregabalin	150-600 mg	Sedation, dizziness, peripheral edema
Nortriptyline	25-150 mg	Sedation, dry mouth, blurred vision, weight gain, urinary retention
Venlafaxine	37.5-225 mg	Nausea
Lidocaine patch, 5%	1-3 patches daily for a maximum of 12 h	Local erythema, rash

Adapted from reference 55.

who cannot tolerate oral medications. Rapid withdrawal of baclofen may precipitate a life-threatening reaction and rebound phenomenon, and it therefore must be tapered slowly.

### TOPICAL AGENTS

Lidocaine 5% patch (Lidoderm, Endo Pharmaceuticals) is FDA-approved for the treatment of PHN. Lidocaine gel reduces ectopic activity in the voltage-gated sodium channels of damaged sensory nerves.<sup>47</sup> The patch also acts as a mechanical barrier that may relieve allodynia in some patients. Because of its delivery system, systemic side effects are rare. The most common adverse reaction is local skin irritation. Additional, unapproved uses include the treatment of painful diabetic peripheral polyneuropathy and low back pain.<sup>48</sup>

Capsaicin, which is derived from chili peppers, stimulates transient receptor potential vanilloid receptors and subsequently depletes substance P from sensory nerve fibers.<sup>49</sup> A meta-analysis of the effectiveness of capsaicin in patients with painful diabetic polyneuropathy demonstrated a benefit of the compound over placebo. Common side effects include local skin irritation and burning.<sup>50</sup> The FDA has approved a high-concentration 8% capsaicin patch (Qutenza, NeurogesX) for the treatment of PHN.<sup>51</sup>

Diclofenac is an NSAID that is available in a 1% gel (Voltaren, Endo Pharmaceuticals and Novartis) and a 1.3% patch (Flector, Pfizer). A recent study reviewed the safety and efficacy of diclofenac 1% gel in patients with knee osteoarthritis and found statistically significant improvement in several measures of pain and function.<sup>52</sup> The most common AE was mild local dermatitis.

Topically applied single or multiagent analgesics compounded by specialty pharmacies also are available. A 2002 email study that surveyed 120 clinicians revealed that 27% (n=32) reported using compounded topical agents as part of their practice. These clinicians perceived that 43% (34%) of treated patients responded favorably to the topical agents, with an average of 47% (33%) reporting pain relief and few AEs.<sup>53</sup> A recent case study showed that a combination topical cream consisting of isosorbide dinitrate 0.4%, capsaicin 0.075%, and lidocaine 3% was effective in decreasing pain in a diabetic patient with painful neuropathy unresponsive to oral pregabalin and topical capsaicin.<sup>54</sup>

## Conclusion

Adjuvant analgesics offer an alternative approach to the monomodal use of opioids for pain and have been noted to be especially useful in treating patients with neuropathic pain<sup>55</sup> (Table 2). They may serve as either primary or synergistic agents. As part of a multimodal approach to the treatment of pain, they offer many potential advantages. Clinicians who incorporate these drugs into their practice may help patients increase activity levels, decrease their dependence on opioid monomodal therapy, experience enhanced analgesia, and enjoy an increased quality of life.

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