

# Pharmacotherapy in Temporomandibular Disorders: A Review

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## ABSTRACT

Temporomandibular disorder (TMD) is a collective term that includes disorders of the temporomandibular joint (TMJ) and of the masticatory muscles and their associated structures. TMDs are characterized by pain, joint sounds and restricted mandibular movement, and drugs are widely used in the management of that pain. Pharmacological agents commonly used for the treatment of TMDs include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, muscle relaxants, antidepressants, anticonvulsants and benzodiazepines. In this paper, we discuss these agents and the potential adverse drug reactions and interactions associated with their use.

Temporomandibular disorder (TMD) is a collective term used for a number of clinical problems that involve the masticatory muscle complex, the temporomandibular joint (TMJ) and associated structures. TMD is one of the most common disorders in the maxillofacial region. Signs and symptoms of TMD may include pain, impaired jaw function, malocclusion, deviation from the midline on opening or closing the jaw, limited range of motion, joint noises and locking.<sup>1</sup> Among other signs and symptoms, headaches and sleep disturbances can appear concomitantly.<sup>2</sup> This disorder is most prevalent in people aged 20–40 years.<sup>3</sup> Approximately 33% of the population have at least 1 TMD symptom, and 3.6–7.0% of the population have TMD with sufficient severity to seek treatment.<sup>3</sup> There is some evidence to suggest that anxiety, stress and other emotional disturbances exacerbate TMD.<sup>4</sup> As many as 75% of patients with TMD have a significant psychological abnormality.<sup>5</sup>

Most TMD symptoms resolve over time, but, for a significant number of patients, this may take a year or more.<sup>3</sup> Treatment is directed toward reducing pain and improving function. Many non-invasive therapies, such as self-care, physical therapy and appliance therapy, are commonly used for the treatment of TMD.<sup>3</sup> Pharmacological intervention has been used for many years, and the most effective pharmacological agents for the treatment of TMD include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, anxiolytics, muscle relaxants, antidepressants, anticonvulsants and benzodiazepines. However, we found only 1 relevant Cochrane study, which included 11 randomized controlled trials of pharmacotherapy for TMD.<sup>6</sup> In this article, we review the pharmacology and research supporting the use of a host of pharmacologic agents that have been prescribed for patients who have TMD. The decision to select any of

these agents depends on a full understanding of the drug's risks and benefits.

## Non-Steroidal Anti-inflammatory Drugs

The NSAIDs are a large group of drugs that inhibit cyclo-oxygenases, thereby preventing the formation of prostaglandins. Traditionally, they have been the drugs most commonly prescribed for pain in the orofacial region.<sup>4,7</sup> NSAIDs are indicated for mild to moderate acute inflammatory conditions in the TMJ and are generally beneficial for patients with acute TMJ inflammation resulting from acute disc displacement without reduction or acute trauma, for example.<sup>3</sup>

To achieve an anti-inflammatory effect in TMD, these medications should be taken for a minimum of 2 weeks.<sup>3</sup> NSAIDs are effective and widely available in over-the-counter formulations or by prescription. A number of NSAIDs, including ibuprofen, naproxen, diflunisal and ketorolac, have been shown to be effective for dental pain. No single NSAID has been shown to be superior to all others<sup>9</sup> and, therefore, if satisfactory pain relief is not achieved with 1 NSAID, a different NSAID would not be of benefit.<sup>3,8,9</sup>

The most important adverse effect of NSAIDs is their effect on the gastrointestinal (GI) tract. NSAIDs cause gastric erosion that can lead to ulcers and then gastric bleeding; this tends to be more severe in the elderly than in younger people.<sup>10</sup> In fact, up to 16 000 patients may die each year in the United States as a result of GI complications from NSAID therapy.<sup>11</sup> Therefore, prescribing NSAIDs in a patient with active GI disease is contraindicated. Naproxen and ibuprofen appear to be the safest NSAIDs with respect to the cardiovascular system, and ibuprofen has been shown to be relatively safe with respect to GI risk.<sup>8</sup> Another possibility for patients at risk of GI bleeding, provided there are no significant risk factors for myocardial infarction or cerebrovascular accident, is the COX-2 inhibitor celecoxib (200 mg twice a day), as it is much less likely to cause gastric bleeding.

In addition to severe adverse reactions, NSAIDs can interact with multiple medications and result in an unwanted effect. For instance, lithium clearance may be decreased by NSAIDs; NSAIDs may increase the serum concentration of lithium and, thus, cause toxicity.<sup>12</sup> Although it is not clear who is predisposed to this interaction, elderly patients are likely most susceptible.<sup>10,12</sup> Moreover, methotrexate may be displaced from its binding protein sites by NSAIDs. This action is generally not relevant clinically with the low doses of methotrexate commonly taken by patients with rheumatoid arthritis, who have normal renal function, but it is significant when methotrexate is used in high doses for cancer therapy.<sup>12</sup> Moreover, the combination of NSAIDs and angiotensin converting enzyme (ACE) inhibitors or loop diuretics has been shown to increase the risk of acute kidney injury<sup>13</sup>;

NSAIDs may also reduce renal blood flow, tubular excretion of drugs and renal prostaglandin production. When given for extended periods ( $\geq 5$  days), NSAIDs may attenuate the effect of antihypertensive drugs, such as diuretics, beta blockers and ACE inhibitors.<sup>12,14</sup> In addition, NSAID-induced inhibition of thromboxane synthesis decreases the ability of blood to clot, resulting in an increase in bleeding. When used with other drugs that also increase bleeding (e.g., warfarin), the likelihood of serious bleeding or complications of bleeding increases.

The efficacy of NSAIDs in the treatment of TMD was studied by Ta and Dionne.<sup>15</sup> In a randomized, double-blind, placebo-controlled trial, they compared the efficacy of celecoxib (100 mg twice a day), naproxen (500 mg twice a day) and placebo for 6 weeks. Compared with placebo, naproxen significantly reduced the symptoms of painful TMJ disc displacement. Celecoxib showed slightly better pain reduction than the placebo, but was not significantly effective for TMD pain. However, other studies comparing ibuprofen and piroxicam with placebo failed to demonstrate a decrease in symptoms among patients with chronic myogenous pain.<sup>16,17</sup> Meloxicam, another commonly used COX-2 inhibitor, may be prescribed at the rate of 7.5–15 mg/day for a minimum of 2 weeks and usually up to 4 weeks. A repeat of the prescription may be considered if the initial regimen is effective, but pain recurs when the drug is discontinued. At most, a 2-month regimen of NSAID use may be considered in consultation with the patient's family physician.

From a clinical perspective, the determining factor in the decision to prescribe an NSAID is based on correlating signs that we pick up on examination with the symptoms noted by the patient. In particular, patients will often use a single finger to point to the joint when describing the origin of pain (as opposed to a broader tracing of pain when muscle pain is indicated). Manual palpation of the joint will elicit a painful response. This will also occur when palpation occurs through the external auditory meatus. If pain and crepitus are noted, further radiographic investigation for degenerative joint disease is indicated.

## Opioids

The possibility of serious GI bleeding associated with chronic NSAID administration combined with the inconsistent efficacy of these drugs for some forms of TMD has led to a look at alternatives. Opioid analgesics have been used for the management of acute pain in dentistry for many years, and their effectiveness in the treatment of moderate to severe pain is well established.<sup>18</sup> In TMD, judicious use of these medications may occasionally be indicated for chronic moderate to severe pain when other drugs are found to be ineffective.<sup>4</sup>

The most common opioids considered for oral administration are codeine and oxycodone, with hydromorphone reserved for severe intractable pain. If the oral route is not a reasonable option, the fentanyl patch can be considered for those with training in its use.<sup>19,20</sup> Parenteral opioids have been used for TMD, particularly in association with arthrocentesis.<sup>21</sup> For instance, in a randomized double-blind study,<sup>22</sup> intra-articular morphine produced a significant increase in the pain threshold in the diseased joint.<sup>22</sup> It has been suggested that a peripheral subtype of the  $\mu$ -opioid receptor exists in the TMJ tissues, thus explaining the possible benefits of this treatment modality.<sup>20,23</sup> However, other studies have demonstrated no pain reduction with injectable opioids.<sup>24,25</sup>

Common side effects of opioid administration may include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance and respiratory depression. All of these are exacerbated in the geriatric patient population.<sup>10</sup> Combinations of opioids and other central nervous system (CNS) depressants, such as benzodiazepines, antidepressants and antipsychotics, may produce additive sedative effects; for instance, the concurrent use of alcohol and opioid analgesics, which are both CNS depressants, may cause increased sedation.

The use of opioids for chronic pain has been discouraged because of their potential for inducing tolerance and physical dependence and the concern over patients who may have a substance use disorder. Thus, prescription of opioids for the management of TMD should be restricted to clinicians with appropriate training in this modality. Furthermore, pharmacotherapy, involving opioids for chronic pain management, ideally should be done in consultation with the patient's physician to lessen the possibility of opioid misuse, abuse or diversion. Moreover, there is little or no evidence that long-term therapy for TMD is any better (or worse) than other treatments.

## Corticosteroids

Corticosteroids are drugs that closely resemble cortisol, a hormone produced by the adrenal glands. These potent anti-inflammatory drugs have been used to treat moderate to severe TMD. They have multiple actions, including blockade of phospholipase A2, thus decreasing the production of prostaglandins and leukotrienes.<sup>4,20</sup>

Corticosteroids may be injected directly into the TMJ, taken orally or applied topically in an attempt to reduce the pain and dysfunction associated with TMD. Numerous corticosteroid formulations are available for intra-articular injection, ranging from solutions of soluble agents to suspensions of triamcinolone hexacetonide and other relatively insoluble steroids.<sup>26</sup> Traditionally, intra-articular corticosteroid formulations are often diluted with a local anesthetic before injection into the TMJ.<sup>26-28</sup> It has been suggested that this

approach decreases the risk of soft tissue atrophy and other complications.<sup>26</sup>

In a controlled study of adults with TMJ arthritis, a single intra-articular injection of methylprednisolone diluted with lidocaine significantly reduced TMJ pain for 4–6 weeks.<sup>28</sup> Another study using intra-articular steroids, including 0.7 mL of methylprednisolone acetate combined with local anaesthetics in children or 1 mL triamcinolone acetonide in adults significantly reduced pain and increased function.<sup>27,29</sup> Finally, in a 4-week study of 3 treatment groups totalling 41 patients with TMD, a corticosteroid, hyaluronic acid or placebo was injected directly into the TMJ. All groups demonstrated improvement in symptoms, but the corticosteroid and hyaluronic acid groups showed a greater decrease in the number of painful muscles and a remarkable increased interincisal opening.<sup>30</sup>

Although injectable corticosteroids have been shown to be very beneficial for pain reduction in TMD, they are associated with various side effects, such as acute adrenal crisis, hypertension and electrolyte anomalies, as well as damage to the fibrous layer and bone resorption.<sup>31</sup> Although systemic corticosteroids are not commonly prescribed in the treatment of TMD because of their side effects, it has been recommended that oral corticosteroid be used together with an NSAID, such as naproxen.<sup>3</sup> Patients are usually advised to start the naproxen on day 4 of the oral corticosteroid use, as this has been shown to decrease the adverse GI effects at the beginning of treatment when the corticosteroid dose is high, and it extends the anti-inflammatory effect.<sup>3</sup>

## Muscle Relaxants

Centrally acting muscle relaxants have frequently been used in the treatment of TMD.<sup>32</sup> They are thought to reduce skeletal muscle tone and, thus, are often given to patients with chronic orofacial pain to help prevent or alleviate the increased muscle activity attributed to some forms of TMD.<sup>7</sup> The patient typically takes these agents at bedtime because of associated drowsiness. The most common muscle relaxants are carisoprodol, cyclobenzaprine, metaxalone and methocarbamol.<sup>20</sup> Carisoprodol, one of the first drugs of this class, was originally used frequently; however, several studies have demonstrated that carisoprodol is no more efficacious than placebo.<sup>33,34</sup>

Many consider cyclobenzaprine the drug of choice for generalized chronic muscle pain, as it provides significant relief from muscle pain and enhances the quality and quantity of sleep. Although this drug has not been shown to be beneficial in directly reducing TMJ pain symptoms, several studies report its superiority to placebo in treating muscle spasms in the cervical and lumbar regions, suggesting that it may be useful for patients with TMD.<sup>20,35,36</sup>

Moreover, in a randomized controlled trial,<sup>37</sup> cyclobenzaprine was superior to placebo or 0.5 mg clonazepam when added to self-care and education in the management of TMD.<sup>38</sup>

These drugs must be used with caution as they may cause significant sedation. Cyclobenzaprine's chemical structure is similar to that of tricyclic antidepressants (TCAs), and it shares many of the properties of TCAs as well. Therefore, this medication is contraindicated for patients with hyperthyroidism and congestive heart failure. Furthermore, it should be avoided during the acute phase of recovery from myocardial infarction and by patients with arrhythmias. Also, cyclobenzaprine may have life-threatening interactions with monoamine oxidase inhibitors (MAOIs), and it may enhance the risk of seizure in patients taking tramadol. Evidence suggests that a very low dose of cyclobenzaprine may still provide positive effects in terms of sleep physiology and pain alleviation.<sup>39</sup> Therefore, to reduce the sedating side effects, cyclobenzaprine is commonly prescribed at a lower dose (10 mg at bedtime) when treating TMD compared with that used to manage acute muscle spasm. In fact, in some cases, patients are encouraged to use fractions of the low dose to reduce the sedating side effects.

The usual course of treatment would encompass a 30-day trial period followed by a 2-week washout period before the patient is reassessed; this allows the clinician to determine the effectiveness of the medication by assessing the patient "on" and "off" the drug. If benefits are noted, a repeat of the prescription for up to 2–3 months may be necessary; however, long-term therapy using cyclobenzaprine should be co-managed with the patient's physician whenever possible.

## Antidepressants

Antidepressant drugs have been used for more than 3 decades for the management of pain arising from TMD. Among these medications, TCAs appear to be most effective<sup>37</sup>; however, selective serotonin reuptake inhibitors (SSRIs) have also been reported to reduce orofacial pain.<sup>40</sup> These drugs are excellent first-line medications for TMD patients who may be refractory to splint therapy.<sup>41,42</sup> TCAs are the most-studied medications in the management and control of chronic pain in the orofacial region.<sup>43,44</sup> Moreover, many patients who suffer from chronic pain often have comorbid depression and, in many instances, some type of disturbance in sleep patterns.<sup>43,44</sup> Thus, pain may be decreased indirectly because of a change in these patterns, especially among patients with depleted serotonin levels in the CNS.<sup>37,44,45</sup>

Numerous reviews of randomized, controlled trials have concluded that TCAs exhibit clear analgesic efficacy in a number of chronic pain conditions.<sup>41–44</sup> For instance, a

double-blind study<sup>37</sup> demonstrated that amitriptyline (25 mg/day) is effective in reducing pain and discomfort among patients with chronic TMJ pain.<sup>37</sup> Increasing the dose of amitriptyline to 50–75 mg/day did not produce an increase in analgesic effects.<sup>37</sup> Similar results were seen in other studies that investigated the efficacy of amitriptyline.<sup>46–48</sup> However, other studies<sup>44</sup> proposed that the effects of amitriptyline were no greater than those observed with a placebo, attributing reported differences to a psychogenic factor present in many cases and to the difficulty patients have measuring subjective sensations of pain and discomfort.<sup>44</sup> When used to treat TMD-related pain and discomfort, the doses of TCAs are usually much lower than those used to control depression.<sup>44</sup> For instance, 25–50 mg/day of amitriptyline has been suggested.<sup>44,49</sup>

Another group of antidepressants commonly used are the SSRIs. Introduced in the late 1980s, these drugs became the first line of treatment for depression because of their favourable side effects profile compared with TCAs. SSRIs block neuronal transport of serotonin leading to increased synaptic serotonin, which in turn stimulates a large number of postsynaptic serotonin receptors.<sup>50</sup> Among the SSRIs, citalopram and paroxetine have been shown to relieve neuropathic pain symptoms.<sup>51,52</sup> Fluoxetine, used in 98 patients with idiopathic facial pain, was found to be more effective than placebo.<sup>53</sup> Furthermore, escitalopram reduced pain in patients with painful polyneuropathy.<sup>54</sup> Finally, in a case report of 2 patients, SSRIs were beneficial in reducing TMD pain complaints (as 1 method of dental therapy).<sup>40</sup>

Although the exact mechanism of the analgesic action of these drugs is as yet unknown, the analgesic effect of TCAs may be a result of serotonin and noradrenaline reuptake inhibition at the synaptic level in the CNS.<sup>20,41</sup> Blocking these 2 amines increases their concentration and availability in the synaptic space at the nerve endings in the posterior horn of the spinal cord (which is involved in the transmission of pain), thus, favouring or prolonging inhibitory action in the transmission of this pain.<sup>44</sup>

The TCAs, amitriptyline, nortriptyline and desipramine, are frequently prescribed in the treatment of TMD pain. TCAs are associated with certain adverse events, which include sedation, dizziness, blurred vision, constipation and dry mouth. These drugs also block the reuptake of catecholamines and, as such, may increase catecholaminergic neurotransmission.<sup>4</sup> Thus, the administration of an exogenous catecholamine, such as epinephrine, as a dental local anaesthetic may cause adverse cardiovascular events, and the amount of epinephrine should be limited to 0.04 mg per appointment for patients taking TCAs.<sup>4</sup> Moreover, TCAs should be avoided among patients taking MAOIs, as this combination may lead to lethal serotonin syndrome, consisting of confusion, fever, ataxia and severe hypertension.<sup>20</sup> These drugs should also be used with caution for patients

with cardiac disease and among the elderly.

SSRIs have been associated with fewer anticholinergic, antihistaminergic and antiadrenergic effects compared with the TCAs, although paroxetine has a relatively high anticholinergic potency among SSRIs.<sup>50</sup> However, these drugs cause GI disturbances, such as nausea and vomiting, headache, sexual dysfunction, dry mouth and sweating.<sup>50</sup>

Overall, although antidepressants are quite effective, the dental community should use them only with caution. Patients who would benefit from this mode of therapy should be comanaged with their physician to ensure that they are medically stable enough to engage in long-term treatment. The physician should also be the primary practitioner managing any side effects or reactions that may arise.

## Anticonvulsants

Anticonvulsant drugs are widely used to treat neuropathic pain. These medications act at several sites that may be relevant to pain, but the precise mechanism of their analgesic effect remains unclear. These agents are thought to inhibit neuronal excitation and enhance such inhibition.<sup>55</sup> Relevant sites of action include voltage-gated ion channels (i.e., sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate and N-methyl-D-aspartate and the inhibitory receptors for gamma-aminobutyric acid (GABA) and glycine.<sup>55</sup>

Gabapentin and pregabalin have been used for the treatment of TMD. Both are synthetic compounds structurally related to GABA, the primary inhibitory neurotransmitter in the CNS. Despite their name and structural similarities, neither agent exerts its mechanism of action through GABA receptors.<sup>56,57</sup> Rather, these drugs interact with the  $\alpha 2\delta$  subunit of voltage-gated calcium channels,<sup>58</sup> thereby reducing neurotransmitter release and attenuating post-synaptic excitability, which may explain their clinical effect of decreased nociception.<sup>56</sup>

Gabapentin has been widely used because of its efficacy in several placebo-controlled trials of various chronic pain syndromes.<sup>20,59,60</sup> Moreover, Kimos and coworkers<sup>61</sup> demonstrated that gabapentin significantly reduces TMD pain along with decreased tenderness in the masticatory muscles (specifically the temporalis and masseter muscles), compared with placebo.<sup>61</sup> Pregabalin has been shown to be effective in randomized clinical trials for a wide array of painful neuropathic conditions.<sup>62-65</sup> However, to date, no studies have been done to demonstrate the effect of pregabalin on TMD pain.

Pregabalin and gabapentin are generally well tolerated and associated with transient mild to moderate adverse effects, which are dose dependent.<sup>20</sup> Dizziness and somnolence are most frequently reported. Other less-common

adverse effects are dry mouth, peripheral edema, blurred vision, weight gain and inability to concentrate.<sup>20</sup> It has been proposed that anticonvulsants should be used as adjuvant analgesics in TMD, particularly for patients who have a history of failed TMJ surgeries or those who have long-standing unremitting pain.<sup>20</sup>

## Benzodiazepines

Benzodiazepines are commonly prescribed for the treatment of acute muscle spasm and sleep disorders. However, this drug class is associated with numerous adverse properties, including tolerance and dependence, which contraindicate their long-term use in the management of TMD or other conditions.<sup>66</sup> These agents act on specific benzodiazepine receptors, which are part of the GABA receptor complex that mediates inhibitory synaptic transmission throughout the CNS. Benzodiazepines enhance the response to GABA by facilitating the opening of chloride channels and, thus, they cause hyperpolarization. These agents have been used primarily as anxiolytics; however, they have been reported to induce both muscle relaxation and sleep. Also, benzodiazepines have been used as anticonvulsant medications, and parenteral benzodiazepines have been used to manage status epilepticus.

Several studies have demonstrated the superiority of these drugs to placebo in double-blind trials for the treatment of TMD. For instance, Singer and Dionne<sup>16</sup> reported that patients taking diazepam displayed a significant reduction in their chronic jaw pain compared with placebo. Furthermore, Harkins et al.<sup>67</sup> showed that 1 month of clonazepam therapy reduced pain associated with TMD. However, in another study, where triazolam was compared with placebo, no pain reduction was found, but sleep improved significantly.<sup>68</sup>

Regardless of the positive outcome of some studies, the use of benzodiazepines for TMD has been discouraged because of numerous adverse drug reactions, such as drowsiness, confusion, amnesia and impaired coordination. Also, tolerance to and physical dependence on benzodiazepines can develop if these drugs are given over a prolonged period. Abrupt discontinuation may result in withdrawal symptoms, including anxiety, agitation, restlessness, insomnia and seizures. Contraindications to their use include allergy, myasthenia gravis and acute narrow-angle glaucoma.<sup>4</sup>

A number of benzodiazepines have been shown to interact with numerous drugs, as these medications are CYP 4503A4 substrates. Thus, concomitant foods, such as grapefruit juice, and drugs, such as azole antifungals, erythromycin and the calcium channel blockers that inhibit the 3A4 isoform, can significantly reduce the metabolism of benzodiazepines and, thus, lead to elevated levels in the blood and enhanced CNS depression.<sup>4,20</sup>

As in the case of opioid use to manage TMD, benzodiazepines have the potential for misuse, abuse and diversion. They should be considered only by those with appropriate training and in consultation with the patient's physician.

## Conclusions

Many modalities have been proposed for the treatment of TMD, including occlusal splints, physiotherapy and pharmacological interventions, to name just a few. Despite the wealth of analgesic options, treating TMJ-related pain is still a significant challenge in dental practice. Given the lack of good randomized controlled trials, clinicians are left to use the best evidence available, which shows that NSAIDs are likely effective but may carry significant risks such as gastric bleeding in some populations and that pharmacotherapies such as TCAs may have some effect. There is an urgent need for high-quality studies to better define the risk-benefit of pharmacotherapy for TMD patients. Finally, given the chronicity of TMD, there must be appropriate training and a full understanding of the risks and benefits of any drug considered for its management.

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