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Challenging Case

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Comorbid Orofacial Musculoskeletal Pain and Central Sensitization Treated with Tapentadol: A Case Report

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CHALLENGING CASE

A 53-year-old female presented with a 15-year history of right facial pain; the consequence of a blow to the jaw. She presented to an Oral Medicine specialist with the complaints of right ear, masseter and temporalis muscle pain, rated at 10/10 on a 10-point numerical rating scale, with the lowest and highest word anchors being “no pain” to “worst pain imaginable” respectively (Hjermstad et al., 2011). The quality of pain was throbbing and burning. It was aggravated by jaw function and cold air. She reported having depression and anxiety as a result of her pain and had difficulty in initiating and maintaining sleep as her “mind races”. Her self-report of depression, anxiety and sleep disturbances were recorded using a 9-item Patient Health Questionnaire (PHQ-9) (Schiffman et al., 2014). A significant psychosocial history of anxiety and depression, for which she was under the care of a psychologist, was noted. She was not using any medications, nor undergoing psychological care when she presented to the Oral Medicine specialist. A review of head and neck computerized tomography obtained at the onset of her pain excluded underlying pathology. Anterior disc displacement with reduction of the right temporomandibular joint (TMJ) was noted on magnetic resonance imaging; however, this finding did not correlate with the patient’s pain. Her injury was deemed primarily myogenous.

Keywords: Musculoskeletal pain, Tapentadol, Central sensitization, Chronic masticatory myalgia, Myogenous pain
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1. CHALLENGE IN DIAGNOSIS AND TREATMENT

Over the years, the patient was treated by an oral and maxillofacial surgeon, an otorhinolaryngologist, a number of dentists, physiotherapists, and chiropractors. Prior treatments included occlusal adjustments, splint therapy, non-steroidal anti-inflammatory medications, paracetamol, codeine, gabapentin, pregabalin, opioids and botulinum toxin, all without significant benefit. She also underwent TMJ manipulation and soft tissue therapies performed by a chiropractor and physiotherapist respectively with only short-term benefits. After much consultation with an Oral and Maxillofacial surgeon regarding her surgical options, she underwent right TMJ arthrocentesis anticipating benefit from this treatment. Unfortunately, there was no change in her pain presentation.

The cranial nerve examination revealed allodynia involving the right mandibular division of the trigeminal nerve (CN V_3). There was no apparent local or systemic pathology that provided an explanation for her allodynia. Her maximum mouth opening was 30mm with right and left lateral movements measured at 8mm respectively. There was a soft-end feel at maximum opening and she was able to gradually increase her opening to 44 mm with pain localized to the right masseter and temporalis muscles. Her protrusive movement was 7mm. Severe pain was reported, and the patient withdrew from palpation of the right masseter and temporalis muscles. An asymptomatic right mid-opening TMJ click was noted. The findings were consistent with myogenous temporomandibular disorder based on the diagnostic criteria for temporomandibular disorders (DC/TMD) (Schiffman et al., 2014).

The diagnosis of myogenous pain and local myalgia was established. Myogenous pain was based on the patient's report of severe pain and withdrawal, allodynia and hyperalgesia upon touch and palpation of the masticatory muscles. Central sensitization was established on the patient's complaint of allodynia and hyperalgesia in the distribution of CN V_3.

Nortriptyline, a better-tolerated tricyclic antidepressant drug with both serotonergic and noradrenergic effects, was recommended, at 10mg at bedtime, which was slowly increased to 50mg at bedtime. The occasional use of diclofenac 600mg for pain flare-up was also prescribed. Diclofenac use has been shown to have a significantly greater reduction in TMJ and myogenous pain as compared to placebo, and its use has been suggestive as a complement to other treatment of acute TMJ pain (Ekberg et al., 1996). The combination of these medications minimally decreased her pain to 7/10.

Given the persistence of pain and associated central sensitization, the patient was subsequently prescribed a trial of tapentadol 50mg slow release twice daily. The rationale for selecting this medication was based on its dual mechanism of action that involves mu-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI). By simultaneously engaging and modulating both the opioidergic and monoaminergic systems of pain control, it was anticipated that tapentadol would be effective for her diagnoses of myogenous pain and central sensitization.

1.1 Clinical outcome with use of tapentadol

Upon review, 4 weeks after the commencement of tapentadol 50mg slow release twice daily, the patient reported a decrease in pain from 7/10 to 2/10. The clinical examination revealed near resolution of allodynia of the right CN V_3. She was able to perform masticatory function and her mandibular range of motion returned to normal without significant pain. Moreover, her maximum mouth opening measured at 58mm, left, right and protrusive excursive jaw function were 10mm, 13mm and 12mm respectively.

Diclofenac was discontinued. She continued taking nortriptyline 50mg at bedtime for its sleep aid properties, which has no known interactions with tapentadol. At 2-year follow-up, her response to tapentadol slow release was maintained, and she had ceased nortriptyline 50mg. The medication was well tolerated. The patient only reported feeling mildly tired at times, and experienced occasional abdominal discomfort. She continues to be on tapentadol and will likely be on it long term.

There were a several attempts to taper down of the dosage and/or frequency of tapentadol intake, however her pain increased accordingly. She retains a psychologist with the option of an appointment if necessary.

2. DISCUSSION

The diagnosis of orofacial pain must be based on an understanding of the potential etiology and mechanism of pain, and not simply on the symptoms and location. Compounding this most complex issue is the paucity of knowledge, for which current research is actively expanding.

Though our knowledge base falls short of being complete, orofacial pain clinicians must always have a current understanding of the changing concepts of pain and potential mechanisms that create these experiences.

Orofacial pain may be nociceptive-inflammatory, neuropathic or a combination of both mechanisms.

Treatment should therefore focus on treating the mechanism of the pain rather than the location and intensity, whilst appreciating our limitations in understanding this field.

As many conditions have mechanisms not yet elucidated, at best we may only provide interventions for the symptoms, but we should also appreciate the personal and psychologic factors accompanying the pain experience.

This case highlights this approach whereby the patient likely had initial musculoskeletal pain.

However, with chronicity and sensitization, a state of amplification and alteration of pain signals developed, which did not correlate with the initial tissue injury (Woolf, 2011; "The way of the Pain Signal-from the Periphery to the CNS", 2011). In sensitization, there is an overall increased excitabil-

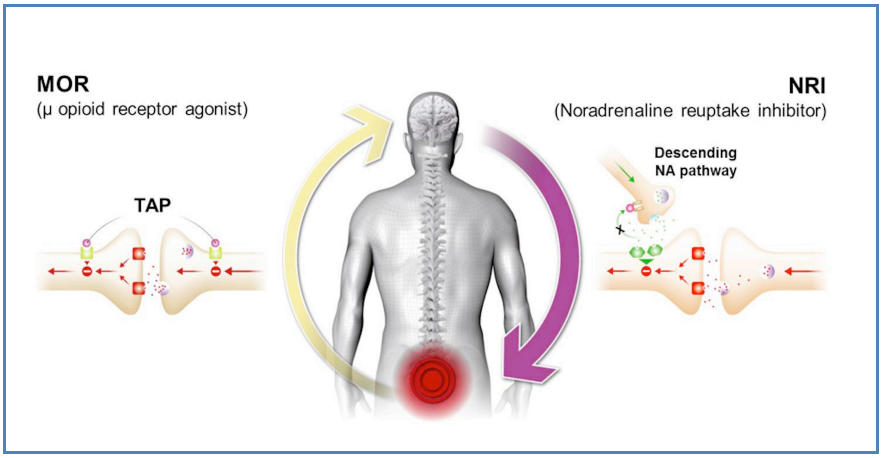

Figure 1. The dual action of tapentadol involves engaging both the opioidergic and monoaminergic systems by u-opioid receptor agonist (MOR) and noradrenaline reuptake inhibitor (NRI) respectively, hence effective in the treatment of chronic musculoskeletal and neuropathic pain. (Courtesy of Seqirus™)

ity of central and peripheral nociceptive circuits and reduced inhibition leading to a shift of the sensitivity of the pain system. This is expressed as a reduction in the pain threshold, a prolonged response to noxious stimuli, and an expansion of the receptive fields resulting in pain from non-injured tissue.

Hence, previously innocuous stimuli can trigger pain (allodynia) and noxious stimuli can result in prolonged and heightened pain sensitivity (hyperalgesia) (Woolf, 2011).

Central sensitization is partially the result of activation of N-methyl-D-Aspartate (NMDA) receptors on post-synaptic dorsal horn neurons as a result of previous tissue injury. Also, in central sensitization, primary afferents exhibit down-regulation of the inhibitory neuropeptide, galanin and loss of inhibitory interneurons containing endogenous opioids, GABA and glycine.

Other changes at the molecular level include alteration of gene expression and hence hyperexcitability of spinal neurons; release of proinflammatory compounds by activated microglia and astrocytes; upregulation of postsynaptic transcription factors and transmembrane signaling molecules; suppression of inhibitory fibers and augmentation of descending facilitation from the brainstem (Latremoliere & Woolf, 2009).

Hence in chronic pain states, there is a disturbed balance between excitatory and inhibitory systems in the central nervous system. Thereby one sees a mismatch between stimulus and response (hyperalgesia), but also a disruption of the normal specialisation of the somatosensory system with aberrant convergence leading to allodynia (Latremoliere & Woolf, 2009; Devor, 2013).

Initially the patient was treated with nortriptyline for her central sensitization and to address her sleep disturbance. Diclofenac was used for treatment of musculoskeletal pain for break-through pain. The result of negligible improvement in her pain with these medications lead to the use of tapentadol to be issued.

Tapentadol was effective in considerably alleviating the patient's symptoms without side effects in this case. The medication acts by two different and complementary mechanisms, which will be discussed.

2.1 Mechanism of Action & Pharmacokinetics

Tapentadol is a centrally acting analgesic with two synergistic mechanisms of action: mu-opioid agonism and noradrenaline reuptake inhibition (Wild et al., 2010; Mercadante et al., 2012). Therefore, tapentadol simultaneously decreases excitatory and strengthens inhibitory system of pain modulation. Reduced excitation is achieved by the MOR agonism, in a similar fashion to conventional opioids, however with a much lower affinity to the receptor ($1/18^{th}$ of morphine) (Vadivelu et al., 2013).

The inhibition of noradrenaline reuptake increases synaptic noradrenaline concentrations, thereby strengthening the effect of descending pathways with an inhibitory effect on pain transmission (Figure 1) (Xu et al, 2010; Hartrick et al, 2009a). The synergistic effect explains the efficacy, in spite of the minimized degree of opioid adverse effects such as nausea, vomiting and constipation as well as low toxicity and low risk of abuse and diversion.

Furthermore, its effect is independent of metabolic pathways, as it has no active metabolites (Hartrick et al, 2009a; Hartrick, 2009b). By having limited protein binding and no significant microsomal enzyme induction or inhibition, tapentadol has a limited potential for drug-drug interactions (Raffa et al., 2012; Hartrick & Rozek, 2011). In contrast to tramadol, it has no relevant serotonergic effect.

2.2 Dosing

Tapentadol may be dispensed as either an extended-release formulation or immediate-release formulation. The dose may be titrated from 50mg up to 250mg twice daily.

2.3 Efficacy and Side Effects

There is scientific evidence supporting the efficacy of tapentadol in the treatment of both musculoskeletal and neuropathic pains.

An open-label, multicenter study demonstrated significantly greater improvements in pain intensity measures for patients with severe chronic osteoarthritis knee pain treated with tapentadol ER (50-250mg twice daily), than patients who were treated with opioids (Steigerwald et al., 2013). Interestingly, the study also showed that the improvements observed in pain intensity scores in the tapentadol ER group were accompanied with improvements in anxiety, depression, quality of life, and health status (Steigerwald et al., 2013).

In another randomized double-blind, parallel group and placebo controlled study, 395 patients with painful diabetic peripheral neuropathy were treated with either tapentadol 100–250mg extended release twice daily or placebo. The tapentadol group had significantly better pain relief, whereby 64% of the tapentadol group reported their pain status as "much" or "very much" improved compared to 38% of placebo patients (Schwartz et al., 2011).

Tapentadol immediate release and extended release have been found to be non-inferior to oxycodone immediate release and controlled-release in a number of trials (Cepeda et al., 2012; Cepeda et al., 2014). The significant improvement in the patient's pain presentation in this case is likely due to the drug's ability to effectively down regulate ascending excitatory pain pathways while strengthening descending inhibitory pathways in a synergistic fashion. The initial masticatory muscle injury was no longer considered the primary mechanism of pain. Hence, tapentadol was used to treat the allodynia and hyperalgesia with good effect.

Common side effects with the use of tapentadol include nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence (Buynak et al., 2010). However, compared to conventional opioids, tapentadol has lower side effects of nausea, vomiting and constipation (Stegmann et al., 2008; Buynak et al., 2010).

2.4 Potential for Drug Abuse

Patients on tapentadol immediate release were less likely to receive an abuse diagnosis compared to oxycodone (Wild et al., 2010; Cepeda et al., 2014). Also, opioid naïve patients who received tapentadol immediate release were less likely to "doctor shop" when compared to those who were prescribed oxycodone immediate release (Steigerwald et al., 2013).

Withdrawal symptoms from the use of tapentadol have been found to be low compared to similar pain medications currently available (Vadivelu et al., 2013; Sanchez Del Águila et al., 2015). Of particular relevance is the lack of interest in tapentadol on drug abuse forums.

In a study that investigated seven recreational drug use internet forums between January 1, 2011 and September 30, 2012, found only 0.03% of posts were related to tapentadol which was significantly less than that of other similar drugs (McNaughton et al., 2015).

Last, but not least, tapentadol seems to be much safer in overdose than conventional opioids; despite extensive use in the USA and Europe over many years, only 2 fatal overdoses have been reported in the literature (Kemp et al., 2013; Franco et al., 2014).

3. CONCLUSIONS

Patients often present to the dentist with diffuse chronic pain complaints that mimic odontalgias and temporomandibular disorders. In this case, the patient presented to a dentist with a long history of chronic orofacial pain in spite of multiple past treatments, which included invasive procedures.

Establishing a correct diagnosis, based on an understanding of pain mechanisms prior to treatment is essential when treating patients with orofacial pain. Here, the patient's initial musculoskeletal injury resulted in long-lasting noxious input and subsequent central sensitization. There was a transition from acute musculoskeletal pain to chronic pain due to central sensitization. The recognition of this transition and alteration of the medication regimen led to effective treatment.

Recognition of the symptoms and clinical findings and how they relate to the mechanism of the complaints in order to arrive at an accurate diagnosis will avoid unnecessary, often irreversible and costly treatments.

Unlike dental pain, treating the location of the pain may not necessarily alleviate the pain complaint. Hence dentists should consider the mechanism of pain that is in play and use treatments that target the pain mechanism. Although the initiating pain mechanism in temporomandibular disorders may be nociceptive-inflammatory in origin, with chronicity, central sensitisation may develop.

This case presents most likely such a change in pain mechanisms with chronification. It highlights the need for an accurate diagnosis and the appropriate use of pharmacotherapy including medications such as tapentadol for the treatment of chronic nociceptive-inflammatory pain with a central sensitization component. With the limitations of a single case report, future studies should evaluate the use of tapentadol in orofacial pain in well controlled randomized clinical trials.

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Conflict of Interest

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Tapentadol.

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