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PHARMACOLOGICAL MANAGEMENT OF TEMPOROMANDIULAR JOINT DISORDERS – A REVIEW

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ABSTRACT:

Patients frequently visit dentists with main intention of pain relief. Among various causes of pain, the temporomandibular disorder representing a group is one of them. Every dental practitioner should be aware of these disorders and the mode of treating them. Pharmacology usually represents the first stage of management or as an additional treatment for these disorders. Commonly used pharmacotherapeutic medicines include analgesics, corticosteroids, muscle relaxants, antidepressants and sedative-hypnotics. Analgesics such as naproxen, diclofenac, ibuprofen and corticosteroids such as methylprednisolone, triamcinolone acetonide are beneficial in relieving pain of acute and chronic temporomandibular disorders associated with inflammation. Muscle relaxants such as cyclobenzaprine and chlorzoxazone can be given for pain of temporomandibular disorders associated with muscular tensions and spasms. Sedative- hypnotics are helpful to patients who have muscular tension together with poor sleep patterns. Antidepressants like amitriptyline are effective in chronic myofascial pain syndrome and in patients with coexistent depression and tension headaches. Benzodiazepines such as clonazepam and diazepam are helpful in chronic myogenous jaw pain. The article attempts to review the pharmacological management of temporomandibular disorders in a concise manner so as to be helpful for medical and dental practitioners.

Key words: Pain, Pharmacotherapy, Temporomandibular disorders
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INTRODUCTION:

Dental practitioners routinely encounter patients with pain arising from several sources like bone, joint, muscles, nerves, and somatic structures. It may be temporomandibular dysfunction as a result of myofascial, neurologic, bone, or joint derangements; Tooth pain as a result of dentin, enamel, pulpal, or periapical defects; atypical odontalgia; pain or burning sensations in the tongue; altered tongue sensations or cracked tooth syndrome. Pharmacology is a cornerstone in the treatment of pain and is aimed towards the source and the nature of pain [1]. The term "temporomandibular disorders" (TMD), is a collective term embracing a number of clinical problems that involve the masticatory musculature, the temporomandibular joint (TMJ) and associated structures, or both [2, 3]. These group of disorders are characterized by facial pain in the region of the TMJ and/or the muscles of mastication; limitation or deviation in the mandibular range of motion, and TMJ sounds during jaw movement and function; headache; generalized tightness around face in the morning and Otalgia [4, 5]. Category 11 of International Headache society (IHS) classification includes temporomandibular joint disease and disorders of teeth, jaws, and related structures [5]. They are frequently associated with acute or persistent pain, and the patients often suffer from other painful disorders. The chronic forms of TMD pain often adversely affects the work or social interactions, resulting in depression, feeling of worthlessness and an overall reduction in the quality of life [6]. Pharmacologic therapy can be an effective method of managing symptoms associated with many TMDs. Medications in conjunction with appropriate physical therapy and definitive treatment can offer the most complete approach to many of these problems [6]. Anxiolytics are indicated for acute TMD pain; Non-Steroidal Anti-inflammatory drugs (NSAIDs), muscle relaxants, and local anesthetics may be used for both acute and chronic conditions; and the tricyclic antidepressants are primarily indicated for chronic orofacial pain management [7]. Treatment of TMD patients initially should be based on the use of conservative, reversible, and evidence based therapeutic modalities. Symptoms with TMDs have been observed to improve or resolve over time. Many conservative modalities of treatment provide symptomatic relief, have less risk of adverse effects and are nearly as effective as the invasive form of treatments [6]. Pharmacological intervention is usually considered an adjunctive therapy because more definitive treatments typically are used to correct the underlying pathophysiological process. Pharmacotherapy often is the primary approach in treating depression and the inflammatory processes that are frequently associated with temporomandibular disorder [8]. The pharmacologic management of TMDs rests on principles such as: demonstrated

efficacy, an acceptable side effect liability, and safety when given for prolonged periods [9]. The commonly used pharmacologic modalities used for treatment of TMDs broadly include analgesics, corticosteroids, antidepressants, muscle relaxants and sedative-hypnotics.

Non-steroidal anti-inflammatory drugs [10]:

Non-steroidal anti-inflammatory drugs (NSAIDs) represent first-line drugs for treating TMD pain. Patients having painful disc displacement, capsulitis, synovitis and myositis [11], musculoskeletal pain, arthritis [10], masticatory myalgia and myofascial pain associated with the TMJ may benefit from these drugs [12]. They are particularly indicated for joint pains secondary to inflammation and painful articular disorders [2, 13]. NSAIDs are considered effective for acute postsurgical dental pain and chronic arthritic pain. A study by Ta and Dionne [14] showed that in patients with TMJ disc displacement, pain significantly reduced with naproxen 500mg taken twice daily for 6 weeks. Also maximal comfortable mouth opening improved in these patients: but there was approximately 40% increase in dyspepsia and pain with naproxen [14]. These groups of drugs should be discontinued after 7-10 days of use, if they fail to achieve the therapeutic goal or patient manifests serious side effects [12]. Topical diclofenac formulated with dimethyl sulfoxide applied four times a day is found to be equal to oral diclofenac sodium 50mg administered twice a day in subjects who have pain and tenderness due to joint osteoarthrosis. [15] A study found that treatment of muscular TMD patients with sodium diclofenac 50mg twice a day promoted higher analgesia when associated to an occlusal splint [16]. NSAIDs are toxic when administered chronically at relatively high doses.

Patients should be monitored very closely during first few weeks of treatment. Chronic use of highly selective cyclooxygenase-2 (COX-2) inhibitors may cause gastrointestinal (GI) events including ulcerations, perforations, and bleeds, than nonselective or semi-selective NSAIDs. Users of NSAIDs have a threefold greater risk of developing serious adverse GI events than nonusers, and the risk is greater in patients older than 60 years of age [17]. In addition, decreased renal function leading to water and sodium retention with concomitant hypertension has been observed in patients taking simultaneous antihypertensive drugs with these drugs. NSAIDs also carry increased cardiovascular risk, especially in elderly, in patients with hypertension, coronary artery and atherosclerotic disease, coronary artery bypass surgery and in patients with previous cardiovascular events.

Chronic pain patients taking antidepressant drugs concomitantly with NSAIDs have up to 16-fold increase in the risk for upper GI bleeds [10, 12]; they should not be used in asthma patients [18].

Corticosteroids:

Corticosteroids are powerful anti-inflammatory agents that can be administered orally or injected directly into the joint space. The primary clinical indication is synovitis that is not infectious, degenerative joint diseases and poorly responding to NSAIDs [9, 18]. They can also be used in acute, generalized muscle and joint inflammation associated with polyarthritides [7]. A 6-day methylprednisolone followed by 3 to 6 weeks of NSAID therapy in TMJ closed lock patients works equally compared to arthroscopy or open joint therapy in reducing jaw pain and dysfunction. Intra-articular steroids containing 0.7mL of methylprednisolone acetate 40mg/mL combined with local anesthetic in children or 1.0mL of triamcinolone acetonide or 1.0mL triamcinolone hexacetonide in adults significantly reduces pain and improves function in TMD arthritis [19, 20].

Schindler et al [21] discovered that intra-articular glucocorticoid injections used in a wrong way caused severe destruction of the joint. Oral methylprednisolone followed by NSAID's for 3-6 weeks are effective with rehabilitation in TMJ closed lock patients [10, 22]. Corticosteroid and hyaluronic acid injected directly into TMJ decreases muscular pain and results in marked increase in the ability to open the mouth [22]. In addition, intra-articular corticosteroid injections and follow up for 8 years, evidenced improvement in clinical signs of TMD together with radiographic findings, suggesting remineralization of areas of condylar erosion [23]. Iontophoretic administration of steroids will result in high drug levels at the site of affected or painful TMJ, by applying an electric current to ionized drug solutions. Reid et al. found that iontophoresis with dexamethasone in a lidocaine vehicle in patients with TMD showed improvement and reported less pain with improved range of motion [24]. However this mode of drug delivery should be used only for severe cases and frequent injections must be avoided. Aggressive use of intra-articular steroids can cause articular cartilage destruction, infection and disease progression. Long term use may promote destruction of joint tissues [8]. Furthermore, oral corticosteroid use should be limited to no more than 2 weeks because of risks of decreased resistance to infection, elevations in blood glucose, osteoporosis, and suppression of hypothalamic-pituitary-adrenal axis. Patients having severe disc interference disorders and inflammatory conditions such as capsulitis, synovitis, and TMJ osteoarthritis/ rheumatoid arthritis, may benefit the most from this category of drugs.

Sodium hyaluronate intracapsular injection has been suggested for the treatment of TMJ articular disease. Its use following arthrocentesis may be helpful in reducing pain [7]. Hyaluronic acid injections are reliable in rheumatoid arthritis. It is also useful in painful disk displacement with reduction [25].

Opioids [11]

Opioid therapy should be considered only when: There is inadequate pain relief from prior nonopioid therapy; there is negative history of substance abuse; a confirmation that the pain being treated is of physiologic rather than psychologic origin; both patients and doctors are willing to adhere to an "opioid contract" between the doctor and patient which includes compliance with a scheduled administration of an oral opioid and close clinical follow-up [26].

Opioid should not be used as first-line drugs in patients with TMD. Also one should be aware of drug-seeking patients complaining of TMD pain. Opioids are indicated in palliative form when patient has severe unbearable TMD pain and is resistant to other modes of treatment [12]. However administration of opiates in patients with intractable TMD pain when other modes have failed is reasonable in specialist hands. Before prescribing an opioid, the patient's level of pain and its interference with the quality of life should be determined. Assessment of previous drug use, past and current psychiatric status should be determined, often in consultation with a psychiatrist. Long-acting or sustained-release preparations of opiates, such as morphine sulfate and oxycodone limits cycles of breakthrough pain and opiate withdrawal symptoms. Doses should be increased to achieve efficacy or decreased to reduce side effects with continuous montioring. Chronic use of opioid leads to constipation [26], and this can be dealt through intake of plenty of fluids and fiber, exercise, stool softeners and laxatives. Side effects like sedation and nausea dissipate with continued use. In TMD patients, morphine can be used as a 10mg intra-articular injection in arthrocentesis, arthroplasty procedure and intracapsular disorders. Long-term reductions in pain have been associated with this mode of arthrocentesis [27, 28]. The combination of acetaminophen 650 mg plus tramadol 75mg seems efficacious in postsurgical dental pain patients [29]. Osteoarthritis, fibromyalgia and diabetic neuropathy effectively respond to tramadol or tramadol with acetaminophen. When tramadol is combined with acetaminophen an opiate-sparing effect occurs compared with tramadol alone, resulting in better tolerability [10]. Any drug that is a Cytochrome P450 2D6 (CYP2D6) inhibitor, including the antiarrhythmic quinidine and antidepressants of the SSRI (selective serotonin reuptake inhibitors) class, such as paroxetine, reduces the analgesic activity of tramadol. Concurrent administration of tramadol with antidepressant class of drugs including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and SSRIs can produce tremors, convulsions, muscle rigidity, and hyperexia [30,31].

Benzodiazepines:

Benzodiazepines bind to specific receptors in the central nervous system (CNS) and are anxiolytic, sedative, and hypnotic. Diazepam

and clonazepam possess potent anticonvulsant activity. These drugs reduce muscle contraction, thus reducing the pain of TMD patients. Improvement of sleep patterns in subjects with chronic pain helps in breaking the pain cycle [32]. Diazepam and clonazepam, have long duration of action. Oxazepam, alprazolam, and triazolam are short acting drugs [10]. They are useful in patients with early disk displacement without reduction. Temazepam 10mg at night in the form of oral suspension is the best choice for these patients. Oral suspensions are used because patients can easily adjust the dose to avoid side effects and also to reach maximum effect when desired. It is contraindicated below 12 years of age [18]. Alprazolam (0.5-3mg/day) plus ibuprofen (2400mg/day) for 6 weeks is found to be effective in fibromyalgia patients [33]. Patients with chronic myogenous jaw pain given diazepam 5 mg four times a day for 4 weeks report significantly great decrease in pain than those taking placebo. Combination of ibuprofen and diazepam provides better pain relief from musculoskeletal origin than ibuprofen alone [34]. In patients with TMD who had failed appliance therapy and physical therapy, 1 month of clonazepam intake at bedtime was effective compared with placebo [35]. Longer-acting benzodiazepines with anticonvulsant activity, such as diazepam and clonazepam, may be more beneficial in relieving muscular pain of TMD [10, 36]. Oral benzodiazepines have side effects like drowsiness and psychomotor impairment. Peak blood levels of these drugs occur when the patient is asleep if taken immediately before sleeping. The dose should be halved in case of elderly people to prevent CNS depressant and memory impairment. Benzodiazepines like alprazolam, diazepam, midazolam, and triazolam, are Cytochrome P-450 3A4 (CYP3A4) substrates. Concomitant foods, such as grapefruit juice, and drugs including azole antifungals, erythromycin, clarithromycin, and calcium channel blockers that inhibit the CYP3A4 isoform, can significantly reduce the metabolism of these benzodiazepines leading to elevated blood levels and enhanced CNS depression. Therapy with these drugs should be limited to less than 4 weeks to prevent physical and psychologic dependence [10, 37]. The natural course of myofascial pain combined with conservative therapy will likely result in lowering of symptoms to acceptable levels [12]. Patients with depression should be referred to psychiatrist before prescribing benzodiazepines [8].

Non benzodiazepine sedative hypnotics:

Sleep disturbances are correlated with degree of pain severity and psychologic distress in patients with TMD. Eszopiclone, zolpidem, and zaleplon represent nonbenzodiazepine sedative hypnotics. In addition to inducing sleep, sedative doses of eszopiclone and zaleplon have muscle-relaxing activity.

However sleep walking has been reported in patients taking zolpidem [10].

Centrally acting muscle relaxants:

Muscle relaxants consist of two broad categories- centrally acting and peripherally acting agents. Peripheral muscle relaxants block muscle contraction and reduce skeletal muscle tone. Centrally acting muscle relaxants provide relaxation of muscle tissue by sedative effect on central nervous system (CNS). Muscle relaxants used in treating TMD are usually centrally acting, depress polysynaptic reflexes and are sedatives. These drugs help prevent or alleviate the increased muscle activity that might have resulted in TMD [8]. They relieve acute musculoskeletal pain without impairment in motor function and are often prescribed in conjunction with NSAIDs [9, 12]. Examples include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, baclofen, and tizanidine. Since they have lower therapeutic indices they must be used with extreme caution in patients with concurrent depression. Cyclobenzaprine has been suggested to potentially benefit patients who have TMD with muscle contraction and spasm [8]. In a study, patients with TMD reported improvement in jaw pain when cyclobenzaprine 10 mg was taken at night. The effect was superior to either placebo or clonazepam 0.5 mg combined with self-care and education in the management. Cyclobenzaprine is effective muscle relaxant. Low dosing 5-10mg taken 1-2 hours before bed time is usually effective [38, 39]. Carisoprodol has abuse potential and appears to be less effective in chronic pain conditions [39]. Sedation is a major side effect of skeletal muscle relaxant group of drugs. Cyclobenzaprine structure resembles tricyclic antidepressants, has anticholinergic activity, thereby causing side-effects like xerostomia and tachycardia. Thus cyclobenzaprine is contraindicated in narrow-angle glaucoma patients. Muscle relaxants are best used before sleep to reduce side effects. Skeletal muscle relaxants should be used for short duration in conjunction with physical therapy [8]. Metaxalone which has a few central effects is appropriate muscle relaxant for patient who must work while taking the medication [7].

Topical medications:

Topical NSAID's are useful in reducing pain in acute and chronic musculoskeletal injuries. NSAIDs can be incorporated in transdermal creams for application on the skin over the painful joint or muscle. Ketoprofen, felbinac, ibuprofen, and Piroxicam have significant efficacy. These are also helpful in chronic conditions such as arthritis and almost are devoid of adverse effects [5]. Andrew [13] recommended their use regularly four times a day for 4 weeks. Food and Drug Administration (FDA)-approved topically applied agents that have potential usefulness in TMD pain include capsaicin 0.025% [40] to 0.075% and the 5%

lidocaine transdermal patch. Capsaicin [41] is a derivative of the chili pepper and is effective in osteoarthritis and neuropathic pain. So, topical capsaicin is likely to benefit TMD patients. Capsaicin is devoid of systemic toxicity. However patients may initially experience burning sensations which will terminate with continued application. Combining capsaicin with a topical anesthetic, such as benzocaine 20% in pluronic lecithin organogel may help reduce this burning sensation [42]. Capsaicin is best used as an adjunct to NSAIDs, benzodiazepines, or other systemic modalities. TMD patients may be benefited from 5% lidocaine transdermal patch. The patch has to be cut into smaller sizes with scissors before removal from the release liner. Various types of pain have been reported to be improved through the use of this patch [10].

Antidepressants:

Antidepressants are grouped into three main categories: TCAs, MAOIs, and SSRIs. Several studies have reported efficacy of the TCA drug amitriptyline in patients who have TMD. Fourteen days of treatment with low-dose amitriptyline (25 mg/d) was significantly more effective than placebo in reducing pain intensity in women who had chronic TMD pain [43]. Low-dose amitriptyline (10–30 mg/d) demonstrated significant improvement in pain in both depressed and non-depressed subjects between six weeks to one year [10]. Tricyclic antidepressants with both serotinergic and noradrenergic effects (e.g., Amitriptyline or doxepin) appear to be most effective. Lower dosages (25 to 75 mg) should be used initially for non-depressive patients with higher antidepressant doses reserved for patients who are depressed. Sedative antidepressants may be useful when patients have sleeping problems and may help to reduce the use of hypnotics [8, 12]. Amitriptyline 10mg just before sleep can have an analgesic effect on chronic pain but has little effect on acute pain. It is an important part of management of fibromyalgia [7]. Duloxetine 60mg/day is helpful in achieving relief of pain in diabetic neuropathy and fibromyalgia [10]. Dothiepin is found to be significantly more effective in a mixed group of TMD and Atypical Facial Pain patients [44]. Common side effects of TCAs and SSRIs include nausea, sedation, psychomotor impairment, xerostomia, and constipation. These drugs must be absolutely avoided in patients taking concomitant MAOIs because the combination can lead to a potentially lethal serotonin syndrome consisting of confusion, fever, shivering, diaphoresis, ataxia, myoclonus, and severe hypertension [10].

Anticonvulsants:

Gabapentin has relatively low side-effects and is efficient in various chronic pain syndromes [45]. Anticonvulsant pregabalin has demonstrated efficacy and favorable tolerability in neuropathic pain. Both drugs are used for the treatment of pain associated with

postherpetic neuralgia and pregabalin is also being used for the treatment of painful diabetic neuropathy [10]. Patients with TMD of myogenous origin who took gabapentin report significantly reduced spontaneous pain together with reduced number of tender sites in the temporalis and masseter muscles, compared with placebo. The initial dose of gabapentin is 300mg, with additional 300mg every 3 days until pain relief is achieved. The daily maximum dose is 4200 mg [45]. Dizziness, drowsiness, xerostomia, peripheral edema, weight gain and memory impairment can occur in patients using gabapentin and pregablin. Anticonvulsants should be used as adjuvant analgesics in TMD patients with history of failed TMJ surgeries or those with chronic unremitting pain.

Botulinum toxin:

Low concentrations and large volumes of injection of botulinum toxin at multiple muscular sites may be helpful for muscular disorders related to TMD and relieve muscular spasms [13, 46].

Local anesthetics:

They are used when a myofascial trigger point is present. As procaine has low toxicity to muscles, concentrations at 1% are used. Also 1% or 2% lidocaine is commonly used. Pain and muscle spasm may be relieved for long term by needling the area with local anesthesia. This may be due to long term release of endogenous endorphins in the area of needling [13, 47, 48].

Miscellaneous medicines:

Local massage with topical Chinese medicinal herb ointment like Ping-On Ointment may provide a cheap and effective relief of pain for TMD patients. The ointment contains peppermint oil, 18%; menthol, 20%; natural camphor 6%, wintergreen oil, 6%, sandal-wood Oil, 1%, eucalyptus Oil, 4%; bee wax, 8% and aromatic oil, 1%. The ointment is to be applied in a circular motion on the affected area for 5 minutes 2 times daily [49]. A gel provided rapid pain relief and patient comfort and speeded restoration of the jaw's functional abilities, usually within 5 minutes after it is applied. It was composed of 18% potassium complex, 10% dimethylisosorbide, and 72% aqueous hydroxyethyl cellulose gel applied and gently rubbed onto the facial skin over the painful TMJs, muscles of mastication, and myofacial areas. This is because potassium and dimethylisosorbide inhibits inflammation and pain [50].

CONCLUSION:

In patients who have inflammatory pain, such as arthritis, capsulitis, or TMJ disc interference disorders, NSAIDs are first choice of drugs. Naproxen is most efficient in this group. In patients with GI problems etodolac is an alternative. Cyclobenzaprine is effective in TMD with muscular etiology.

Long acting benzodiazepines with anticonvulsant properties, such as diazepam and clonazepam, are used once a day in patients who don't respond to other muscle relaxants. Topical agents capsaicin and transdermal lidocaine have high therapeutic index and their use is encouraged. TCAs or anticonvulsants may be considered in patients who do not respond to NSAIDs, benzodiazepines, or muscle relaxants. The injection of corticosteroids directly into the joint space should only be used in patients who have severe pain and limitations in function attributable to intracapsular inflammation. Narcotic therapy should be reserved for the patient who has truly intractable pain. Patients for whom therapy such as behavioral modification, appliance therapy, physical therapy, or TMJ surgery greatly improves the quality of life, should only use drugs on an as-needed basis. Because many TMDs present symptoms that are periodic or cyclic, there is a tendency to prescribe drugs on a "take as needed" basis. This type of management encourages drug abuse, which may lead to physical or psychologic dependency. Frequent use of drugs tends to lead to more frequent pain cycles and less drug effectiveness. When drugs are indicated for TMDs, they should be prescribed at regular intervals for a fixed specific period. Further, definitive treatment should be provided so that medication will no longer be necessary.

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