



# Top 60 Medications Used for Orofacial Pain Treatment

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**ABSTRACT** This article introduces the 60 top pharmacologic treatments provided for chronic orofacial pain patients. It explains that the majority of “chronic” orofacial pain patients will not find a “cure” to their pain with medications but may find a way to manage their pain. The medications in this article are the most commonly utilized “pain” medications and where it exists. This article reviews some of the current evidence supporting their use on chronic orofacial pain disorders.

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**W**hat is chronic orofacial pain and pharmacologic treatment success? There are a multitude of review articles that describe what defines an orofacial pain diseases.<sup>1-8</sup> The purpose of this article is not to restate or clarify which disorders are in this group but instead introduce and briefly review the 60 top pharmacologic treatments provided for chronic orofacial pain patients. Before reviewing the relative efficacy and evidentiary basis of these 60 medications, it is appropriate to explain that the majority of chronic orofacial pain patients will not find a “cure” to their pain with medications. However, chronic pain patients can, with medications added to physical and behavioral treatment methods, find a way to manage their pain.

Some patients ask the question, “How

long will I have to take these medications?” Of course, if they were being treated for diabetes or hypertension this question would be not be logical because these two diseases, like chronic pain, are not usually cured, but are instead are managed with medications. A 2005 study examined what defines treatment success from the patient’s perspective.<sup>9</sup> Specifically, this study asked chronic pain patients (n=110) what they would consider a success on four dimensions (pain, fatigue, emotional distress, interference with daily activities). They described that the mean level of pain, fatigue, emotional distress, interference with daily activities was moderately high at their first visit to the clinic, and these patients reported they would consider their treatment “successful” if their pain scores were reduced between one-half to two-thirds.

The problem is that while patients and doctors expect and hope for this level of change, the actual long-term results for treatment of chronic orofacial pain is more modest in a large percentage of patients. The general rule with chronic pain is that the longer they have the pain, the lower the reduction in pain achieved with treatment.

Two studies actually provide follow-up data on the long-term treatment results from patients seen in a chronic Orofacial pain center. The first study reported on 109 consecutive patients seen in a chronic orofacial pain clinic.<sup>10</sup> This group of patients had between four to nine years of time from their first visit to the follow-up and of the 109, 85 percent responded to the questionnaire.

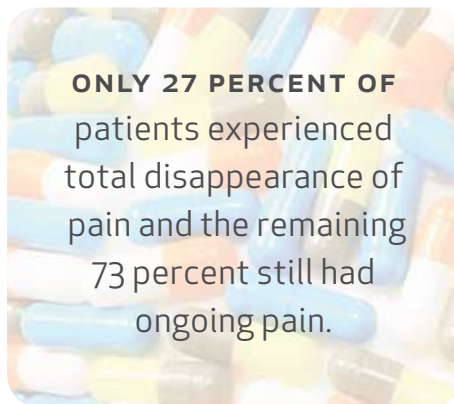
The bad news was only 27 percent of patients experienced total disappearance of pain and the remaining 73 percent still had ongoing pain. The second study examined the outcome of a cohort of 74 patients suffering chronic idiopathic facial pain who were first seen at a chronic pain center a minimum of nine to 19 years prior.<sup>11</sup> Of the 74 cases eligible for follow-up, 13 had died; 16 did not wish to participate; but the 45 remaining cases reported the following outcome: Ten out of 45 (22 percent) were free of orofacial pain at follow-up, and similar to the prior study, the remaining 78 percent reported ongoing pain.

Based on these two studies, it may be speculated that a full cessation or cure of chronic orofacial pain with treatment is between 22 and 25 percent. It almost goes without saying that the relative mix of diseases in the orofacial pain clinic population, the method of treatments and medications used, and, most importantly, the ability of the clinicians to explain and render care would greatly influence these long-term results and

two studies are not enough for a definitive prediction of success. Nevertheless, the message taken from these two studies is that most chronic orofacial pain patients are managed not cured.

### What Are the Top 60 Medications Used to Manage Chronic Orofacial Pain?

The 60 medications mentioned in this article were the most commonly utilized “pain” medications based on a review of 1,049 consecutive patient cases at the Uni-



versity of Southern California’s Orofacial Pain and Oral Medicine Center<sup>12</sup> (TABLE 1). Of course, the actual number of medications being used by the previously mentioned patients produces a list longer than 60 drugs, but to make the article manageable, the author arbitrarily stopped at this number. The author then searched Medline cross-referencing the name of the drug with the words (1) pain; (2) facial pain; and (3) orofacial pain (TABLE 1).

TABLE 1 shows that there were many studies linking these drugs to the pain literature, but there are relatively few literature citations where these medications have been linked with orofacial pain disorders. Another example of this point is a study published in 1999 that examined the literature available for treatment

of temporomandibular disorders.<sup>13</sup> This meta-analysis examined the literature from 1980 to 1992 and found more than 4,000 references but among these only 15 percent were clinical studies and only approximately 1 percent (N=55) were randomized controlled trials, which provided the type of evidence usually considered essential for evaluating the efficacy of a therapeutic modality. Based on this, the authors concluded it was not clear whether any of the therapies currently in use for temporomandibular disorders provided any benefit over placebo alone.

### What has the Recent Literature Said About Pharmacologic Treatment of Chronic OFP?

The issue of what medications are useful for TMD/OFP and various other orofacial pain disorders has been addressed in a two review articles. The first was a 1997 paper that focused on pharmacologic therapy for temporomandibular disorders.<sup>14</sup> This article reviewed NSAIDs, opioids, antidepressants, muscle relaxants, hypnotics, and anxiolytics. Regarding NSAIDs, they found little data on their use long term and quite a few reports on the potential side effects of these medications used in this fashion. The authors suggested that a short trial of an NSAID may be considered in patients with an apparent inflammatory component to their pain complaint but after two weeks, if great benefit is not achieved, they should be discontinued.

Regarding the use of opioids for pain, this review suggested that further studies are needed but this class of drugs has potential for those patients with chronic severe orofacial pain. Of course, careful patient selection to rule out drug-seeking behavior or other personality disorders; careful monitoring to individualize dose, thereby minimizing side effects and

dose escalation; and careful attention to regulatory procedures. Regarding the use of antidepressants for chronic nonmalignant orofacial pain the review concluded that tricyclic antidepressants (e.g., amitriptyline or doxepin) were potentially effective used in the lower dose range. The dose of antidepressants will usually be limited by anti-cholinergic side effects (dry mouth, constipation, blurred vision, and urinary retention) and should be adjusted in response to individual variation in analgesic response and side effects.

Regarding the use of benzodiazepines, the review was neither supportive nor opposed to their value in chronic OFP. It also suggested they should not be prescribed in large amounts and careful monitoring for dose escalation and undue dependency on these medications was warranted. This review also suggested they not be used in a patient with depression, and when used, they should be given only for a two- to four-week course, and predominately in muscle pain and trismus cases. Regarding more traditional skeletal muscle relaxants for orofacial pain-based myogenous pain and trismus, the review concluded that these medications, like the benzodiazepines, are used best only for a brief time period (e.g., two weeks) and in conjunction with physical therapy regimens.

In 2003, another systematic review of the literature was published that again assessed the pain-relieving effect and safety of pharmacologic interventions in the treatment of chronic temporomandibular disorders, including rheumatoid arthritis, atypical facial pain, and burning mouth syndrome.<sup>15</sup> The study reported on randomized clinical trials on adult patients with the previously mentioned diseases. They found a total of 11 studies with a total of 368 patients who met the inclusion criteria. They concluded

that amitriptyline was effective in one study and benzodiazepine in two studies. The authors described one study that showed that intra-articular injection with glucocorticoid relieved the pain of rheumatoid arthritis of the TMJ, and another showed the combination of paracetamol, codeine, and doxylamine was effective in reducing chronic TMD pain.

Finally, this review found no effective pharmacologic treatment for burning mouth syndrome and interest-



ingly only minor adverse effects were reported in these studies. The conclusions drawn from these two review articles are that there is limited data supporting a strong therapeutic benefit for most chronic orofacial pain medications. It also is critical to assess the balance between therapeutic benefit and safety for each drug for each patient.

### Why Should We Be Cautious About the Current Literature?

As mentioned, there is a great paucity of studies on medications used specifically for orofacial pain management. Among those that exist, many are methodologically flawed and the population of patients with OFP studied was very heterogeneous. Patients with myogenous pain,

for example, are often not distinguished in clinical trials from those who have TMJ disorders such as degenerative arthritis or displacement of the meniscus.<sup>16,17</sup> Observations by clinicians and case series often fail to use standardized methods for measurement of pain and dysfunction. The main evidence of a positive treatment outcome is too often the clinician's impression of improvement or the patients' failure to seek further treatment.<sup>18,19</sup>

Another major weakness in previous studies has been the lack of an adequate control group receiving either a placebo, a drug with known efficacy as a positive control, or no treatment. These deficiencies in study design are particularly significant given the high rate of success reported for manipulations such as placebo splints, placebo drugs, sham occlusal equilibration, a positive doctor-patient relationship, and enthusiastically presented treatment.<sup>20-22</sup>

An important factor that may affect the evaluation of treatment outcome to drug therapy is the fluctuating nature of orofacial pain, which may undergo remissions and exacerbations independent of treatment. The high incidence of concurrent psychological problems described in this population may also influence the onset of symptoms, reporting of pain levels, and treatment response.<sup>23-25</sup>

For some disorders, especially those that are not neuropathic in character, many patients eventually improve even if an initial course of therapy is not successful or if they receive no treatment at all.<sup>26</sup> The pharmacologic management of OFP rests on the same principles that apply to all other drugs: demonstrated efficacy for the indication (chronic orofacial pain), an acceptable side effect liability, and safety when given for prolonged periods.

If one stopped reading at this point one might conclude that few medications

TABLE 3

Time Delimited Medline Search (1997/01/01 to 2007/12/31: 10 years)

#	Drug Name	Classification	Orofacial Pain	Facial Pain	Pain
1.	Morphine	Strong opioid	31	31	6228
2.	Oxycodone	Strong opioid	1	1	430
3.	Methadone	Strong opioid	2	2	466
4.	Codeine	Medium opioid	16	17	712
5.	Hydrocodone	Medium opioid	6	7	116
6.	Tramadol	Analgesic	9	11	757
7.	Acetaminophen	Analgesic	40	40	1466
8.	Aspirin	Analgesic	17	20	1556
9.	Ibuprofen	NSAID	40	40	720
10.	Naproxen	NSAID	9	8	338
11.	Nabumetone	NSAID	1	1	27
12.	Piroxicam	NSAID	2	2	215
13.	Sodium Diclofenac	NSAID	4	5	1003
14.	Celecoxib	NSAID	14	12	458
15.	Meloxicam	NSAID	1	3	153
16.	Methylprednisolone	Steroid	14	19	1024
17.	Triamcinolone	Steroid	4	4	222
18.	Fluocinonide	Steroid	0	0	5
19.	Lidocaine	Sodium channel blocker	41	41	2595
20.	Benzocaine	Sodium channel blocker	9	9	64
21.	Carbamazepine	Strong anti-convulsant	22	31	345
22.	Oxcarbazepine	Strong anti-convulsant	0	1	55
23.	Lamotrigine	Strong anti-convulsant	4	6	172
24.	Levetiracetam	Strong anti-convulsant	0	0	33
25.	Zonisamide	Strong anti-convulsant	0	0	31
26.	Gabapentin	Mild anti-convulsant	9	10	802
27.	Pregabalin	Mild anti-convulsant	0	0	141
28.	Valproate	Migraine preventive [anti-convulsant]	1	1	130
29.	Topiramate	Migraine preventive [anti-convulsant]	2	3	115
30.	Tizanidine	Alpha adrenergic blocker	2	4	54
31.	Sumatriptan	Migraine abortive [triptan]	4	6	429
32.	Eletriptan	Migraine abortive [triptan]	0	0	74
33.	Frovatriptan	Migraine abortive [triptan]	0	0	19
34.	Rizatriptan	Migraine abortive [triptan]	0	0	128
35.	Butalbital	Barbiturate	0	0	19
36.	Dihydroergotamine	Ergotamine	1	2	61
37.	Timolol	Beta adrenergic agonist	0	0	15
38.	Propranolol	Beta adrenergic agonist	2	2	74
39.	Verapamil	Calcium channel blocker	2	2	208

TABLE 3 CONTINUED

## Time Delimited Medline Search (1997/01/01 to 2007/12/31: 10 years)

40.	Amitriptyline	Tricyclic antidepressant	18	20	411
41.	Nortriptyline	Tricyclic antidepressant	3	3	64
42.	Venlafaxine	SNRI	2	2	130
43.	Duloxetine	SNRI	1	1	134
44.	Escitalopram	SSRI	0	0	47
45.	Citalopram	SSRI	0	0	57
46.	Fluoxetine	SSRI	1	1	139
47.	Metaxalone	Anti-spasmodic	0	0	4
48.	Methocarbamol	Anti-spasmodic	0	0	5
49.	Carisoprodol	Anti-spasmodic [other]	0	0	11
50.	Cyclobenzaprine	Anti-spasmodic [tricyclic]	0	0	26
51.	Botulinum Toxin	Anti-spasmodic [neurolytic]	23	24	685
52.	Baclofen	GABA-agonist	5	7	278
53.	Tiagabine	GABA reuptake inhibitor	1	1	26
54.	Diazepam	Benzodiazepine	3	3	224
55.	Clonazepam	Anti-spasmodic /Benzodiazepine	4	4	54
56.	Alprazolam	Benzodiazepine	0	0	24
57.	Indomethacin	NSAID	25	26	1012
58.	Ketamine	NMDA blocker	4	6	882
59.	Anti-virals (e.g., acyclovir)	Anti-viral: other	5	6	266
60.	Antibiotics (e.g., azithromycin)	Macrolide antibiotic	0	1	62

are proven and even fewer should be used for chronic orofacial pain. However, this is not the case and a quick visit to chronic pain centers shows that they use multiple medications. These medications are usually given in a series of titration trials to see if the patient achieves substantial benefit. Because of this, this article provides a partial description of the characteristics and possible use of the top 60 pain-related medications, and reviews some of the current evidence supporting their use for the chronic orofacial pain disorders.

#### Drugs No. 1-5: Opioids (Morphine, Oxycodone, Codeine, Hydrocodone, and Methadone)

The first and most important category of medications for chronic pain relief are the natural and synthetic derivatives of the opium plant, labeled opioids. These

medications provide pain relief because they bind to opiate receptors in the CNS thus altering pain perception. Unfortunately, the opiate receptors produce other effects leading to physical and emotional dependency on this drug with prolonged use. Among the five opioids listed previously, the most commonly used in an outpatient orofacial pain clinic are hydrocodone and codeine drugs.

In the United States, hydrocodone, and codeine mandatorily come in combination with another nonopioid analgesics when prescribed. The most common combination is with acetaminophen, aspirin, or ibuprofen. The stronger opioids (morphine, oxycodone and methadone) are prescribed as a stand-alone analgesic agents although oxycodone also can be prescribed combined with nonopioid analgesics.

There are certainly some patients who attend an orofacial pain center who are candidates for morphine, oxycodone, or methadone, especially those patients with neuropathic pain that cannot be controlled with nonopioid analgesics, anti-convulsants, and other adjunctive pain analgesics. While opioids are powerful and have a proven efficacy at reducing pain, the long-term consequence of opioids for nonmalignant pain is controversial.

One recent study examined the long-term effects of opioids on pain relief, quality of life, and functional capacity in long-term/chronic noncancer pain, and reported that while pain is certainly managed with these agents, these patients are not cured and still have substantial problems plus the additional problem that using a drug that produces a powerful physical dependency causes.<sup>27</sup> For

TABLE 3

**Suggested List of Steps for Opioid-based Management of Chronic Nonmalignant Orofacial Pain**

1. Document the presence of pain	Document the location, quality, intensity (patient’s self-report using rating scale; e.g., 0-10, or mild, moderate, severe) and temporal characteristics of the pain. The patient’s self-report is the single most reliable indicator of pain.
2. Modifying factors	In addition to severity, assess the pain’s effect on the patient including documenting what makes the pain better or worse (e.g., how the pain affects sleep, eating, movement, mood, and quality of life) response to prior and present analgesic medications and nonpharmacologic interventions.
3. Physical examination	Perform a complete physical exam of the head and neck region and make sure they have also had a recent physical examination by their physician.
4. Look for the etiology	If possible, determine the cause and type of the pain and institute diagnosis specific therapy if one is available.
5. Patient-doctor agreement	Discuss and establish realistic goals and limitations of pain medication therapy (e.g., quality of life improvement) with the patient appropriate for their specific pain diagnosis.
6. Pain severity dictates drug choice	Base the initial analgesic choice on the severity and type of pain. Use nonopioids for mild pain (rating 1-3/10); use opioids, often in combination with a nonopioid; for moderate (rating 4-6/10) to severe (rating 7-10/10) pain and neuropathic pain may require an antidepressant or anti-convulsant drug.
7. Establish nonopioid drug dose limit	Dose to therapeutic ceiling of nonopioid if side effects permit. There is no maximum dose or analgesic ceiling with opioids. Increase initial opioid dose until pain relief is achieved or side effects are unmanageable before changing medications. This will require several follow-up medication review visits.
8. Administer drugs P.O. (by mouth)	Avoid IM injections and IV infusions, and, if needed, they would only be administered in a hospital setting for in-patients.
9. Switch to long-acting opioids	Once an initial acceptable pain relief level is achieved switch from short-acting opioids to long-acting preparations. In addition to the long-acting opioid, an as-needed (PRN) analgesic should be available but it should be used only for breakthrough pain, and, its dose will be equivalent to a 10-20 percent increase of the 24-hour dose of the long-acting opioid.
10. Reassess, re-examine, document and adjust	With opioid therapy conduct a periodic patient reassessment and re-examination. After this exam, document and adjust the opioid dose as needed and make these visits quarterly visits (Q3M) minimum. The purpose of the visit is to make sure pain is controlled and improved quality of life goals have been met. If a patient’s goal for pain control are not being met, refer patient to a chronic pain service for further work-up and treatment.
11. Start a bowel protocol	A bowel protocol of a laxative and stool softener should be started at the time opioids are initiated unless contraindicated (e.g., Senokot-S).
12. Watch for adverse opioid effects	Dependency occurs in all but addiction occurs very rarely in patients who receive opioids for pain control. Hallmarks of addiction include: a) compulsive use, b) loss of control, and c) use of opioids in spite of harm.

these reasons, the chronic use of opioids for patients with persistent orofacial pain requires careful patient selection to rule out those patients who might be exhibiting drug-seeking behavior or other personality disorders that would make opioid contraindicated.

Logically, any patient who is a candidate for opioid use must fully understand the drug dependency issues that long-term use entails. When opioids are used, the cautious clinician will perform careful

periodic monitoring of the patient while they individualize the patient’s dose. A suggested list of steps is given (TABLE 2) that a pain-knowledgeable dentist or physician should follow when prescribing opioid medications. Only by following this process can side effects and abuse and dose escalation be minimized.

**Drug No. 6: Analgesic (Tramadol)**

Tramadol is a centrally acting synthetic codeine analogue that was approved by

the FDA in 1995 for moderate to moderately severe pain. It is not categorized as a schedule II or III drug, and is actually currently categorized as a nonopioid analgesic so it does not have a narcotic schedule classification. For all of these reasons, tramadol is being discussed separately from the other opioids mentioned previously. Tramadol comes either alone or in combination with nonopioid analgesics such as aspirin, acetaminophen, and ibuprofen.

Even though it is classified by the FDA

as a nonopioid analgesic this drug does bind to the mu-opioid receptor in the central nervous system. It also acts like a tricyclic antidepressant agent causing inhibition of serotonin and norepinephrine at the synaptic cleft.<sup>28,29</sup> The effects of these actions (mu-opioid binding and serotonin-norepinephrine reuptake inhibition) both produce inhibition of the ascending pain signals and can activate the descending pain inhibitory pathway.

Tramadol's opioid affinity and activity are also substantially less than those of morphine. Due to tramadol's (albeit weak) opioid activity, there have been questions about potential abuse. A proactive surveillance program revealed that the vast preponderance of patients who abuse tramadol have a previous record of substance abuse.<sup>30</sup>

### **Drugs No. 7-8: Analgesics (Aspirin, Acetaminophen)**

The World Health Organization recommends nonopioid analgesics for the initial treatment of pain. The three most common analgesics that do not have opioid receptor-binding action are aspirin, acetaminophen, and the nonsteroidal anti-inflammatory drugs. Generally, the WHO analgesic ladder is designed for acute pain management, and, unfortunately, this organization does not modify their recommendations for chronic pain. This is a problem since while aspirin (acetylsalicylic acid) is an important analgesic for acute pain, it does not appear appropriate for chronic pain use because of the known gastropathic-inducing side effects (gastric irritation and nausea). The same concern (induced gastropathic disease) also exists for NSAIDs.

Nevertheless, aspirin is widely available and used for pain since it is an over-the-counter product. The primary mechanism of action of the aspirin is

that it inhibits prostaglandin synthesis and acts on the hypothalamus to reduce fever. When nociceptive fibers are being stimulated by an endogenous inflammatory reaction in the peripheral injury site, prostaglandin is a critical component of the inflammatory cascade of events. For this reason inflammatory pain is effectively blocked by aspirin. A review article on aspirin as a postoperative analgesic suggests it is effective but has substantial side effects, even in short-term use.<sup>31</sup>

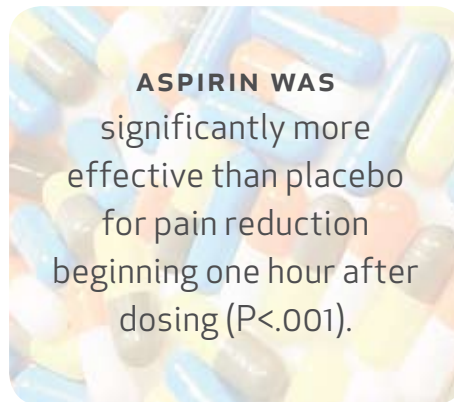
This meta-analysis examined 72 studies where aspirin was compared to other analgesic agents or placebo agents. These studies included in total more than 6,550 subjects divided between those getting placebo and those getting active agents. These studies were all short term because the primary use of aspirin is for postoperative pain. Aspirin was found to be significantly superior to placebo with single oral doses of 600/650 mg, 1,000 mg and 1,200 mg. Of course, aspirin is used by patients with chronic pain and especially by patients with episodic pain due to headache, sometimes resulting in benefit and sometimes with harm.

One study examined the efficacy and tolerability of aspirin versus placebo for the acute treatment of a single acute attack of migraine.<sup>32</sup> This prospective, randomized, double-blind, parallel-group, placebo-controlled study evaluated the efficacy of a single, 1,000 mg dose of aspirin for the treatment of acute moderate to severe migraine, with or without aura. Again, this study examined only the short-term efficacy of aspirin looking at headache pain response at two hours.

Of 485 subjects with migraine attacks enrolled, 201 used aspirin and 200 used placebo. The two-hour headache response rate was 52 percent with aspirin versus 34 percent with placebo ( $P < .001$ ).

Aspirin was significantly more effective than placebo for pain reduction beginning one hour after dosing ( $P < .001$ ) and continuing throughout the six-hour evaluation period. This study demonstrated that aspirin used in this fashion was safe and effective for treatment of acute migraine in appropriately selected patients.

In addition to aspirin, acetaminophen is another over-the-counter nonopioid analgesic used by pain patients. Like



aspirin, this drug is an important analgesic for acute pain, and, if used at levels that are nontoxic, can be used for chronic pain use. While this drug does not cause gastropathy as a side effect, the major concern with acetaminophen is that it is not uncommon for patients to inadvertently take more than maximum daily dose (4,000 mg/day) and produce a liver toxicity that causes rapid irreversible liver damage, which can be fatal.<sup>33</sup> The primary mechanism of action of acetaminophen is that it inhibits prostaglandin in the central nervous system and peripherally blocks pain impulse generation, and it acts on the hypothalamus to reduce fever.<sup>34</sup>

A recent meta-analysis examined this drug assessing 46 clinical studies that compared acetaminophen to placebo.<sup>35</sup>

These studies in total included 2,530 subjects who received acetaminophen, and 1,594 who received placebo and its analgesic benefit above and beyond a placebo is well established. Both aspirin, and, to a much greater extent, acetaminophen and its European equivalent, paracetamol, are used as headache abortive agents, and depending on the frequency of the headache, this can mean daily use of these drugs. A recent study examined the effectiveness of nonprescription combination of acetaminophen, aspirin, and caffeine at alleviating migraine headache pain.<sup>36</sup>

The study was a triple-double-blind, randomized, parallel-group, single-dose, placebo-controlled experiment that included migrainers with moderate or severe headache pain. The study enrolled 1,357 patients, and 1,250 took study medication and 1,220 were included in the efficacy-evaluable data set. The results showed that significantly greater reductions in migraine headache pain intensity occurred one to six hours after dose in patients taking the acetaminophen, aspirin, and a caffeine combination than in those taking a placebo. Pain intensity was reduced to mild or none two hours after dose in 59.3 percent of the 602 drug-treated patients, compared with 32.8 percent of the 618 placebo-treated patients ( $P < .001$ ). In addition the obvious efficacy, this drug combination also has an excellent safety profile and is well tolerated.

Unfortunately, because it has a good effect for episodic headaches, over-the-counter analgesic sometimes are overused and this can lead to a disorder called medication overuse headache. The basic concept behind this is that analgesic use can cause central sensitization of the trigeminal and somatic nociceptive systems, and these changes are thought to be occurring in the cerebral supraspinal structures.<sup>37</sup>

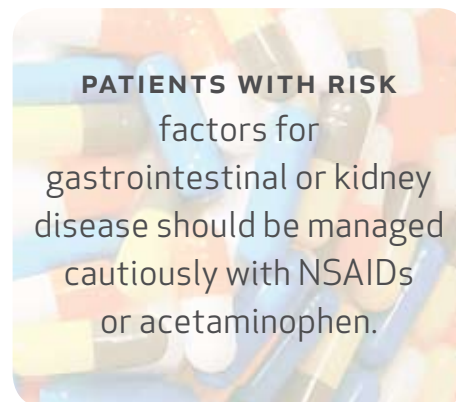
### Drugs No. 9-15: NSAIDs (Ibuprofen, Naproxen, Nabumetone, Piroxicam, Sodium Diclofenac, Celecoxib, Meloxicam)

In this category, five commonly used nonspecific cyclooxygenase (COX) inhibiting nonsteroidal anti-inflammatory drugs for arthritis pain (ibuprofen, naproxen, nabumetone, piroxicam, and sodium diclofenac) and two cyclooxygenase-2 specific inhibiting medications (celecoxib, meloxicam) are included. Like aspirin, these drugs are used for acute pain and for phasic arthritic pain. The primary mechanism of action of the all of the NSAIDs reviewed herein is that they inhibit prostaglandin synthesis by decreasing the activity of the cyclooxygenase enzyme. The main drawback for the five nonspecific COX inhibiting NSAIDs when used on a continuous basis is that they cause gastropathy (gastric irritation and nausea).<sup>38</sup>

Retrospective studies have established an association between increased risk of upper gastrointestinal bleeding and ingestion of aspirin or NSAIDs.<sup>39</sup> <sup>41</sup> This side effect is less likely with the two COX-2 inhibitors, but they have the added side effect of an increased risk of cardiac damage.<sup>42</sup> Nevertheless, NSAIDs are used widely for both headache and arthritic pain since two of them (ibuprofen and naproxen) are available as an over-the-counter product. Considering the adverse effects of long-term NSAIDs, and the lack of clinical evidence demonstrating a therapeutic effect for these nonopioid analgesics in the symptomatic treatment of myalgia or fibromyalgia, this must be weighed against the potential for serious toxicity with chronic use in for myogenous-based disease.

A short trial of an NSAID may be considered in patients with an apparent TMJ inflammatory component to their pain complaint but a lack of therapeutic

effect after a seven- to 10-day trial or the development of any gastrointestinal symptoms should prompt discontinuation of the NSAID. Patients with risk factors for gastrointestinal or kidney disease should be managed cautiously with NSAIDs or acetaminophen and should not take these drugs for prolonged periods of time. For those patients with gastritis the possibility exists for them to use a topic NSAID, and a recent study examined the efficacy and tolerability of



a topical ketoprofen patch in the treatment of uncomplicated ankle sprain.<sup>43</sup>

Of course it would be nice if such data were available for TMJ strain, unfortunately such data is not available. Nevertheless, for ankle strain, a randomized, double-blind, placebo-controlled, multicenter, two-week trial was performed on 163 subjects. Pain levels were the primary outcome measure and it was found that the ketoprofen patch was better than a placebo. Specifically, ketoprofen demonstrated a greater reduction in pain after seven days than those assigned to a placebo. Adverse events, mostly local skin reactions, occurred in 30.9 percent of the ketoprofen group and in 24.4 percent of the placebo group.

The issue of safety of COX-2 selective NSAIDs such as celecoxib or meloxicam has received great attention in recent years. A recent review examined the clinical effectiveness of several COX-2 selective NSAIDs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis.<sup>44</sup> This review included only randomized controlled trials and they concluded that although the COX-2 selective NSAIDs as a class of medications offered protection against serious GI events, the amount of evidence for this protective effect varied considerably across individual drugs.

The relative cardiovascular safety also varied substantially between COX-2 selective NSAIDs. An increased risk of MI compared to nonselective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient years. There is no study that has examined meloxicam for TMJ-related arthritis or pain but a 2004 study on TMD did examine the relative efficacy of celecoxib versus naproxen and a placebo in a randomized controlled clinical trial.<sup>45</sup>

This study included 68 subjects with painful TMJs secondary to disc-displacement with reduction. The results showed that naproxen significantly reduced the symptoms of painful temporomandibular joint disc-displacement with reduction as determined by most efficacy measures, and also showed a significant improvement in pain intensity during the study. Celecoxib and naproxen were equally well tolerated, with similar number of reported adverse effects. In conclusion, the final choice to use a COX-2 selective NSAID or a nonselective NSAID is left up to the practitioner who will weigh the benefit of the medication with the risk of an adverse event.

**Drugs No. 16-18: Corticosteroids (Methylprednisolone, Triamcinolone, Fluocinonide)**

Three commonly used corticosteroids are methylprednisolone, triamcinolone, and fluocinonide. The first agent is often given systemically or via injection for acute pain and inflammation.<sup>46</sup> The second agent is also available for systemic use, but it is more commonly used as an intracapsular injections for joint pain or for topical application to for skin reactions where inflammation is present.

These agents are powerful anti-inflammatory agents, and, like aspirin, are used for acute pain and even sometimes for chronic pain, but they are not specifically FDA-approved for pain. They are approved for a wide variety of inflammatory diseases including autoimmune disease (e.g., erosive lichen planus, pemphigus, graft versus host disease, rheumatoid arthritis). Like aspirin and NSAIDs these agents when used continuously will cause gastropathy (gastric irritation and nausea) as well as many other major side effects. Both methylprednisolone and triamcinolone are generally used short term either as a system dose for inflammatory disease or as an injectable agent for arthritic pain.

Only occasionally will these agents be used chronically and then in generally lower doses. The primary mechanism of action of these two agents is to decrease inflammation by suppression of migration of leukocytes and reversal of increased capillary permeability. By producing a general suppression of the immune system, inflammatory-related pain is effectively blocked.

The third corticosteroid in this category is fluocinonide and in a recent double-blind clinical trial examined the efficacy of topical steroids for treatment of chronic oral vesiculoerosive disease.<sup>47</sup> This study

conducted a double-blind clinical trial comparing two potent topical corticosteroids (clobetasol propionate and fluocinonide ointment in orabase) as treatments for controlling oral vesiculoerosive diseases. Sixty patients were included (43 women and 17 men) and final data were available for 55. The study duration was 28 days and outcomes included pain, erythema, atrophy, and size of lesion. The results showed that both medications had a beneficial effect in the control of



symptoms and signs of oral vesiculoerosive diseases with minimal side effects although candidiasis was observed in 13 patients at the end of treatment in this population. The authors suggested that concurrent treatment with anti-fungal therapy might be indicated in some cases.

**Drugs No. 19-20: Local Anesthetic/Sodium Channel Blockers (Lidocaine, Benzocaine)**

The anesthetics lidocaine and benzocaine are both membrane stabilizing agents that work by blocking voltage-gated Na<sup>+</sup> channels.<sup>48</sup> Local anesthetic agents have been shown to effectively treat neuropathic pain in animal models.<sup>48</sup> Clinically, neuropathic pain states respond transiently to intravenous infusion of

lidocaine, but unfortunately the effect is only present during the infusion. There are two clinically available cutaneous local anesthetic preparations: (1) EMLA cream (AstraZeneca, Wayne, Penn.), which is a eutectic mixture of the local anesthetics lidocaine and prilocaine, and (2) Lidoderm, which is a 5 percent lidocaine patch (Endo Labs, Chadds Ford, Penn.).<sup>49</sup> Although EMLA is useful for venipuncture and cutaneous biopsy, it has not found a role in chronic pain management.<sup>50</sup>

In contrast, the topical 5 percent lidocaine patch may be useful in management of peripheral neuropathic pain conditions. An open-label trial showed that the patch gave moderate or better pain relief in 81 percent of a small group of patients with cutaneous refractory neuropathic pain states.<sup>51</sup> Controlled studies are ongoing, but the Lidoderm patch has been approved by the FDA for treatment of postherpetic neuralgia. The dose is one patch to the affected area every 12 hours, and serum levels are insignificant. In general lidocaine and even benzocaine are safe to use topically, but there is a risk of methemoglobinemia.<sup>52</sup>

**Drugs No. 21-25: Anti-convulsants (Carbamazepine, Oxcarbazepine, Lamotrigine, Levetiracetam, Zonisamide)**

In this category are five anti-epileptic drugs, AED, also called anti-convulsants that are known to depress abnormal neuronal discharges and raise the threshold for the propagation of neural impulses. AEDs have been found to have therapeutic efficacy in all neuropathic pain including orofacial neuropathic pain states. The most frequently used is carbamazepine, which is the AED of choice for treating trigeminal neuralgia for many years.<sup>53</sup> These agents do not have an FDA narcotic schedule classification

but are dangerous nonetheless. These five agents reviewed here (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, zonisamide) are approved for control of epileptic seizures and carbamazepine is approved for trigeminal neuralgia as well.

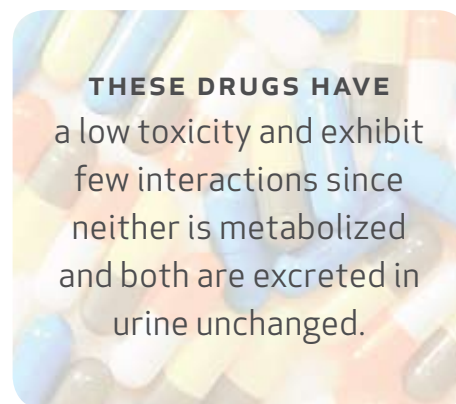
Carbamazepine and oxcarbazepine are the mainstay of trigeminal neuralgia therapy. While it is not specifically approved for trigeminal neuralgia, oxcarbazepine is a ketocarbamazepine and its metabolite is the active agent. This metabolite has many of the therapeutic properties of carbamazepine while avoiding some of its toxicities. The primary mechanism of action of carbamazepine and oxcarbazepine is based on their ability to block voltage-gated Na<sup>+</sup> channels and modulating voltage-activated Ca<sup>++</sup> currents as well.

Since this disease is stimulation-triggered pain when the nerves are suppressed, the pain is completely stopped. Unfortunately, carbamazepine is a self-inducing drug, which means it acts to stimulate the liver enzymes that metabolize it to work faster. The end result is that after several weeks of continuous use, the drug level in the blood drops as it is metabolized much faster so the dose must be increased.

The substantial advantage of oxcarbazepine is that it is not a self-inducer so once dose is established it is more stable. Since there are known adverse effects on liver function the starting dose is 200 mg b.i.d. and the patient is titrated upward to the effective dose ranges from 400 to 1,000 mg/day. The most common side effects are drowsiness, diplopia, and unsteadiness. Aplastic anemia occurs in 1:200,000, reversible leukopenia and thrombocytopenia are more common. Published reports have shown efficacy in trigeminal neuralgia.<sup>54</sup> For oxcarbazepine, the starting dose is 300 mg at bedtime, with weekly increases of 300 to 600 mg/day up to a maximum of 1,200 to 2,400 mg/day.

### Drugs No. 26-27: Anti-convulsants (Gabapentin, Pregabalin)

The two anti-convulsants discussed here are gabapentin and pregabalin. These two drugs are separate and distinct from the previously mentioned anti-convulsants since they have much less risk of adverse events when used in pain patients. Gabapentin has been in use since 1994 and pregabalin was approved in 2005. Both have been used frequently for suppression of neuropathic pain.



These agents do not have an FDA narcotic schedule classification and are approved for control of epileptic seizures. Pregabalin is also approved for diabetic peripheral neuropathy. These drugs have a low toxicity and exhibit few interactions since neither is metabolized and both are excreted in urine unchanged. Caution must be used in any patient with compromised renal function. Moreover, because gabapentin is not approved for neuropathic pain it is used off-label. The mechanism of action of gabapentin is uncertain but most likely acts similarly to pregabalin, which is known to affect a central voltage-dependent L-type Ca<sup>++</sup> channel.

Unfortunately, neither drugs can stop neuronal activity, only suppress it, so efficacy of these agents for pain is limited. The

most common side effects of gabapentin and pregabalin are drowsiness, somnolence, nausea, and fatigue. The common adverse side effects are usually self-limiting and subside after a couple of weeks allowing gradual dose escalation. The usual starting dose for gabapentin is 100 to 300 mg per day taken at bedtime. The dose is gradually increased to 1,200 mg/day and is taken over 10 to 15 days in a divided dose schedule. Some patients may require 3,600 mg/day for a clinical effect. The starting dose for pregabalin is 150 mg/d and maximum dose is 300 mg/d. After the initial titration and adjustment period, these drugs can be switched from before sleep to dosing on a three times a day schedule.

### Drugs No. 28-30: Chronic Daily Headache Preventives (Valproic Acid, Topiramate, Tizanidine)

This category includes three medications that are used as headache preventive agents. The first two are anti-convulsants and the third is an alpha-adrenergic agonist. The first is valproic acid and it is in the anti-convulsant category and it has been shown to be effective in prophylaxis of migraine headache.<sup>55</sup>

Valproic acid blocks voltage-gated Na<sup>+</sup> channels as carbamazepine and phenytoin do, but also increases levels of aminobutyric acid (GABA) by decreasing its degradation. Side effects include nausea, vomiting, sedation, ataxia, rash, alopecia, and appetite stimulation. Forty percent of patients experience elevated transaminase levels, and 1 in 50,000 develop hepatic failure. The second drug in this group is topiramate, which was approved for use in 1997 and it has shown promise for cluster headache and diabetic neuropathy.<sup>56</sup>

Topiramate is a unique monosaccharide compound structurally unlike other AEDs. It potentiates GABA responses, significantly increasing central nervous

system GABA levels, and also blocks the AMPA kainate excitatory receptor. Topiramate is also a weak carbonic anhydrase inhibitor. The effective dose range is 200 to 400 mg/day b.i.d. The dose is 25 mg b.i.d. and is increased 50 mg/week up to the dose range. Side effects include unusual central nervous system effects such as abnormal delusional and psychotic thinking. Occasionally, patients develop renal stones. These side effects are rare, occurring in <2 percent to 3 percent of patients, but are troubling to those patients.

Finally, the third drug in this section is tizanidine, an alpha-adrenergic agonist has both a peripheral and a central mechanism of action in migraine headache. A recent review examined the relative value of various medications, including tizanidine for preventative treatment when dealing with patients who have chronic migraine or tension-type headaches.<sup>57</sup> The individual results for the other two drugs (baclofen and botulinum toxin) are discussed later in this article. This article was based on a literature review of clinical drug trials. The author concluded that the literature supported the use of tizanidine as a preventive treatment of chronic daily headache was better than placebo therapy. The author noted that it is often used in combination with a long-acting NSAID to aid in the treatment of medication rebound headache.

**Drugs No. 31-34: Migraine Abortives (Sumatriptan, Eletriptan, Frovatriptan, Rizatriptan)**

The triptan medications have been described as a miracle drugs for episodic migraine sufferers. Unfortunately, they are moderately expensive and don't always work or the patient may not be able to tolerate the medications side effects. The introduction of triptans has essentially changed how new migraine patients are now managed. For example, one

study compared pharmacoepidemiology of headache treatment in two different groups. One group were patients (n=612) who were attending a headache center for their first visit and another group were more chronic headache patients (n=620) attending a headache specialty center for a follow-up treatment assessment.<sup>58</sup>

Most of these headache patients suffered from migraine. The 49.4 percent of the first visit headache group patients were taking drugs prescribed by a doctor and 41.5



percent were taking over-the-counter analgesics, but 9.1 percent were not taking any drug. For the recall headache patients, 81.3 percent were taking prescription drugs; 15.8 percent took over-the-counter analgesics; and 2.9 percent did not take any drugs. Triptans were being used by only 9.1 percent of the first-time visit group whereas 31.8 percent of the recall chronic headache patients were using triptans. Amitriptyline was the drug most commonly used for prophylaxis.

**Drugs No. 35-36: Miscellaneous Migraine Medications (Butalbital, Dihydroergotamine)**

This section is focused on two older medications that have been, and still are, commonly used for recurrent episodic and chronic headaches. The first is butalbital,

the main agent in a combination drug that usually contains acetaminophen, caffeine, and butalbital. Butalbital is categorized as an analgesic but acts as a barbiturate, and, as such, has many of the adverse events and dependency complications associated with this class of drug. A recent study examined the amount of health resources utilized by patients who repeatedly use emergency department services for headache care.<sup>59</sup>

Specifically the study involved a retrospective review of urgent care/emergency department charts, clinic charts, and pharmacy rosters for patients who made three or more visits for a headache to an urgent care/emergency department (UC/ED) facility over a six-month study period. The study included data on 54 subjects who were classified as "repeaters." This number represented more than 10 percent of the 518 patients who visited the UC/ED for primary headache complaints. This group of 54 repeating patients produced more than 502 visits (50 percent of total visits) during the study period. Pharmacy rosters showed use of narcotics in 41 of these patients and butalbital products were used in 27 patients. The authors concluded these two medications — opioids and butalbital — did not seem to provide a successful approach to the recurrent migraine or tension-type headache problems, and it is possible the medications themselves were contributing to the repeated visit pattern.

In agreement with the above study are two reports that discuss the problems of using opioids and barbiturates for headache management. The first is a study that examined the national trends of prescription medication use for headache.<sup>60</sup> The study involved secondary analysis of data obtained during the 2000 Medical Expenditure Panel Survey, a representative survey of the U.S. noninstitutionalized

population. These authors reported that 46 percent of patients reported using at least one medication for the treatment of headache and migraine-specific abortive medication (i.e., selective serotonin receptor agonists and ergotamine derivatives) were the most frequently (36 percent) used medications. Opiate analgesics and butalbital-containing products also experienced extensive prescribing reported by 22 percent and 17 percent of survey respondents, respectively.

The second is a review of the literature on the topic of butalbital-containing drugs for migraine.<sup>61</sup> This study described a qualitative systematic literature search and reported that between 14 percent and 36 percent of diagnosed migraineurs are prescribed butalbital-containing products, often as initial therapy in spite of the fact that the only identified controlled trial of these drugs for migraine treatment showed that butalbital-containing products were inferior to butorphanol (an opioid). The article discussed a consortium of U.S. headache specialists' published guidelines and it discouraged administration of butalbital-containing products for migraine due to serious dependency issues with this medication.

Finally, in a recent single center open-label pilot study, the efficacy of dihydroergotamine (DHE 45) for migraine headaches with allodynia was examined.<sup>62</sup> This drug is occasionally used for severe migraines when a patient is nonresponsive to a triptan medication rather than giving the patient an opioid to control the pain. The study involved nine patients who were treated on two occasions for episodic migraine with allodynia using the drug dihydroergotamine 1.0 mg administered via an intramuscular injection. The authors concluded that whether they took the dihydroergotamine early or late in the attack, most patients (>55 percent) had headache relief within two hours, and at

least 44 percent of patients achieved headache-free status by eight hours postdose. The authors suggested a large, placebo-controlled trial of dihydroergotamine in allodynic patients was now warranted.

### Drugs No. 37-39: Miscellaneous Headache Preventatives (Propranolol, Timolol, Verapamil)

Beta-adrenergic receptor blockers and calcium channel blockers have been used for many years to help prevent chronic

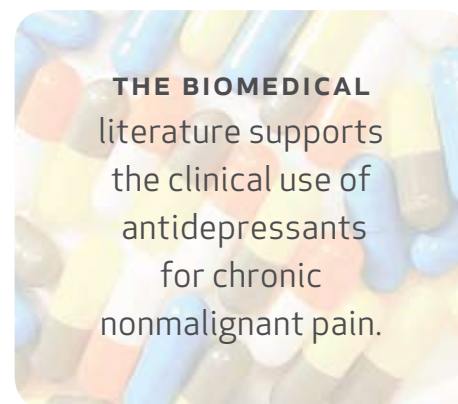
of beta-blocker plus topiramate showed a benefit in around 60 percent of patients who had not previously responded to monotherapy. Adverse events led to discontinuation in one out of six patients.

Regarding calcium channel blockers such as verapamil, this class of drug has been used for migraine and cluster headache prophylaxis. A report by the European Federation of Neurologic Societies task force recently examined the available literature on treatment of the trigeminal autonomic cephalgias.<sup>64</sup> The headaches included in this review included cluster headache, paroxysmal hemicrania, and short-acting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome. They concluded that the literature supported the use of oxygen (100 percent) with a flow of at least 7 l/min over 15 minutes and 6 mg subcutaneous sumatriptan for the acute treatment of cluster. Prophylaxis of cluster was best performed with verapamil at a daily dose of at least 240 mg (maximum dose depends on efficacy or tolerability).

Finally, they noted that while the quality of the studies were lower, the use of corticosteroids (100 mg methylprednisone or an equivalent corticosteroid given orally or at up to 500 mg IV per day over five days then tapering down) was another method of managing a cluster headache.

### Drugs No. 40-41: Tricyclic Antidepressants (Amitriptyline, Nortriptyline)

Often described as adjunctive pain medications are the tricyclic antidepressant (TCA) drugs and they have been used for more than 30 years for the management of pain from a wide variety of conditions, including chronic orofacial pain.<sup>65</sup> The biomedical literature supports the clinical use of antidepressants for chronic nonmalignant pain



and frequent migraines. A recent open label study examined the efficacy of combining a beta-blocker plus topiramate in migraine patients previously resistant to the two medications in monotherapy.<sup>63</sup> Those patients who had not responded to a beta-blocker and topiramate received a combined treatment; 58 patients completed the study. Of these 33 (57 percent) met criteria for chronic migraine/medication overuse headache; 18 (31 percent) for migraine without aura; and 7 (12 percent) for migraine with aura. The results showed 10 patients (17 percent) discontinued due to adverse events but 36 of the other 48 patients who tolerated the combination showed a >50 percent reduction in frequency of headache. The authors concluded that the combination

when other treatments have failed or if depression accompanies the pain.

Tricyclic antidepressants with both serotonergic and noradrenergic effects (e.g., amitriptyline, nortriptyline) appear to be most effective. There are multiple tricyclic medications that are useful alternatives to amitriptyline, and have some differences in the side effect profiles and the half-lives. For example, desipramine, the least anti-cholinergic and sedative of the TCAs, showed pain relief after three weeks, independent of mood alterations in a placebo-controlled randomized clinical trials of 26 patients with postherpetic neuralgia.<sup>66</sup> Nortriptyline, the active metabolite of amitriptyline, is also popular, maybe because it seems to be better tolerated than amitriptyline. The starting dose is 10 mg at bedtime and increased after three to five days to 20 mg at bedtime and then carefully titrated.

A recent study compared whether selective serotonin reuptake inhibitor (SSRI) antidepressants were associated with an increased or decreased risk of cardiovascular adverse events (AEs).<sup>67</sup> The study examined the published literature and it defined serious AEs as death due to a cardiovascular cause, heart failure, stroke, transient ischemic attack, and myocardial infarction. Nonserious adverse events were defined as palpitations, chest pain, angina, arrhythmia, hypertension, hypotension-syncope, and unspecified cardiovascular or neurologic events.

Adverse event rates were calculated in four medication groups: (1) SSRIs; (2) tricyclic antidepressants (TCAs); (3) other active therapies but not an SSRI or TCA; and (4) placebo. The authors reported that they were unable to detect differences in odds between SSRI and placebo for both serious or nonserious AEs. There were more nonserious AEs for TCAs versus SSRIs.

**Drugs No. 42-43: Serotonin-Norepinephrine Reuptake Inhibitor: Duloxetine, Venlafaxine**

Duloxetine and the similar but earlier drug venlafaxine have been used for both chronic muscle pain and for neuropathic pain. There are two studies that examine duloxetine efficacy for fibromyalgia.<sup>68,69</sup> Both enrolled patients with fibromyalgia using ACR (American College of Rheumatology) criteria, and with at least moderate pain, and had sensible exclusions. One was exclusively



and one predominantly in women. In the 532 randomized women, 38 percent had at least 50 percent improvement in pain over 12 weeks with 60 mg duloxetine (once or twice a day) compared with 21 percent with placebo. There were improvements in quality of life, and more adverse events with duloxetine, especially nausea and dry mouth.

**Drugs No. 44-46: Selective Serotonin Reuptake Inhibitor (Escitalopram, Citalopram, Fluoxetine)**

Clinically, it is well known that chronic pain induces depression, anxiety, and a reduced quality of life. Several animal studies have proven that experimental neuropathic pain induces anxiety with changes in opioidergic function in the central nervous system.<sup>70</sup> In a follow-up study, the

anxiolytic-like effects of several types of antidepressants were examined on a chronic neuropathic pain-like state.<sup>71</sup> The study used a sciatic nerve-ligated mouse model with demonstrated thermal hyperalgesia and tactile allodynia. It then administered the tricyclic antidepressant (TCA) imipramine, the serotonin noradrenaline reuptake inhibitor (SNRI) milnacipran, and the selective serotonin reuptake inhibitor (SSRI) paroxetine and showed a reduction in anxiety behavior of the mouse after the medication.

These antidepressants also produced a significant reduction in thermal hyperalgesia and tactile allodynia. The authors concluded that serotonergic antidepressants were effective for treating anxiety associated with chronic neuropathic pain.

Another study compared the use pattern of an SSRI (paroxetine or citalopram) versus an anti-convulsant medication (gabapentin) on 101 painful diabetic neuropathy patients.<sup>72</sup> The authors reported that over a six-month study period, the patients receiving SSRIs reported greater satisfaction and fewer concerns of the side effects with their treatment ( $P < 0.05$ ) compared with the patients taking gabapentin. There was statistically significant better mood in the SSRI group, but overall, 43.5 and 40.5 percent of those taking SSRIs and gabapentin, respectively, noticed no effect of the medication on their pain. The authors concluded that the lack of negative effects on quality of life, the better compliance, and the comparable efficiency of SSRIs on patient mood suggests that these drugs may be considered as an alternative to gabapentin in painful diabetic neuropathy.

**Drugs No. 47-49: Muscle Relaxants (Carisoprodol, Metaxalone, Methocarbamol)**

Muscle relaxants or anti-spasmodics are often used as adjuvants for patients with chronic musculoskeletal pain but the

clinical evidence for their long-term use in true chronic pain states is weak. Two agents that are commonly for short-term masticatory muscle spasm and pain are clonazepam and caridisprodol. These two agents are thought to reduce skeletal muscle tone because of their anxiolytic effects.

Clonazepam is a benzodiazepine-type medication and is used for the treatment of certain types of seizures. It is also used in painful conditions, including myoclonus and muscle spasms.

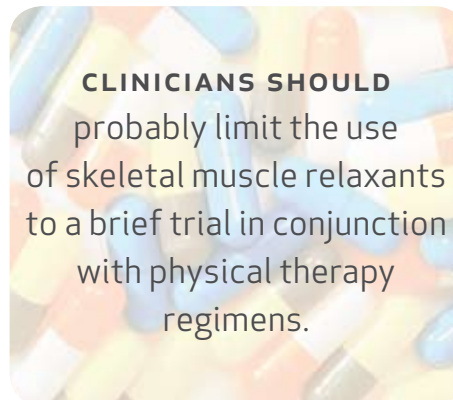
Clonazepam acts by enhancing the GABA-induced increase in chloride conductance. Side effects include sedation, lethargy, ataxia, and dizziness.

Caridisprodol is one of the oldest drugs of this class and most likely acts centrally to depress polysynaptic reflexes.<sup>73</sup> It was first evaluated for chronic orofacial pain in a study published in 1960.<sup>74</sup>

Finally, because some of these drugs may have an addictive potential, the daily dosage and duration of treatment requires a careful open doctor-patient discussion and agreement. The clinician should consider the alternative nonpharmacological treatment options, such as physiotherapy (with myofascial release techniques), massage, relaxation/biofeedback techniques, or acupuncture. There is insufficient evidence to assist clinicians in a rational approach to the use of muscle relaxants as analgetic and anti-spastic treatments.

Overall, the scientific literature does not provide unequivocal support for either the use of benzodiazepines or their condemnation on the basis of lack of efficacy or potential toxicity. Like all drugs, they should only be used in patients whose symptoms are suggestive of potential efficacy and should not be prescribed in large amounts that would permit dose escalation without professional supervision or the development of dependence with long-term therapy.

For patients whose pain appears to be of musculoskeletal origin, they may benefit from a two- to four-week course of a benzodiazepine, possibly in combination with an NSAID. A lack of efficacy or the onset of sedative side effects or depressive symptoms should be an indication to reduce the dose or discontinue the benzodiazepine. If difficulties in sleep onset or duration are the primary complaint, consideration should be given to the use of a benzodiazepine indicated for hypnosis (triazolam)



to minimize drug effects during the day. Patients who appear to have depressive symptoms before therapy should be referred to a psychiatrist for consultation and possible antidepressant therapy rather than being prescribed a benzodiazepine with putative antidepressant properties.

In any event, therapy with a benzodiazepine should not be extended beyond a few weeks, because the natural course of myofascial pain combined with conservative therapy will likely result in a lowering of symptomology to acceptable levels that would not justify the risks of pharmacologic intervention. Patients for whom such a therapeutic course fails should be re-evaluated for additional physical medicine and behavioral therapy rather than “managed” with long-term benzodiazepine treatment.

### Drug No. 50: Anti-spasmodic (Cyclobenzaprine)

An anti-spasmodic drug that has less abuse potential than clonazepam and caridisprodol is cyclobenzaprine. This drug is used and is thought to be partially effective for some chronic musculoskeletal disorders.<sup>75</sup> For example, cyclobenzaprine has been found to be superior to placebo for pain in the cervical and lumbar regions associated with skeletal muscle spasms and reduces electromyographic signs of muscle spasm.<sup>76,77</sup> Although it has not been directly assessed for TMD, these findings are suggestive of efficacy for muscle relaxation in the orofacial region.

There appears to be a discrepancy between the common clinical use of skeletal muscle relaxants and the results of controlled clinical trials evaluating their efficacy in comparison with placebo. It is also not clear whether they are specific for muscle relaxation or produce nonspecific central nervous system depression, thereby reducing muscle tone. Little supporting evidence exists for their efficacy in chronic orofacial pain of myogenic origin, nor is it clear if they provide an additive effect with exercises or splint therapy aimed at muscle relaxation.

Given this modest scientific support, clinicians should probably limit the use of skeletal muscle relaxants to a brief trial in conjunction with physical therapy regimens. Further studies are needed to document efficacy for chronic orofacial pain in comparison with an active placebo with sedative properties to help differentiate nonspecific sedative properties from muscle relaxation. Five randomized trials were included in a meta-analysis, but neither trials nor review appear to be of a particularly high standard.<sup>78</sup>

**Drug No. 51: Anti-spasmodic (Botulinum Toxin-A)**

Botulinum toxins are potent neurotoxins produced by *Clostridium botulinum* that can block acetylcholine release at the neuromuscular junction. *C. botulinum* was first identified as a causative agent in food poisoning in 1895 and by the 1920s, isolation of a relatively crude form of toxin had occurred. A crystallized form of the “A” subtype, BTA, became available and stimulated scientific interest. The FDA-approved botulinum toxin-A for the treatment of strabismus in 1989.<sup>79</sup> With appropriate dosing, the injected muscles motor function is only partially blocked. These effects occurs within a few days to two weeks after injection and they last from six weeks to six months, but the typical duration is two to three months.<sup>80</sup>

During the peak effect, histologic studies showed evidence of atrophy, but fiber size and function return to normal, even after multiple cycles of injection and recovery.<sup>81</sup> Botulinum toxin-A was approved by the FDA for use in painful orofacial and craniocervical muscle hyperactivity syndromes, including cervical dystonia (torticollis) and hemifacial spasm.<sup>82</sup> The recommended treatment interval between injections is at least three months and numerous studies confirmed that injecting multiple sites within a muscle improves spasticity relief and decreases side effects.

Most recently it has been shown helpful for chronic migraine problems that do not respond to medications, but this is an off-label usage of this medication. There is much ongoing research on the efficacy of and indications for these injections for other conditions including nonspastic neuropathy and even trigeminal neuralgia.<sup>83</sup>

At this time, evidence suggests these injections are best used for conditions

where a clear-cut muscle spasticity is present and the literature on botulinum toxin-A for nonspastic pain disorders has been unconvincing. Finally, a 2003 review of the literature by Freitag examined preventive treatments used for dealing with patients with chronic migraine or tension-type headaches. One of the agents he reviewed was botulinum toxin injections. He concluded that this agent has some efficacy for medication-resistant chronic migraine sufferers, but this is not so for



chronic tension-type headache patients. Fortunately, there are relatively few significant adverse events seen with the use of botulinum toxin-A in headache treatment.

**Drugs No. 52-53: GABAergic Drugs (Baclofen, Tiagabine)**

Drugs that target GABA-A and B receptors are proven to suppress motor activity and also play a role in pain suppression. Baclofen is a GABA agonist and tiagabine is a selective GABA reuptake inhibitor. Regarding baclofen, a 2003 review of the literature by Freitag examined this agent as a preventive treatment for dealing with chronic migraine or tension-type headache patients. He reported that while there has been very limited research on the use of baclofen for CDH prevention,

this agent does act centrally via GABA(A) receptors, in migraine and cluster headache, and therefore has potential. The two open trials conducted to date both suggest and support the use of baclofen for the preventive treatment of headache. Obviously the data is not conclusive yet.

Regarding tiagabine, this drug is both an anxiolytic and an anti-convulsant GABA reuptake inhibitor commonly used as an add-on treatment of refractory partial seizures. This drug has been reported to have some value in the suppression of bruxism in severe cases.<sup>84</sup> Specifically, a case report described that in four of the five cases, tiagabine was able to effectively suppress nocturnal bruxism, trismus, and consequent morning pain in the teeth, masticatory musculature, jaw, and temporomandibular joint areas. Tiagabine has a benign adverse-effect profile, is easily tolerated, and retains effectiveness over time. Bed partners of these patients report that grinding noises have stopped; therefore, the tiagabine effect is probably not simply anti-nociceptive, but motor suppressive. The doses used to suppress nocturnal bruxism at bedtime (4-8 mg) are lower than those used to treat seizures.

Clearly additional data is needed on this drug used in this way. Tiagabine has been proven to be of value for anxiety; and, for patients with pain-induced anxiety, this medication shows promise. A recent study examined the efficacy and tolerability of tiagabine in 266 adults with generalized anxiety disorder over an eight-week period.<sup>85</sup> The study was a randomized, double-blind, multicenter, placebo-controlled study, and doses ranged from 4 to 16 mg/day. The results showed that tiagabine reduced symptoms of GAD but it was not much better than placebo agents. Overall, tiagabine was generally well tolerated and not associated with changes in sexual functioning or depressive status.

### Drugs No. 54-56: Benzodiazepine Drugs (Diazepam, Clonazepam, Alprazolam)

A recent study reported on a randomized blinded controlled trial of the effect of topical clonazepam on burning mouth pain.<sup>86</sup> The study included 48 patients, of whom 41 completed the study. The 14-day long protocol had the patients suck a tablet of 1 mg of either clonazepam or a placebo three times a day. They were told to hold the dissolved medication/saliva mix near the pain sites in the mouth without swallowing for three minutes and then to spit. The clonazepam treatment was shown to reduce pain significantly versus the placebo and the blood level of the clonazepam was negligible. A 1997 study examined the clinical efficacy, the side effects of ibuprofen and diazepam on chronic myogenous facial pain in a double-blind, randomized, controlled clinical trial.<sup>87</sup> The study included 39 subjects (35 women, four men) with daily or near-daily orofacial pain of at least three months' duration and tenderness to palpation of masticatory muscles.

The treatment groups included placebo, diazepam, ibuprofen, or a combination of diazepam and ibuprofen. Pain, mood, muscle tenderness, maximal interincisal opening were measured following two-week baseline and four-week treatment periods. The authors reported that pain was significantly decreased in the diazepam and diazepam plus ibuprofen groups, but not for the ibuprofen or placebo groups. Analysis of variance showed a significant drug effect for diazepam, but not for ibuprofen, indicating that pain relief was attributable to diazepam. This study supported the efficacy of diazepam in the short-term management of chronic orofacial muscle pain.

### Drug No. 57: Episodic Headache Abortive (Indomethacin)

There are a group of headaches (e.g., hemicranial continua, paroxysmal hemicranias and short-lasting unilateral neuralgiform headaches) that have been shown to be very responsive to a specific NSAID medication (indomethacin).<sup>88</sup> One study examined the use of indomethacin on three cases of hemicranias continua and found the intramuscular injection of 50 mg of this medica-



tion relieved pain and thus served as a diagnostic test for these headaches.<sup>89</sup> Another study reported on two cases of hemicranias continua masquerading as a TM disorder.<sup>90</sup> The report described that indomethacin could help differentiate this headache from a TMJ problem.

### Drug No. 58: NMDA Blocking Drug (Ketamine)

A recent study reported on the use of ketamine infusion for the treatment of complex regional pain syndrome (CRPS).<sup>91</sup> Ketamine's mechanism of action is that it is a N-methyl-D-aspartate (NMDA) receptor blocking agent. The study specifically looked at pain reduction in CRPS patients using an open label, prospective, pain journal evaluation of a 10-day infu-

sion of intravenous ketamine. Patients made journal entries each day prior to the infusion of 40-80 mg of ketamine. The reported data showed that there was a significant reduction in pain intensity from initiation of infusion (Day One) to the 10th day, with a significant reduction in the percentage of patients experiencing pain by Day 10 as well as a reduction in the level of their "worst" pain.

The side effects of ketamine, when used for chronic pain, was reported on by a recent study.<sup>92</sup> This study described and evaluated the side effects of this drug based on 32 patients with diabetic polyneuropathy and with postherpetic neuralgia. They found that substantial sedation and dizziness were observed in 15.6 percent and 44 percent of patients after the initial infusion and in 19 percent and 22 percent of patients in the course of the subsequent oral therapy, respectively.

Interestingly, during the observed three-month treatment period, five patients (15.6 percent) withdrew from the treatment due to a failure of therapy and four patients (12.5 percent) due to intolerated side effects (dizziness, sedation, loss of appetite, nausea, and vomiting). One study examined the efficacy of ketamine when used in the management of orofacial pain.<sup>93</sup>

The specific problem being treated with ketamine was atypical odontalgia, AO, and the study included 10 AO patients and 10 matched healthy controls. Treatment involved intravenous infusion of ketamine or a mu-opioid agonist fentanyl on spontaneous AO pain. Outcomes included the effect of the medications on their chronic pain and for both the AO and the control patients, intraoral pain was evoked by topical application of capsaicin. The study was performed in a randomized, placebo-controlled, cross-over manner.

The results showed that both drugs failed to produce an analgesic effect on spontaneous AO pain, but fentanyl effectively reduced capsaicin-evoked pain. Finally, a 1995 and a follow-up 2001 study examined the effect of ketamine intramuscular injection test dose followed by oral ketamine for three nights on the neuropathic orofacial pain patients.<sup>94,95</sup> The study reported there was reduction in pain after the intramuscular injection. The authors noted a positive correlation between a long pain history and lack of analgesic effect in these cases.

**Drug No. 59: Anti-virals (Acyclovir and Others)**

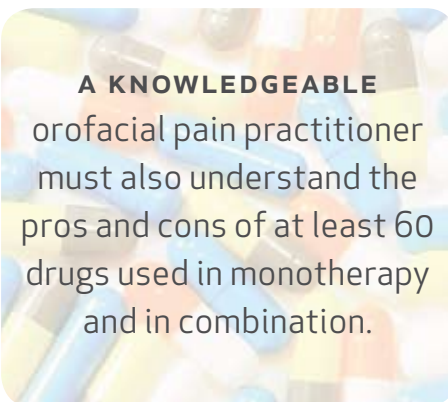
Anti-viral drugs (e.g., acyclovir) are used mostly for acute viral disease with clear-cut clinical manifestations. However, sometimes patients are placed on a viral prevention protocol, especially for idiopathic pain in the face and mouth. The efficacy of anti-viral agents used in this fashion is not established by the literature and recently the use of anti-viral medications for a condition such as Bell's palsy has been questioned.<sup>96</sup> A recent double-blind placebo-controlled study on 551 patients with Bell's palsy concluded that early treatment with prednisolone significantly improved the chances of complete recovery at three and nine months, but there was no evidence of a benefit of acyclovir given alone or an additional benefit of acyclovir in combination with prednisolone.

These findings are remarkable since another recent paper with a smaller data set of Bell's palsy case (n=221) reported that valacyclovir was helpful.<sup>97</sup> Specifically, the study involved a prospective randomized placebo-controlled design and they concluded that the combination of valacyclovir and prednisolone therapy was more effective in treat-

ing Bell's palsy than the conventional prednisolone-only therapy. Overall, there is no evidence basis for using anti-viral agents (acyclovir or valacyclovir) for the suppression of chronic pain.

**Drug No. 60: Anti-bacterial Drugs (e.g., Azithromycin and Others)**

Many physicians and dentists use antibiotics as a standard aspect of their postoperative protocol after a tonsillectomy or oral surgery. One recent study



actually examined if antibiotics were of value for reducing pain postoperatively after tonsillectomy.<sup>98</sup> Specifically, this study review all randomized controlled trials to see if any consistent effect existed for antibiotics versus placebo. Based on their review of nine trials that met the eligibility criteria, the authors concluded there was no consistent or significant reduction in pain as a result of antibiotic usage postoperatively. The authors also concluded that antibiotics used postoperatively also were not associated with a reduction in significant secondary hemorrhage rates, although they did appear to reduce fever.

If the problem was inappropriate antibiotic used after surgery as a preventive for infection, then the answer is to use to fewer, if any, antibiotics under

these conditions. However, the problem is also antibiotic use for chronic pain of unknown origin. This problem is compounded by the fact that certain antibiotics do suppress pain. In fact, there is growing evidence that a specific class of antibiotics (macrolides, e.g., azithromycin) exert their beneficial effect not only by inhibiting or killing bacterial pathogens but also by down-regulating proinflammatory mechanisms. Three recent articles described the immunomodulatory properties of macrolide antibiotics in chronic rhinosinuitis.<sup>99-101</sup> Specifically, these articles described how macrolides antibiotics' inhibition of proinflammatory cytokines such as interleukin-8. This effect is probably secondary to inhibition of the activation of transcription factor NF-kappaB. As a result, there is an attenuation of neutrophilic inflammation and then pain takes place.

Caution must be used when using macrolides because macrolide-resistant bacterial strains might be developed, although, to date, they have not been of clinical importance. Of course, not all antibiotics are immunomodulatory and others that provide pain relief might work because of a strong placebo effect. At present, it does not seem logical or appropriate to recommend antibiotic therapy for chronic orofacial pain, at least until more information about the pain suppression effect is known and the possible risk of bacterial resistance is elucidated.

**Conclusions: Pharmacotherapeutic Management of Orofacial Pain Disorders**

There are many very painful diseases that cause chronic orofacial pain. Some involve acute inflammation, chronic inflammation, neurovascular, neurogenic and neuropathic pain, and myogenic pain. These disorders are treated with many physical and behav-

ioral, and even surgical, methods. The review provided herein demonstrates that a knowledgeable orofacial pain practitioner must also understand the pros and cons of at least 60 drugs used in monotherapy and in combination.

Some of the drugs in this article are being used on-label and some are clearly off-label. Dentists who treat these patients with off-label medications must fully understand the literature and evidence supporting any drug they use. This article showed there is a paucity of well-controlled studies of these 60 medications used specifically for chronic orofacial pain in the relevant patient population and used for periods of administration that approximate their use clinically. This paucity does not mean that these medications cannot be used, only that they must be used with caution, with reasonable concern and full knowledge of the existing literature.

For example, assuming there is a reliable differential diagnosis, pain with a neuropathic or an atypical neurogenic component would logically be managed with a trial with a tricyclic antidepressants, sodium channel blockers, and, possibly, even anti-convulsants. Pain of musculoskeletal origin is probably best managed by physical medicine procedures using tricyclics and SNRIs as supplements. Patients with manifestations of psychosocial dysfunction may not benefit from drug therapy aimed at pain and should be considered as candidates for physical medicine modalities and behavioral methods and SSRI medications.

For patients on whom other therapeutic modalities have failed, or for whom a specific treatment is not readily apparent, such as patients for whom the non-narcotic analgesic medications and physical and behavioral medicine procedures have not worked adequately, might be eligible for a trial with opioids. What is

evident is that a wide variety of adjuvant analgesic and anti-convulsant drugs show efficacy in the treatment of chronic painful conditions. Recently, a European pain task force evaluated the existing published evidence about the pharmacological treatment of neuropathic pain.<sup>102</sup>

Only pharmacologic treatments feasible in an outpatient setting were evaluated, and they used the effect of these agents on pain symptoms/signs, quality of life, and other disease comorbidities as outcomes. They reported that most of the randomized controlled trials included patients with postherpetic neuralgia (PHN) and painful polyneuropathies (PPN) mainly caused by diabetes.

Using these diseases, the task force concluded that the data provides high level of evidence for the efficacy of tricyclic antidepressants, gabapentin, pregabalin, and opioids, with a large number of class I trials, followed by topical lidocaine (in PHN), and the newer antidepressants venlafaxine and duloxetine (in PPN). The biggest problem is that the previously mentioned recommendations apply only to PHN and DN, and, if used on other similar but untested conditions, like atypical odontalgia and burning mouth syndrome, it is not clear if the efficacy will carry over to these disorders.

For this reason, using medications such as these requires caution. Given the complex nature of chronic orofacial pain, a multidimensional treatment approach, including nonpharmacological methods, is advocated, avoiding use of several adjuvant medications prone to side effects.

Furthermore, periodic trials of decreasing dosages and eliminating chronic medications should be considered. However, the targeted and limited use of adjuvant analgesic treatments for defined pain syndromes provides a valuable addition toward relief of pain. ■■■■

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