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Management of Chronic Pain in Temporomandibular Disorders

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In chronic temporomandibular disorders (TMDs), constituent tissues such as muscles are sensitive to pain and psychological stress, which negatively affect the quality of life. In addition, since chronic TMDs is often accompanied by diseases such as psychological disorders and other chronic pain disorders, the diagnosis of those diseases and patient referrals are mandatory. The management of chronic pain in TMDs requires a multidisciplinary and holistic approach. Pharmacological therapy using cyclobenzaprine, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, progressive relaxation, and psychological approaches using cognitive behavioral therapy such as shifting negative thoughts about pain are all valid treatment options.

Keywords: Chronic pain; Pharmacological therapy; Temporomandibular joint disorders

INTRODUCTION

Chronic pain refers to pain that persists even after the initial injury or the cause of pain has been resolved. The International Association for the Study of Pain defines chronic pain as pain that persists for more than three months [1]. Chronic pain can be classified according to its pattern, location, severity, related psychological condition, and consequent functional impairment. The International Classification of Diseases for chronic pain lists chronic headache, chronic orofacial pain, and temporomandibular disorders (TMDs) as the most common types of chronic orofacial pain [1].

TMD can occur due to various anatomical causes, such as degenerative changes of the temporomandibular joint, displacement of the TMJ disc, and pain in the masticatory muscles. The International Classification of Orofacial Pain, the International Headache Society's classification system for oral and facial pain, defines chronic primary myofascial orofacial pain and chronic primary temporomandibular joint pain as follows [2]:

Chronic primary myofascial orofacial pain is mild-to-moderate deep aching or dull pain in the masticatory muscles that occurs episodically or unremittingly, often associated with functional limitations such as difficulties in moving the mandible, chewing, or yawning, with a history of more than three months that is often associated with psychosocial factors. (Diagnostic criteria: A. Myofascial pain that meets the criteria for 2.1 primary myofascial orofacial pain, and criteria B and C below: B. Onset >3 months; C. Recurring in at least 10 episodes or unremitting).

Chronic primary TMJ pain is limited to the TMJ. It occurs at rest, during function, or during palpation; also, it has a history of more than three months and recurs at least 10

times or occurs continuously [2].

During chronic pain in TMD, prolonged peripheral stimulation of a nociceptive pathway induces central sensitization seen in many other chronic pain conditions. People with a variety of body pains such as those caused by irritable bowel syndrome, migraines, fibromyalgia, and pelvic pain account for a significant proportion of TMD patients. These patients show hypersensitivity and amplification of pain due to the central sensitization mechanism [3].

The risk factors of TMD chronic pain will be further considered. The Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) Study Model presents two major intermediate phenotypes contributing to the onset and persistence of TMD-related pain, namely chronic pain. One is psychological stress and the other is pain amplification. Each intermediate phenotype represents a more specific set of risk factors associated with genetic regulation. When environmental factors are added, the interaction between psychological distress and pain amplification results in the onset and persistence of painful TMD. Additionally, the passage of time is the necessary condition required to develop chronic pain [4]. Therefore, TMD patients with anxiety, depression, and sleep disorders are classified as having risk factors for chronic pain. In general, pain caused by TMD does not wake one up; however, up to 90% of TMD patients suffer from sleep disorders and TMD patients with myofascial pain have been reported to sleep less than patients suffering from arthralgia or healthy controls [5,6]. Such changes in the severity of insomnia symptoms can also predict an increase in TMD-related pain intensity [7]. These patients are considered high-risk and should be referred to a specialist for treatment at an early stage of the disease.

OPPERA identified at least three individual groups with different severity of symptoms and the number of chronic overlapping pain states. This shows that the more chronic overlapping pain conditions such as chronic back pain, neck pain, and headaches exist, the more severe the symptoms of chronic TMD appear, and the psychosocial sensory function and autonomic profile are abnormal [4].

The Chronic Pain Grade Scale is a validated tool used to assess pain-related disorders in patients with TMD. If risk factors for chronic pain such as anxiety, depression, or sleep disorders using the Patient Health Questionnaire/Generalized Anxiety Disorder scale, etc., are identified, patients should be considered high-risk and referred to a specialist early for professional care, with a multidisciplinary team approach [3].

In summary, chronic TMD negatively affects the quality of life because constituent tissues such as muscles become sensitive to pain, and the disability and psychological stress caused by pain are significant. Risk factors and comorbidities like anxiety, depression, sleep disorders, and chronic pain conditions in other areas are often concomitant; so, confirmation, risk assessment of chronic pain, and referral are required. This review intends to consider the evidence-based treatment that is effective for chronic pain in TMD, which can cause so much discomfort to patients.

TREATMENT OF CHRONIC PAIN IN TMDS

Chronic pain in TMD, like other chronic pain disorders, is characterized by various symptoms, including pain and dysfunction originating from constituent tissues of the TMJ, as well as abnormal psychosocial sensory function and autonomic profiles. A holistic approach is required to comprehensively manage the condition, including integrative patient education and encouragement of self-care [8]. For this, pharmacotherapy, psychological interventions, and physical therapy are performed through collaborations with multidisciplinary experts.

1. Pharmacotherapy

The pharmacology of the management of chronic TMD-related pain is challenging. First, in chronic TMD, the mechanism of pain, such as how the patient's psychological state affects pain, has not yet been elucidated. Second, it is because a multifaceted approach to pain management is needed; for example, blocking additional peripheral pain input to the chronic pain and controlling the descending pathway in the central mechanism [9]. Medications previously used for other chronic pain have also been proven effective for chronic TMD. The following subsections describe the various central and peripheral mechanism agonists currently being prescribed; e.g., non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antidepressants, anticonvulsants, antianxiety drugs, and opioids (Table 1) [10].

Table 1. Efficacy, indications, contraindications, and side effects of pharmacotherapy on chronic pain in temporomandibular disorder

Pharmacotherapy	Efficacy, indications, contraindications, and side effects
Non-Steroidal Anti-inflammatory Drugs	No unequivocal recommendations
Muscle Relaxants	
Cyclobenzaprine	10 mg at night Prescription for up to 2-3 months Caution is required for long-term treatment Side effects: drowsiness, tiredness, headache, dizziness, xerostomia, stomach upset, nausea, and constipation Contraindication: hyperthyroidism, severe cardiovascular disease, and the administration of a MAO inhibitor within the previous 14 days
Antidepressants	
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine)	Most effective amitriptyline (25 mg/day) Side effects: sedation, dizziness, blurred vision, constipation, and xerostomia Contraindications: acute porphyrias, arrhythmias, heart block, severe hepatic impairment, and severe renal impairment (lofepramine).
Selective serotonin reuptake inhibitors	Relieve neuropathic pain symptoms Fewer anticholinergic, antihistaminergic, and antiadrenergic effects
Serotonin and norepinephrine reuptake inhibitors	30 mg/day increasing progressively, over six months, to 120 mg/day Side effects: nausea, dry mouth, dizziness, headache, and sweating
Anticonvulsant	
Gabapentin	300 mg/day, increased by 300 mg every three days until the pain is controlled with no adverse effects Decrease tenderness in the masticatory muscles Side effects: dizziness, somnolence
Pregabalin	Effective in painful neuropathic conditions. Few studies on TMD-related pain
Benzodiazepines	Long-term use contraindicated Side effects: drowsiness, confusion, amnesia, impaired coordination, withdrawal symptoms (anxiety, agitation, restlessness, insomnia, and seizures) Effective for chronic myogenous jaw pain
Opioids	Discouraged Potential for inducing tolerance and physical dependence Little or no evidence that supports long-term therapy for TMD
Botulinum toxin	No high-quality evidence
Anesthetics	
Lidocaine (1%, without epinephrine) or procaine (1%, without epinephrine)	Apply via the Trigger Point Injection method Higher treatment efficacy of pain reduction Contraindications: anticoagulation or bleeding disorders, local or systemic infections, allergy to anesthetic agents, acute muscle trauma, extreme fear of needles Side effects: vasovagal syncope, skin infections, needle breakage, hematoma formation (avoid by applying direct pressure for at least two minutes after the injection)

MAO, monoamine oxidase; TMD, temporomandibular disorder.

1) NSAIDs

Due to the limited number of randomized studies evaluating the efficacy of NSAIDs in TMJ osteoarthritis (OA) treatment and the high heterogeneity of published studies, it is difficult to make a clear recommendation for the use of NSAIDs in TMJ OA treatment. However, when administering NSAIDs, it is desirable to use the minimum effective dose for the shortest possible duration. In addition, for patients with an increased risk of gastrointestinal complications, an auxiliary gastrointestinal protector should be prescribed. With careful consideration for gastrointestinal disorders and cardiovascular side effects, it should be possible to safely prescribe ibuprofen and diclofenac for OA. Randomized-controlled trials (RCTs) comparing the effects of diclofenac to splint therapy have demonstrated that when 50 mg was administered three times a day for three months (if there were side effects such as gastrointestinal issues, the dosage was changed to twice daily), showed that there was an

equivalent degree of therapeutic effect and a similar safety profile (in terms of the low incidence of side effects) compared with a splint [11,12].

There is not enough evidence to support the use of topically applied NSAIDs to relieve chronic myogenous pain. These studies are generally of low quality and methodologically problematic; thus, recommendations cannot be made based on their findings. Topical NSAIDs may have some effect on acute myogenous pain; however, they have not been reported to be effective for chronic pain [13].

2) Muscle relaxants

Centrally-acting muscle relaxants have often been used for the symptomatic treatment of TMD. They are useful for reducing skeletal muscle tension and preventing and relieving increased muscle activity. Muscle relaxants are generally taken at bedtime at low doses because they cause somnolence. The two most commonly used muscle relaxants are carisoprodol and cyclobenzaprine. Carisoprodol, the first drug in the family, has been frequently used in the past; however, it has proven to be no more effective than placebo [12].

Cyclobenzaprine is indicated for systemic chronic muscle pain because it significantly relieves muscle pain and improves the depth and duration of sleep. A randomized-controlled study reported that when cyclobenzaprine was added to TMD dosing, it performed better than placebo or 0.5 mg clonazepam [14]. The typical course of treatment is 30 days, followed by a two-week recess. If its efficacy is confirmed, the prescription can be continued for up to 2-3 months. However, during the long-term use of cyclobenzaprine, side effects should be managed through co-evaluation and management with the patient's regular doctor if possible [12].

Cyclobenzaprine has a chemical structure similar to that of tricyclic antidepressants (TCAs) and shares many of their characteristics. Therefore, patients with hyperthyroidism and certain cardiovascular diseases (unstable angina, a heart rhythm disorder, congestive heart failure, and recent myocardial infarction) are advised to avoid this drug. The concomitant use of cyclobenzaprine and monoamine oxidase inhibitors (MAOIs) may cause serious, life-threatening interactions. Also, cyclobenzaprine can increase the risk of seizures in patients taking tramadol [12].

3) Antidepressants

For over 30 years, antidepressants have been used in managing pain caused by TMD. Of these drugs, TCAs appear to be the most effective. However, serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) also have been reported to be effective for orofacial pain [15-17].

When a TCA is prescribed to relieve TMD-related pain and discomfort, a dose of 25 mg/day is used, which is much lower than the antidepressant dose of amitriptyline [15]. Common adverse reactions of TCA include dizziness, drowsiness, sedation, constipation, blurred vision, and xerostomia. TCAs inhibit the reuptake of catecholamines and increase catecholamine neurotransmission; so, when dental local anesthetics that contain exogenous catecholamines such as epinephrine are used, it may lead to an overdose, resulting in cardiovascular side effects. Therefore, in patients taking TCA, it is necessary to limit the dose of epinephrine to <0.04 mg per dental appointment [17]. In addition, the co-administration of an MAOI and a TCA should be avoided as it can cause fatal serotonin syndrome, which presents clinically as confusion, fever, ataxia, and severe hypertension. As with cyclobenzaprine, the careful use of TCA is required in patients with heart diseases and elderly patients [17].

Another group of commonly used antidepressants are SSRIs; however, there are not many studies investigating the use of SSRIs in the treatment of TMD patients. In a case report of two patients, SSRIs were observed to be effective in alleviating TMD-related pain. SSRIs have fewer antihistaminergic, anticholinergic, and antiadrenergic effects than TCAs; however, paroxetine has relatively high anticholinergic effects among SSRIs [17,18].

When SNRIs (milnacipran) were given to patients with chronic TMD at an initial dose of 30 mg/day that was gradually increased over six months to 120 mg/day, improvements in occlusal discomfort, generalized pain and sleep disturbance, chronic fatigue, stiffness, numbness, and depressed mood were reported in dose-dependent and time-dependent improvement patterns.

SNRIs are safe for most people. However, duloxetine may adversely affect liver disease, while levomilnacipran, venlafaxine, and desvenlafaxine may increase blood pressure.

SNRIs may also raise the risk of bleeding, especially when taken concurrently with medications that affect blood clotting pathways, such as ibuprofen (Advil, Motrin IB, etc.), aspirin, warfarin (Coumadin, Jantoven), and other blood-related drugs [17,18].

Overall, antidepressants are quite effective but they should be used with caution in dentistry. Although rare, serotonin syndrome can occur when combined with antidepressants that can increase serotonin levels in the body. The treating physician must ensure that the patient has a medical condition that warrants long-term treatment. In addition, it should be possible to sufficiently manage any reactions of the patient or side effects that may occur [18].

4) Anticonvulsants

Anticonvulsants are widely used in the treatment of neuropathic pain. Although these drugs act on a variety of pain-related areas, the exact mechanism of action is not yet clear. The efficacy of gabapentin has been widely demonstrated in a few placebo-controlled studies for a variety of chronic pain syndromes. According to these studies, gabapentin is superior to placebo in reducing the tenderness of the masticatory muscles, especially that of the temporal and masseter muscles. The gabapentin dosage is increased from 300 mg per day, adding 300 mg every three days, until the pain is controlled to a level where there are no side effects. The daily maximum dose is 4,200 mg; however, doses higher than 1,200 mg per day are capable of increasing the incidence of minor side effects. Pregabalin has been shown to reduce pain in randomized clinical trials of a variety of painful neuropathies; however, there are few studies demonstrating the effectiveness of pregabalin for TMD-related pain. The application of pregabalin to a rat model of chronic TMD-related pain significantly attenuated orofacial mechanical allodynia and returned mechanical hypersensitivity to baseline-like levels. Gabapentin and pregabalin are generally well-tolerated and have transient, mild-to-moderate side effects that are dose-dependent. The most common adverse reactions in patients are dizziness and drowsiness. Xerostomia, nausea, peripheral edema, blurred vision, rash, weight gain, and difficulty concentrating are side effects that may appear relatively less frequently. Anticonvulsants may be used as adjunctive analgesics for people with long-lasting, persistent, chronic TMD-related pain [12,19,20].

5) Antianxiety agents (benzodiazepines)

Benzodiazepines are usually prescribed to treat acute muscle spasms and sleep disorders. Patients taking diazepam have demonstrated a significant reduction in chronic orofacial pain compared to those taking placebo; however, its long-term use is prohibited due to the high incidence of tolerance and dependence, as well as many side effects like drowsiness, confusion, memory loss, and coordination disorders. Furthermore, the abrupt cessation of benzodiazepine therapy can cause withdrawal symptoms, including agitation, anxiety, seizures, and insomnia. Contraindications include allergies, acute narrow-angle glaucoma, and myasthenia gravis [21].

There are several well-designed studies supporting the safety and efficacy of benzodiazepines when TMD-related pain includes significant pain of muscular origin. A placebo-controlled, double-blind study of patients with chronic muscular jaw pain reported that there was a greater reduction in pain among those taking diazepam at a dose of 5 mg four times a day for four weeks than among those taking placebo [21].

In this study, taking 600 mg of ibuprofen four times a day produced no effect, whereas the combination of diazepam and ibuprofen had a superior pain-reducing effect to ibuprofen alone. There is another study in which placebo and clonazepam were administered to TMD patients who did not respond to splints and physical therapy. In this trial, one month of taking clonazepam at bedtime (average dose: 0.375 mg) was reported to be more effective than placebo [22]. However, a crossover study reported that short-term use of triazolam (the dose of 0.25-0.5 mg) for four days yielded significant improvements in sleep patterns but no improvement in muscle tenderness or pain intensity compared to placebo [23]. Taken together, these findings suggest that long-acting benzodiazepines, such as diazepam and clonazepam, which have proven anticonvulsant activity, are more effective for muscle pain reduction in TMD patients than short-acting ones. However, more studies are needed on drug selection, treatment duration and drug dosage, and considerations of side effects such as drug dependence and

tolerance, etc., to make long-term treatment plans.

6) Opioids

The use of opioids to treat chronic pain is not recommended because of concerns regarding their potential for dependence and tolerance. Therefore, the prescription of opioids for the management of TMD should be limited only to specialists who are adequately trained in this domain. Additionally, opioid-related drug therapy for chronic pain management should be performed after thorough discussions with the patient's doctor to reduce the likelihood of opioid abuse. Moreover, there is little or no evidence that long-term opioid therapy for chronic TMD-related pain is better (or worse) than treatment with other pain killers [24].

2. Injections: Botulinum Toxin & Trigger Point Injections (TPIs)

A previous study demonstrated that botulinum toxin type A reduced pain slightly more than placebo after one month in chronic TMD; however, there are no high-quality and evidence-based studies supporting the injection of botulinum toxin type A for the management of pain in patients with TMD.

For chronic TMD-related myofascial pain, TPIs can be used as an effective treatment option. Injection solutions of 1% lidocaine or 1% procaine are commonly used as infusion medications. Several other substances have been used for TPIs, including diclofenac, botulinum toxin type A, and corticosteroids; however, these substances are associated with significant myotoxicity. Procaine is the least myotoxic of all anesthetics. Contraindications to TPIs include anticoagulant or bleeding disorders, local or systemic infection, allergy to anesthetics, acute muscle trauma, extreme fear of needles, etc., which require attention [25].

In most cases, post-injection pain is expected, and the relief of the pain pattern according to the patient indicates the success of the TPIs. Re-palpation of the injection site might be necessary; however, re-injection of the trigger point is not recommended until the pain is resolved after injection (usually after 3-4 days). Repeated injections into specific muscles are unnecessary in patients who have failed two or three previous attempts. It is recommended that the patient avoid strenuous activity for the first 3-4 days after the TPI; however, it is beneficial to maintain an active state using the muscles throughout the entire range of motion for one week after the injection [25].

Complications of TPIs include skin infections, vasovagal syncope, needle breakage, and hematoma formation (which can be avoided by applying direct pressure for at least two minutes after injection) [26].

In summary, the drugs that can be used appropriately to treat chronic TMD-related pain are cyclobenzaprine (10 mg at night), TCAs (amitriptyline, nortriptyline, and desipramine) such as amitriptyline (25 mg/day) if side effects can be well-controlled, SNRIs such as milnacipran and gabapentin, etc. For myofascial pain of masticatory muscles with trigger points, it is thought that 1% procaine, with low myotoxicity, or lidocaine (1%, without epinephrine), could be used for the TPI [26].

3. Psychological Interventions

1) Cognitive behavioral therapy (CBT)

CBT includes discussions on shifting negative thoughts about pain, the psychological aspects of pain, relaxation and other behavioral techniques for managing pain, avoiding fear, and preventing relapse [27,28]. CBT has been used for non-invasive pain management of chronic pain such as chronic back pain, primary headache, and irritable bowel syndrome, and its effectiveness has been proven [29]. CBT, alone or in combination with other forms of therapy, has improved outcomes for patients with these conditions, particularly with regard to pain intensity, pain-related activity interventions, and the ability to cope with pain [29,30].

However, it is difficult to perform CBT uniformly in patients, and it has a great effect on the results depending on the patient's motivation for treatment and the dentist's communication skills such as facial expressions, tone, and gestures. Therefore, it is difficult to clearly prove the effect because there are many changeable factors such as these potential mediators. Nevertheless, it has no negative effects on patients and is also inexpensive; thus, it should be performed primarily in patients with chronic TMD [31].

4. Physical Therapies

1) Physical exercise

There are studies that reported that physical exercise therapy such as aerobic stretching is effective in reducing pain intensity and improving function in chronic musculoskeletal disorders similar to TMD, such as fibromyalgia [32]. In parallel, yoga exercises address sensory input and adjust dealing with potential emotional responses linked to sensory input, resulting in positive changes in connectivity within the pain connection center [32]. Therefore, regular and long-term yoga exercise increases pain tolerance [32]. The gradual application of physical exercise to the patient's daily life is the first step in managing chronic TMD.

2) Physical self-regulation training (posture training, jaw stretch, masticatory muscular relaxation)

Physical self-regulation training for TMD improvement, which reduces muscle pain and improves jaw function through posture training, jaw stretching, and muscle relaxation, is considered a desirable management strategy because it has the advantage of being less invasive and allowing patients to manage their own conditions [33,34]. This self-regulation training is usually combined with physical therapy methods such as thermal packs and relaxation [34]. Although the effectiveness of such physical therapy is useful for preventing acute exacerbations of TMD, the long-term effect on chronic TMD management is still unknown [35].

3) Spray-and-stretch technique

The spray-and-stretch technique is employed to passively stretch the masticatory muscle while at the same time topically applying ethyl chloride, etc., by spraying [26]. A sharp drop in skin temperature is considered to cause temporary anesthesia by blocking spinal stretching reflexes and sensations [26].

Decreased pain sensation enables muscles to passively stretch toward their normal length, helps in deactivating trigger points, alleviates muscle spasms, and reduces associated pain. Spray-and-stretch techniques have been reported to have short-term (<6 hours) effects on pain reduction after TPIs of latent trigger points [36].

4) Acupuncture

One of the widely used methods for managing chronic pain is acupuncture. A study performed on patients with back pain, chronic headache, and pain from OA demonstrated that acupuncture was more effective than conventional treatment. However, both acupuncture and placebo acupuncture showed similar effects; so, the precise mechanism of action is unidentified. Based on this, acupuncture could be used to manage TMD; however, more RCTs with larger sample sizes are needed [37,38].

5) Electrophysiotherapy modalities

Electrophysical therapies, such as pulsed shortwave therapy, ultrasonography, and low-level laser therapy are widely used in managing TMD [39,40]. In a previous study, improvement was observed compared to placebo; however, a recent review of the relevant literature found that the methods used in published clinical trials lacked theoretical quality, suggesting that further studies are needed to deduce more obvious conclusions about these therapies in the management of TMD [39,40].

To summarize physical therapy, physical exercise therapy, including aerobics and stretching, has been reported to relieving pain and enhance function in other chronic musculoskeletal disorders similar to TMD, such as fibromyalgia. However, evidence of the efficacy of several forms of physical therapy, such as acupuncture and electrophysiotherapy in chronic TMD-related pain, is unclear.

5. Occlusal Splints

The exact mechanism of action of occlusal splints is unclear. Michigan splint treatment has been demonstrated to reduce TMD-related pain by decreasing sensorimotor stimulation, increasing activity levels of the frontal, temporal, occipital, and cerebellar networks, increasing symmetrical movement of the condyles during occlusion, and decreasing cerebral insular expression. Evidence of chronic TMD-related pain is unclear [41-43].

CONCLUSION

Chronic TMD management requires a multidisciplinary and holistic approach to patients. As such, the patient's

Table 2. Effective treatment that can be applied to chronic pain in temporomandibular disorder

Pharmacotherapy
Cyclobenzaprine: 10 mg at night
TCAs (amitriptyline, nortriptyline, and desipramine): amitriptyline (25 mg/day)
SNRIs (milnacipran): 30 mg/day increasing progressively, over six months, to 120 mg/day
Gabapentin: 300 mg/day, increased by 300 mg every three days until the pain was controlled with no adverse effects
Anesthetics: Lidocaine 1%, without epinephrine by Trigger Point Injection
Psychological Interventions
Cognitive Behavioral Therapy

TCA, tricyclic antidepressant; SNRI, serotonin and norepinephrine reuptake inhibitor.

comorbidities, the degree of pain, and the patient's psychological state are comprehensively identified and the necessary referrals are made. Medications such as cyclobenzaprine, TCAs, or SNRIs, progressive relaxation, and psychological approaches using CBT such as the conversion of negative thoughts about pain can be applied; also, physical therapy can be applied although there is insufficient evidence to support its application (Table 2).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: SMO. Funding acquisition: SMO. Methodology: HMJ (Hye-Mi Jeon). Project administration: SMO. Visualization: HMJ (Hye-Mi Jeon). Writing original draft: KHK, HMJ (Hye-Min Ju). Writing review & editing: KHK, HMJ (Hye-Min Ju), SHJ, YWA, SMO.

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