

# Pain Management Part II: Pharmacologic Management of Chronic Orofacial Pain

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The pharmacologic management of chronic orofacial pain involves the use of medications not used routinely in dental practice. Additionally, many drugs are used for long periods of time necessitating careful monitoring for adverse effects and potential drug interactions. This article will review commonly used medications for chronic orofacial pain and highlight important areas of concern.

**Key Words:** Chronic pain; Orofacial pain; Pain management.

**C**hronic orofacial pain (COP) comprises a heterogeneous group of disorders that cause ongoing pain in the head and face region. Although there are many proposed taxonomies, one system divides these pains into musculoskeletal, neuropathic, and neurovascular pains. Psychogenic pains comprise yet another category, but true psychogenic pains, such as those associated with conversion disorder or schizophrenia, are so rare that their management will not be addressed in this article.

Musculoskeletal pains consist of temporomandibular joint disorders and masticatory muscular disorders but also include a variety of cervical conditions which refer pain to the head and face, such as cervical myofascial syndromes and cervical facet arthropathies. Neuropathic pains involve those with damage or alteration to peripheral or central pain pathways; the most well known of these is trigeminal neuralgia, but post-traumatic neuropathies are also quite common. Sympathetically mediated pains, such as complex regional pain syndrome, Type 1, are also known to occur in the face. Many nonodontogenic toothaches are, in fact, neuropathic pains—either atypical forms of trigeminal neuralgia or so-called deafferentation pains associated with alteration in pain transduction, transmission, or modulation. Common neurovascular pains include migraine, tension-type headache, cluster headache, and the numerous variants associated with each of these headaches. Because of the wide variety of conditions, many different medication classes are utilized. It

should be noted that there are many sources of chronic orofacial pains—for example, those that arise from ocular, salivary gland, nasal mucosal and intracranial lesions; even from lung cancer. Many of these conditions are not usually treated by the dentist, but the dentist treating orofacial pain must be familiar with the wide range of differential diagnoses for any given presentation.

## CHRONIC VERSUS ACUTE PAIN MANAGEMENT

The management of COP differs significantly from that of acute pain. Although all pain has both sensory-discriminative (nociceptive) and motivational-affective (psychological) components affecting overall perception, chronic pain frequently has significant effects on psychological health and, in turn, the patient's ability to cope with daily pain. Depression and anxiety are common and can profoundly affect pain perception; hence, the use of psychotropic medication is common. This article will review pharmacologic management of chronic pain, but the reader should not presume that medication management is the primary treatment modality. For many patients who suffer with chronic pain, psychological therapies are at least as, and sometimes more, important than sound pharmacologic and interventional measures.

Many different medication classes are commonly used as analgesics for chronic pains versus acute pain. These include antidepressants, particularly the tricyclic antidepressants (TCAs)<sup>1,2</sup> and the selective serotonin-norepinephrine reuptake inhibitors (SNRIs),<sup>3-5</sup>

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nonsteroidal anti-inflammatory agents (NSAIDs) when an inflammatory component is present, and the opioids. The latter 2 groups were discussed in the previous article, "Pain Management: Part I: Managing Acute and Postoperative Dental Pain."<sup>6</sup> Only relevant issues associated with the use of these medications in chronic pain versus acute pain will be highlighted in this article.

In addition to these agents, the anti-epileptic drugs (AEDs) are also very commonly used for neuropathic and neurovascular pains.<sup>7</sup> The muscle relaxants are not as useful in chronic as in acute musculoskeletal pain,<sup>8</sup> although the antispastics, a different group including baclofen and tizanidine, show utility in a number of disorders. The various primary headaches utilize a wide array of medications from many classes in addition to those above: beta blockers, calcium channel blockers, lithium, "triptans," ergots, and others.

In regard to dosing for COP, medications should be prescribed on a time contingent basis and, if appropriate, medications with longer dosing intervals are preferable. The need for patients to take medications frequently during the day, as well as on an as-needed basis, reinforces pain behaviors in some individuals. Compliance is a much more complicated issue in COP versus acute pain mentioned in the previous companion article.

## **NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

NSAIDs are most commonly used for musculoskeletal COP, such as temporomandibular joint disorders and myofascial syndromes. Part I of this series discussed NSAID pharmacology. As opposed to acute pain pharmacotherapy, when any medication is used on a long-term basis as for many chronic pain conditions, the risk of adverse effects increases and monitoring becomes more essential. Long-term NSAID use requires laboratory monitoring for GI bleeding, adverse renal effects, and possible hepatic effects. An initial complete blood count and chemistry to include at least blood urea nitrogen and creatinine blood levels are useful, but baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are helpful because frequently these patients are taking multiple hepatically metabolized agents. Depending on the patient's underlying medical conditions, follow-up laboratory studies at 1–3 months and regularly thereafter should be instituted. The patient can also be questioned as to dyspepsia, dark stool, or worsening of pre-existing asthma. Long-term medication use also increases the risk and consequences of adverse drug in-

teractions. These include loss of hypertension control with any antihypertensive, due in part to NSAID-induced decreased renal blood flow and increased renin release. Renal toxicity is of particular concern in patients taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and beta blockers because the combination of NSAIDs and these agents can cause loss of renal blood flow autoregulation. Patients with congestive heart failure who are using these medications are particularly at risk. Those taking sulfonyleurea oral hypoglycemic agents may have increased free plasma drug concentration, with resultant hypoglycemia, when NSAIDs, which are highly plasma protein bound, are used long term. Of course, warfarin (Coumadin) and traditional NSAIDs should not be prescribed concomitantly. Toxicity with methotrexate, as used for many autoimmune conditions, and lithium salts, as used for bipolar disorder or cluster headache, can occur when NSAIDs are prescribed with these agents. Interestingly, of all the drugs used for COP, NSAIDs are some of the most concerning when used for long periods of time.

## **OPIOIDS**

Opioids have been used for the management of pain for centuries, and the pharmacology of these agents was also discussed in Part I of this series. There is less controversy today over the use of opioids for chronic pain than in the past.<sup>9,10</sup> Nevertheless, there are reasons that long-term opioids are not appropriate for many patients with chronic pain, but that discussion is beyond the scope of this article. When used, long-acting and/or sustained-release formulations of agents, such as morphine (MS Contin, Oramorph SR, Avinza, Kadian), oxycodone (OxyContin), oxymorphone (Opana), methadone, and levorphanol are preferred. The latter 2 agents have N-methyl-D-aspartate (NMDA) blocking effects as well. Fentanyl transdermal patches are also available. Short-acting agents can be considered for breakthrough pain but only when clear indications exist. It can be challenging, however, for even the most experienced clinician to distinguish between tolerance and exacerbation of the existing pain condition. It must be remembered that the use of combination opioids (eg, hydrocodone or oxycodone with acetaminophen) can easily lead to acetaminophen toxicity in the chronic pain patient. If acetaminophen or NSAIDs are indicated, they can be added as separate agents to opioid-only medications in order to control nonopioid dosage. An important opioid issue in COP is that long-term analgesic use in migraine and tension-type headache leads to a condition termed "analgesic rebound headache," which is refractory to normal therapy until analgesics are discontinued.<sup>11</sup>

If long-term opioids are used for chronic pain, a pain contract identifying the responsibilities of patients and prescribers is highly recommended and required in some states. Continued prescribing should be tied to increased activity and productivity levels, as well as other documentation of efficacy. The support of a pain psychologist to further evaluate mental health and improvement in function is very desirable. Laboratory testing to identify diversion and use of illicit substances should be considered at regular, unscheduled intervals. Addiction is not thought to be a frequent concern in the chronic pain population but can occur.<sup>12</sup> As the definition of addiction implies continued use despite harm, and the chronic pain patient presumably derives a medical benefit from pain reduction, “addiction” may need to be defined differently for this patient population or another term used. Certainly, dependence and tolerance can and do develop, but many patients can maintain a stable opioid dose for long periods of time. Others require changing to different opioids periodically to maintain benefit. The most common and disturbing adverse effect is constipation, which is managed initially whenever long-term opioids are prescribed. Respiratory depression and orthostatic hypotension are rarely observed with careful titration. Nausea, when it occurs, can usually be managed with a change in opioid without having to rely on adjunctive agents. Opioids are remarkably safe from a physiological standpoint when titrated appropriately. Regardless, the use of long-term opioid therapy should be reserved for dentists with special training or experience. Dentists are strongly encouraged to follow state medical board (physician) requirements for chronic opioid therapy, as this is becoming a highly scrutinized and regulated area of practice. For most dentists, patients requiring long-term opioid therapy should be referred to qualified medical or dental practitioners. For patients who are currently prescribed opioids for chronic pain by another physician, dentists should consult with or at least notify the opioid prescriber regarding additional opioids that may be prescribed for postoperative pain.

## ANTIDEPRESSANTS

Antidepressants have been used for chronic pain for some time (despite lack of FDA approval until recently for some agents), and the link between depression and chronic pain is clear. It is known that descending pain modulation pathways release serotonin (5-hydroxytryptamine or 5-HT) and norepinephrine (NE) to suppress pain transmission. The depressed patient has a dysfunctional 5-HT or NE system, which likely implies

a dysfunctional 5-HT or NE pain modulation pathway. This may explain comorbid pain symptoms in patients with depression. Likewise, patients with chronic pain are more prone to depression due to the burden that daily, continuous pain can inflict. It is usually impossible and unnecessary to separate these components. What is clear is that not all antidepressants have analgesic characteristics and that the analgesic effect is independent of the antidepressant effect.<sup>1,13</sup> Particularly for TCAs, the dose for analgesia is well below therapeutic doses for depression, and the time to analgesic effect is much sooner than for antidepressant activity. It also appears that NE reuptake blockade, not just 5-HT reuptake blockade, is particularly important; hence, TCAs and SNRIs are the most widely used antidepressants for pain control. When TCAs are used, secondary amines (nortriptyline, desipramine) are frequently preferred due to fewer adverse effects such as sedation, dry mouth, and orthostatic hypotension. However, when sleep is poor and nocturnal bruxism is present, a tertiary amine (amitriptyline, imipramine) can be used at bedtime. TCAs are useful for most COP, including musculoskeletal pains, neuropathic pains, migraine, and tension-type headache. The newer SNRIs, venlafaxine (Effexor), duloxetine (Cymbalta), and desvenlafaxine (Pristiq), are used increasingly for chronic pain, and particularly neuropathic pain. Cymbalta and Pristiq are FDA-approved for certain neuropathic conditions. The selective serotonin reuptake inhibitors (SSRIs) such as paroxetine (Paxil) and fluoxetine (Prozac), while as effective as other antidepressants for depression, do not possess analgesic properties.<sup>14</sup> They certainly may be useful for treating depression in the COP patient and hence improve coping and daily function, but actual pain levels may not decrease. The monoamine oxidase inhibitors (MAOIs) are no longer used for pain except possibly for refractory migraine. The other miscellaneous antidepressants are less useful, although trazodone can be used as a non-dependence-producing sleep adjunct, and bupropion has less adverse sexual effects than other antidepressants and has some support for neuropathic pain.<sup>15</sup> An important issue for dentistry is that SSRIs and probably SNRIs can initiate bruxism in some patients. The use of antidepressants for pain is complex, and the limitations of this article do not allow an in-depth review of indications, adverse effects, drug interactions, and other considerations in prescribing these agents.

## ANTI-EPILEPTIC DRUGS

The use of AEDs is common in pain practice, particularly for neuropathic pain and the primary headaches. These agents are thought to limit neuronal excitation

and enhance inhibition. Various sites of action include voltage-gated ion channels (ie, sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate including N-methyl-D-aspartate receptors, and the inhibitory receptors for GABA and glycine. Carbamazepine (Tegretol) was classically the first line agent for typical trigeminal neuralgia (tic douloureux). Phenytoin has also been used but with less success. These drugs, however, have many adverse effects and can induce serious blood dyscrasias requiring careful and regular laboratory monitoring. Divalproex sodium (Depakote) is frequently used for headache and neuropathic pain and is currently FDA-approved for migraine prophylaxis. Lamotrigine (Lamictal) is useful for neuropathic pain but life-threatening rash (epidermal necrolysis) makes this a second or third line agent. The introduction of gabapentin (Neurontin) to the USA in 1994 led to a resurgence in the use of AEDs for pain management. Although developed to mimic GABA, the agent has no effect on GABA receptors but instead inhibits CNS voltage dependent calcium channels and likely those involved in pain transmission. Later evidence suggested a role in increasing GABA synthesis, so the exact mechanism of action is unclear. What is clear is that the medication was useful for a wide range of pain conditions with minimal adverse effects except for sedation and rare fluid retention.<sup>16,17</sup> The agent is renally excreted unchanged and not significantly plasma protein bound, making it very prescriber friendly. Newer AEDs were subsequently developed and have proven useful for chronic pain. These include tiagabine (Gabitril), topiramate (Topamax), and pregabalin (Lyrica), which all have GABA-ergic and for some, other pharmacodynamic effects such as inhibition of calcium channels. Many of these agents are also used off-label by psychiatrists for anxiety and bipolar disorders. Lyrica is the only drug FDA-approved for fibromyalgia. The mechanism of levetiracetam (Keppra), another newer agent, is not known. Common to these newer agents is the lack of serious adverse effects such as was seen with the older generation AEDs. Yet another recently introduced drug, oxcarbazepine (Trileptal) functions similarly to carbamazepine as a sodium channel blocker but without the significant incidence of serious blood dyscrasias. It does, however, have a relatively high incidence of hyperammonemia and syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) which can also arise with other AEDs with varying occurrence rates. As with the antidepressants, the limitations of this article do not allow an in-depth review of indications, adverse effects, drug interactions, and other considerations in prescribing these agents.

#### Muscle Relaxants

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- Carisoprodol (Soma)
  - Chlorzoxazone (Parafon Forte)
  - Cyclobenzaprine (Flexeril)
  - Metaxalone (Skelaxin)
  - Methocarbamol (Robaxin)
  - Orphenadrine (Norflex)
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### MUSCLE RELAXANTS/ANTISPASTICS

As mentioned above, the CNS-acting muscle relaxants (see Table) are generally not very useful for chronic muscular conditions and all are quite sedating. Importantly, cyclobenzaprine (Flexeril) is structurally related to the TCA amitriptyline, has similar effects, and can be useful for some pains and nocturnal bruxism. Additionally, carisoprodol (Soma), a derivative of meprobamate, has anxiolytic properties and the potential for dependence. The antispastic agents baclofen (Lioresal) and tizanidine (Zanaflex) are interesting medications, however. Baclofen, a GABA<sub>B</sub> agonist, is useful for some muscular complaints but is also effective for trigeminal neuralgia.<sup>18</sup> Tizanidine, an alpha-2 agonist, has good muscle relaxing properties and like all alpha-2 agonists has sedative and analgesic properties as well.

### HEADACHE

The treatment of the primary headaches—migraine, tension-type headache, cluster headache, and their variants—is too complex a topic for this review. What can be said is that pharmacologic therapy is divided into symptomatic treatments (opioid and nonopioid analgesics and antiemetics where indicated), abortive treatments for migraine and cluster headaches (“triptans,” ergots, oxygen, steroids), and preventive agents (antidepressants, AEDs, beta blockers, lithium, verapamil). The decision to proceed from symptomatic/abortive therapy to preventive therapy is generally based on the number of disability days per month due to headache. Although this varies among practitioners, approximately 6 disability days or more per month usually leads to consideration of preventive therapy.

### CONCLUSION

There are many more medications that can be discussed, including topical agents, but those drugs addressed above are the most commonly used. Important to the anesthesia provider or the dental surgeon is to distinguish why a patient may be using

these medications, as many are used “off-label,” such as the AEDs for psychiatric purposes or for pain management. Patients with chronic pain can be a challenge for the general dentist as well as the dentist with sedation or general anesthesia training. These patients, in general, have dysmodulated pain control systems. They are frequently very somatically focused, so seemingly small, altered sensations can be magnified. We must understand that these perceptions are as real to them as they seem unlikely to us as dentists. Added to this, patients with chronic pain are frequently, and understandably, distressed and also depressed. Those with COP are all the more challenging since the surgical interventions we provide, or for which we provide anesthesia, are in the area of pain reference. With compassionate care, however, these people frequently become our greatest ambassadors.

Pain is a part of the human experience and has benefits as well as liabilities. In chronic pain, the liabilities usually outweigh the benefits. It is hoped that as advances in pain pathophysiology and pharmacology are made, newer agents will be developed to reduce the human suffering that chronic pain inflicts on individuals, families, and society.

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**CONTINUING EDUCATION QUESTIONS**

1. Blood dyscrasias are possible side effects of which anti-epileptic drug?
  - A. Carbamazepine (Tegretol)
  - B. Gabapentin (Neurontin)
  - C. Levetiracetam (Keppra)
  - D. Pregabalin (Lyrica)
2. The risk for renal toxicity is enhanced when prolonged use of NSAIDs is combined with which of the following antihypertensive drug classes?
  - A. Diuretics
  - B. Alpha-2 agonists
  - C. ACE inhibitors
  - D. Calcium channel blockers
3. Which of the following side effects is most common when opioids are prescribed continuously for chronic pain?
  - A. Respiratory depression
  - B. Nausea
  - C. Orthostatic hypotension
  - D. Constipation
4. Which CNS neurotransmitter is thought to be most critical in mediating the analgesic effect of antidepressants?
  - A. Dopamine
  - B. Glutamate
  - C. GABA
  - D. Norepinephrine