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REVIEW ARTICLE

Management protocols of chronic Orofacial Pain: A Systematic Review

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Abstract *Objective:* Chronic orofacial pain (CP) is a persistent and debilitating condition that affects the face, mouth, and jaw and can have a significant impact on an individual's quality of life by posing problems to eat, speak, and perform everyday activities. By the means of this narrative review, we aim to assess different types of management modalities that exist to combat chronic orofacial pain.

Design: Various databases were explored with MeSH keywords of *chronic orofacial pain*, *orofacial pain*, and *interventions and treatment protocols* for eligible articles. After an extensive literature search, it was ascertained that this review identified four major categories of treatment modalities for the management of chronic orofacial pain, namely pharmacological management, psychological management, lifestyle interventions-based management, and current stimulation-based management.

Results: Of the four categories discussed, although pharmacological intervention offered the most immediate relief—especially from orofacial pain that was of a sudden, stab-like in nature—

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psychological management demonstrated a remarkable ability to reduce/alleviate the more serious aspect of chronic orofacial pain and was deemed better in comparison to the rest. Lifestyle-based techniques and current stimulation-based management were of limited use since they tended to focus more on the causal and not the symptomatic aspect of orofacial pain.

Conclusions: Many patients with persistent orofacial discomfort can experience notable improvements in their symptoms and general well-being by all the treatment modalities evaluated.

Contents

1. Introduction

Chronic orofacial pain is a common yet debilitating condition that affects the mouth, face, and jaw regions. It is defined as pain that lasts for more than three months and can impact the quality of life of affected individuals. (Macfarlane et al., 2002; Quinzi et al., 2021)The causes of CP are varied, ranging from dental problems to nerve disorders, and can be challenging to diagnose and manage. (Riley & Gilbert, 2001) Diagnosing chronic orofacial pain can be challenging, as the symptoms can be vague and overlap with other conditions. The first step in managing chronic orofacial pain is to identify the underlying cause, which may involve a comprehensive physical examination, imaging tests, and consultations with dental and medical specialists. Once the underlying cause is identified, a treatment plan needs to be developed as per the individual's needs. (Headache Classification Committee of the International Headache Society (IHS), 2013).

CP has a multifactorial etiology. Temporomandibular disorders (TMD) are a common cause behind it, as they describe a wide range of conditions which have a significant impact on the temporomandibular joint (TMJ)(Qazi et al., 2023), which connects the jaw to the skull.200B (Di Francesco et al., 2022; Minervini, D'amico, et al., 2022; Nicholas et al., 2019)TMD can cause pain in the jaw, face, and neck, and may be associated with clicking or popping sounds in the jaw. Neuropathic pain, caused due to dysfunction of the nerves carrying sensory data from the mouth and facial region to the brain, can also be a contributing factor.

Chronic headaches that originate in the face, head, or neck can be a type of orofacial pain. These headaches may be tension-type headaches, migraines, or cluster headaches. Myofascial pain involves pain and discomfort in the muscles and soft tissues of the face and jaw. Such pain may be caused by muscle tension or trigger points and can be associated with limited jaw movement or difficulty opening the mouth. Other possible culprits can include tooth decay; gum disease; periodontal problems; sinus infections; previous trauma to the face, head, or neck; or autoimmune disorders such as rheumatoid arthritis or lupus (Cicciù et al., 2012; Nastro et al., 2007). In addition, psychological factors such as stress, anxiety (Minervini et al., 2023), or depression can also contribute to chronic orofacial pain. (Aggarwal et al., 2006; Rengo et al., 2015).

Chronic orofacial discomfort can occur due to various reasons, of which TMDs rank the highest in prevalence. (Crescente et al., 2022) The treatment for CP requires a multidisciplinary approach to alleviate pain and reduce its impact on an individual's quality of life and promote their overall well-being. (Aggarwal et al., 2019) In this context, it is important to properly diagnose and manage chronic orofacial pain to reduce its impact on an individual's quality of life and promote their overall well-being. Through this narrative review, we examine the existing major categories of management modalities employed for chronic orofacial pain.

2. Materials and methods

2.1. Focus question: "What are the various interventions available in literature for the management of chronic orofacial pain?"

2.2. Literature search: two reviewers conducted the search independently. Databases of Pubmed, Scopus, Embase, and Cochrane were explored. Grey literature search included exploring technological reports, letters to

editors, and speeches and conference proceedings discussing the management protocols for orofacial pain of chronic nature. Medical subject headings terms (MeSH) applied for the search strategy included: [Chronic orofacial pain OR management] AND [Orofacial pain] AND [Interventions or treatment protocols]. References of the included articles were further looked into which met our inclusion criteria. Any disagreements between the reviewers were solved by discussion. Kappa statistics were calculated to check for inter-examiner agreement for the articles.

2.3. Exclusion criteria

- Case studies and reports.
- Publications not describing the details of intervention therapies for orofacial pain.

2.4. Selection of studies

The eligibility of articles was assessed independently by two reviewers. The opinion of a third reviewer was sought in case of any disagreement.

2.5. Data extraction

Data was tabulated by two investigators based on various treatment modalities.

2.6. Quality appraisal of included studies

The methodological assessment of the studies was not formally evaluated.

3. Results and discussion

3.1. Literature search

The PRISMA flowchart (Fig. 1) shows the selection process of articles. The database searches identified a total of 237 articles; 90 duplicate articles were excluded, resulting in 158 to be screened for titles and abstracts. A total of 48 articles of full text literature were evaluated for eligibility, and 47 were

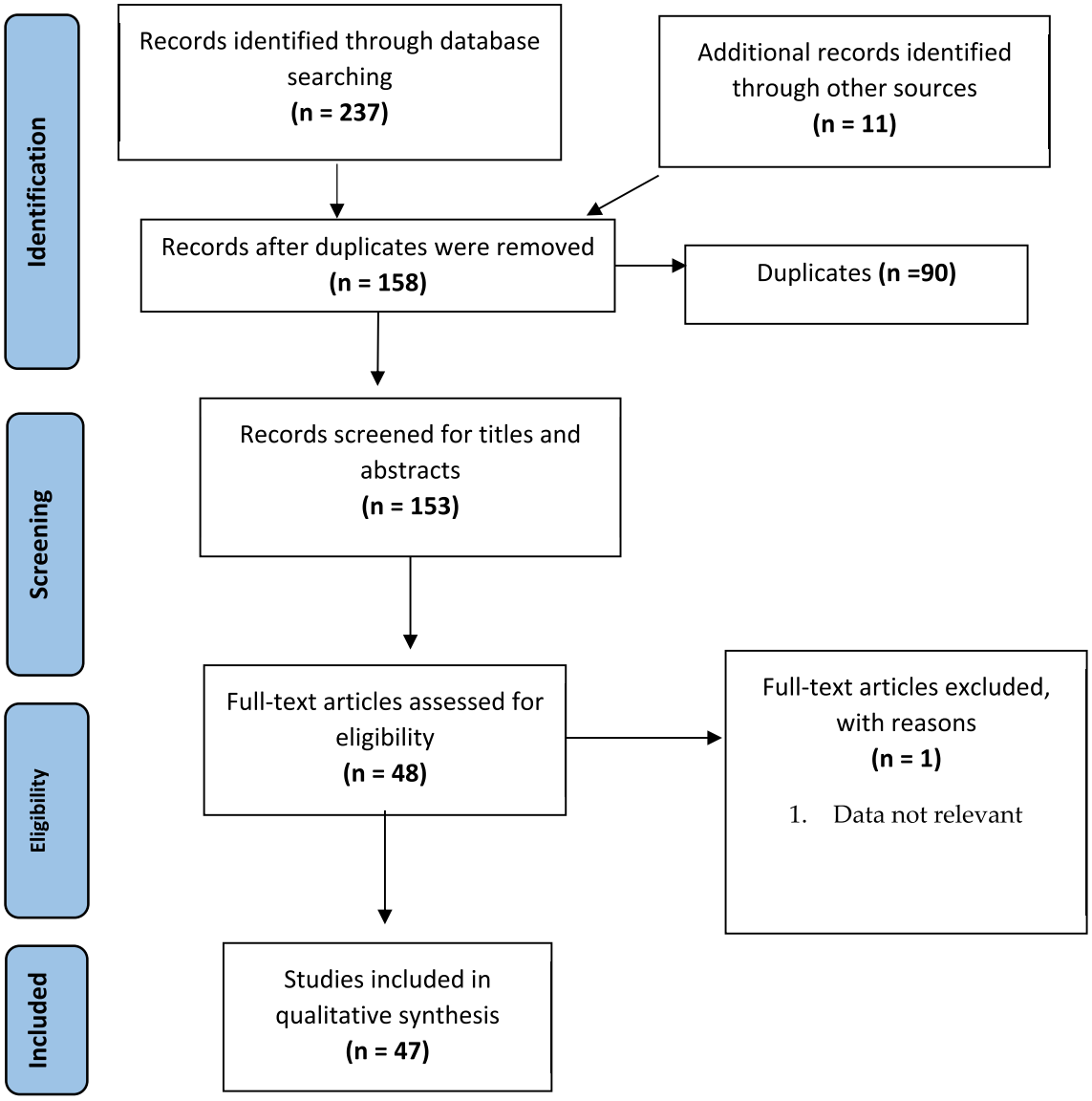

Fig. 1 Flowchart summarizing the article selection process (*n* – number of studies).

included for data extraction. A thorough and extensive search of the literature yielded four major intervention areas, namely psychological management, pharmacological management, lifestyle-oriented management, and current stimulation-based management, which are presented below.

3.2. Psychological management

Cognitive behavioural therapy (CBT) for pain relief helps individuals in recognising and altering unhelpful thought patterns, reducing unhelpful behaviours, promoting helpful behaviours, and improving physical and role function with the objective of reducing psychological suffering and enhancing function. The purpose of treatment is to promote physical, social, and occupational activity while addressing anxiety, sleep difficulties, and mood instability. (Gore et al., 2012).

It is a time-bound, action-focused, and present day-based intervention. While there are no established procedures for cognitive behavioural therapy, some of the strategies include problem-solving training, activity pacing assistance, relaxation training, goal-setting, systematic increases in exercise, and cognitive restructuring (Ehde et al., 2014). To practise new abilities, patients are frequently urged to accomplish tasks between sessions; this could include filling out thought diaries, practising relaxation techniques, or working towards behavioural objectives. Additionally, a few researchers have also proposed that people who have TMJ dysfunction experience some orofacial discomfort as well. (Kotiranta et al., 2014; List & Axelsson, 2010; Randhawa et al., 2016) According to Turner et al., patients receiving CBT showed more improvements in pain-related beliefs, catastrophizing, and coping than a control group. (Turner et al., 2005) Additionally, literature has shown that after 12 to 16 sessions of cognitive behavioural treatment, patients with BMS experience decreased pain and discomfort levels, and these effects last for six to 12 months. (Femiano et al., 2004).

Another psychological intervention method is the mindfulness-based acceptance and commitment therapy (ACT) proposed by Steven C. Hayes, who has conducted substantial studies on both the model and the active processes. (Hayes et al., 2006) ACT is a non-linear paradigm that aims to improve change-effecting psychological flexibility. (Trompetter et al., 2015) ACT aims to help individuals learn how to accept and cope with their pain instead of trying to eliminate it. It helps individuals develop psychological flexibility, which can lead to better management of CP. (Hughes et al., 2017) The usefulness of this strategy specifically in treating chronic pain and mental health issues is supported by a growing body of literature. A *meta*-analysis evaluation for chronic pain comparison between ACT and controls reported clinically effective results of the former in pain reduction. (Feliu-Soler et al., 2018) However, this has to be interpreted cautiously, as yet another *meta*-analysis pointed out that many research studies were of low quality and that high quality randomised controlled trials were required to arrive at conclusive evidence. (Graham et al., 2016).

By observing and embracing present-moment experience without passing judgement on it or seeking to control it, mindfulness-based interventions seek to transform how people relate to internal events, such as feelings, sensations, and thoughts. (Kabat-Zinn, 2011)With mindfulness meditation, an individual can train their ability to be aware of their thoughts and feelings in the moment instead of trying to alter things or find a solution. Since the ground-breaking work of Jon Kabat-Zinn, mindfulness has been widely employed in pain management settings. (Kabat-Zinn et al., 1984) Khan AA et al. studied the effectiveness of mindfulness meditation in patients affected with myofascial pain dysfunction syndrome (MPDS) and reported that the mindfulness meditation group succeeded better than the control group in reducing pain; however, the best results were seen in the sample administered conventional treatment along with mindfulness practice. (Khan et al., 2018) A review hypothesised mindfulness meditation practice for treating MPDS by reversing the cellular, neurobiological, and neuro-architectural changes. Research based on this compassion focused therapies are less, but they do show potential in pain management settings. (Penlington, 2019).

3.3. Pharmacological management

The pharmacological intervention for chronic orofacial pain may involve the use of different classes of medications, depending on the underlying cause and kind of pain; it is also the most common intervention method. However, it is imperative for researchers to distinguish between a lack of proof and evidence for an absence of effect. Due to the current gaps in our understanding of the pharmacologic effects on CP, comparison of orofacial pain can be made to other types of pain. Pharmacological agents proven to be beneficial for these diseases include analgesics, tricyclic antidepressants, serotonin or adrenaline reuptake inhibitors, gabapentin, pregabalin, opioids, and lidocaine patches, which would likely also be effective for orofacial discomfort. (Derry et al., 2014).

A network metanalysis conducted by Haggman-Henrikson B et al. in 2017 reported the effectiveness of pharmacological intervention in reducing chronic orofacial pain. A total of 13 randomised controlled trials (RCTs) were tested for TMD muscle disorders, TMJ pain, and BMS. TM joint pain was alleviated using NSAIDs, hyaluronate, and corticosteroid injections, while clonazepam and corticosteroid injections reduced discomfort in BMS, and cyclobenzaprine was prescribed for TMD muscle disorders. (Häggman-Henrikson et al., 2017).

A trial of a different class of medication, such as an antiepileptic drug, may be considered for patients who report with persistent orofacial pain and do not respond to basic analgesics. (Moavero et al., 2020) Additionally, because caffeine has been proven to have a negative link with acute pain, it may be important to keep track of the patient's daily caffeine intake. In contrast, a 2014 Cochrane Review found that adding 100 mg of caffeine—the equivalent of one cup of coffee—to a standard dose of commonly used analgesics resulted in greater pain relief than analgesia alone. (Derry et al., 2014).

The European Academy of Neurology (EoAN) published recommendations for treating trigeminal neuralgia (TN). In case of acute exacerbation of the condition, antiepileptic drugs are given. For patients experiencing chronic pain in primary TN, carbamazepine remains the documented drug of choice. They strongly advocated the use of long-term care for CTN and gave a moderate rating to the evidence in favour of carbamazepine's usage in this condition. However, the studies have reported a failure rate of 50%. Oxcarbazepine, lamotrigine,

gabapentin, and botulinum toxin A were other drugs recommended for the intervention of TN. Despite the lack of high-quality evidence, oxcarbazepine received a good recommendation based on clinical experience. (Bendtsen et al., 2019) As first-line treatments for CTN, carbamazepine and oxcarbazepine are sodium channel blockers. Long-term treatment may begin with either carbamazepine 200–1200 mg per day or oxcarbazepine 300–1800 mg per day.

The number-needed-to-treat (NNT) for carbamazepine is between 1.7 and 1.8 for TN; a dosage of 400–1200 mg/day is considered effective. The numbers-needed-to-harm (NNHs) for these adverse events are, however, 3.4 for minor and 24 for severe. Drowsiness, light-headedness, rash, liver damage, ataxia, and the possibility of various medication interactions are some of the negative effects. These are the typical reasons for treatment discontinuation and make medication titration difficult. (di Stefano et al., 2018).

Lamotrigine stabilises neuronal membranes and affects voltage-sensitive sodium channels, thus affecting the release of excitatory neurotransmitters. The daily dosing cap is 400 mg. Slow titration is advised due to the potential for CNS side effects such as rashes or, even worse, Stevens-Johnson syndrome. (Bendtsen et al., 2019).

Pregabalin, baclofen, and levetiracetam are second-line medications. An open-label cross-over trial comparing carbamazepine/pregabalin and carbamazepine/lamotrigine in 22 patients with refractory TN found similar efficacy and greater patient tolerance in the pregabalin group. (Obermann et al., 2008) Baclofen inhibits excitatory neurotransmission by acting as an agonist at GABA B receptors, and it can be used as an adjunct therapy and may have an analgesic effect in TN. Levetiracetam affects brain synaptic neurotransmitter release by interacting with the synaptic vesicle glycoprotein SV2. (Mitsikostas et al., 2010) For people whose treatments have failed or who require an adjuvant to medical treatment, a serotype of botulinum neurotoxin generated from Clostridium botulinum is an alternative. Numerous open-label studies, RCTs, and one systematic review have examined its analgesic impact. (Morra et al., 2016).

There is some evidence to suggest that people with multiple sclerosis (MS) may be more likely to experience TMD symptoms, such as pain in the jaw, difficulty in opening the mouth, and clicking sounds in the jaw joint. However, further research is needed to fully understand the relationship between MS and TMD, including the potential mechanisms underlying this association and the most effective treatment strategies for individuals with both conditions. Nevertheless, pharmacological intervention is the treatment of choice in such conditions. (Minervini, Mariani, et al., 2022).

3.4. Lifestyle-based management

While pharmacological treatment can be effective for managing chronic orofacial pain, there are also lifestyle-based management strategies that can help improve symptoms and enhance overall well-being. Stress can exacerbate chronic orofacial pain, so managing stress levels can be an important part of pain management. Stress management techniques such as deep breathing, meditation, and mindfulness can help reduce stress and promote relaxation. Physical exercise and regular physical activity can also help reduce stress levels and improve overall well-being. Moreover, eating a healthy and balanced diet can help improve chronic orofacial pain symptoms. (Banerjee et al., 2019; Lassmann et al., 2022) Poor posture can contribute to chronic orofacial pain by placing strain on the neck and facial muscles. (Romero-Reyes & Uyanik, 2014) Therefore, maintaining a good posture can help reduce tension in the neck and face and alleviate chronic orofacial pain. individuals can try exercises that focus on strengthening the neck and upper back muscles to improve posture and reduce pain. (Garstka et al., 2022) Sleep disturbances can exacerbate chronic orofacial pain, and improving sleep quality and quantity can be an effective strategy for managing such symptoms. Individuals should aim to get seven to nine hours of sleep every night and stick to a consistent sleep routine. Additionally, avoidance of electronic devices before bedtime and creating a relaxing sleep environment can promote better sleep. Alternative therapies such as acupuncture, massage, and chiropractic care can help manage chronic orofacial pain. (Penlington, 2019) These therapies can promote relaxation, reduce muscle tension, and improve blood flow to the affected area, although it must be mentioned that the evidence supporting these techniques are insufficient, to say the least. (Slade et al., 2016).

Currently, it is well established that depression increases the chance of developing TMD and is a significant predictor of chronic orofacial pain. (Liao et al., 2011; Nevalainen et al., 2017) Overlapping pathways may be the cause of this comorbidity. The reason why depression, a negative emotion, frequently results in an enhanced pain response, may be due to the fact that emotional brain regions project to brainstem structures that regulate pain.

Based on the multicentric analysis of TMD intervention conducted using research diagnostic criteria for TMD (RDC/TMD), a psychosocial aspect was well recognised in TMD patients, suggesting a correlation of TMD pain with depression, anxiety, and somatisation. (Banafa et al., 2021) Several authors have highlighted the significance of the psychological component in the pathophysiology of TMD. (Kotiranta et al., 2014; Rollman & Gillespie, 2000) Given this information, it is sensible to speculate on the molecular causes of sadness, anxiety, and generally elevated pro-inflammatory cytokines. In fact, our intestines—often referred to as our "second brain" (Yap et al., 2002)—are emerging as the main suspect.

Dietary proteins that contain tryptophan can convert the amino acid into a variety of compounds, including anxiety-inducing indole derivatives. Additionally, tryptophan can be metabolised via the kynurenic route, which in microglia results in the production of the neurotoxin quinolinic acid, whereas astrocytes create the excitatory-decreasing kynurenic acid. (Lassmann et al., 2022) Melatonin can be made in the pineal gland, which controls circadian rhythm, or in the gut, where it enhances microbial activity. GABA is an inhibitory neurotransmitter that can be produced in the gut by bacteria such Lactobacillus spp., Bifidobacterium dentium, and Bifidobacterium spp. and produces desensitisation. (Müller & Schwarz, 2007; Xu et al., 2021) A crucial element in orofacial pain is the idea of communication between the central nervous system (CNS) and the gut bacteria. Stress can cause the HPA (hypothalamus–pituitaryadrenal) axis reaction to be activated inside the neurological system; this causes the release of ACTH, which then starts the synthesis and release of cortisol.

By lowering occludin levels, cortisol in turn has an impact on the integrity of the intestinal barrier. Several different brain cell types, such as microglia and astrocytes, can receive signals from the body's external organs, including the digestive system. (Du et al., 2017; Pokusaeva et al., 2017; Sharon et al., 2016) Therefore, we should develop therapies that are anti-inflammatory, enhance the function of the gut microbiota, and subsequently improve sleep and mood considering the potential metabolic pathways causing sensitization. (Duan et al., 2018).

An extensive review conducted recently by Lassmann et al. analysed the role of gut microbiome, sleep, and the role of the hormone melatonin in managing CP. (Lassmann et al., 2022) They also examined several other factors (though not on a direct correlative basis as such). The results of the experiment showed that inflammation hindered body regeneration and increased pain sensitivity, stress, and anxiety through the disturbance of the sleep cycle.

3.5. Current stimulation based management

A different approach to treat chronic pain was conceptualised in the beginning of the 1990 s by Tsubokawa et al. (Tsubokawa et al., 1991) The Motor Cortex Stimulation (MCS) technique directly modifies brain activity using intracranial electrodes. Since then, conditions with chronic pain have been treated using MCS. Pain experienced is lesser when compared to other brain stimulation, though evidence is inconclusive. MCS is also more expensive and intrusive, which restricts its widespread adoption. Contrarily, safe and inexpensive techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have shown to offer long-lasting pain alleviation. (Cruccu et al., 2016; Lefaucheur, 2016) In short, tDCS uses surface electrodes with anode and cathode poles to deliver a steady low-amperage electric current to the central nervous system (often 1–2 mA or even up to 3 mA). Electrodes are placed on the scalp. (Tremblay et al., 2014) According to the ailment being treated, the conventional approach (commonly referred to as conventional tDCS) targets various cortical regions with larger electrodes (5x7 cm), which all adhere to the electroencephalogram (EEG) markers 10–10 or 10–20. The most common electrode placements are M1-SO (also known as motor cortex-supraorbital, with the anode electrode positioned over C3 and the cathode electrode positioned over Fp2), DLPFC (dorsolateral prefrontal cortex), and Cz-Oz (vertex-occipital cortex), with the anode electrode positioned over Cz and the cathode electrode positioned over Oz. A different method that uses smaller (ring) electrodes has recently been developed and used in several experiments. This modified version of the standard tDCS technique aims to increase focality and reroute most of the electrical current to the motor cortex, which is more anatomically similar to the MCS technique's initial target as described by Tsubokawa et al. High-definition tDCS, or HD-tDCS, is the name given to all these techniques. (Tsubokawa et al.,1991) In contrast, TMS alters magnetic fields to increase or reduce neuronal activity. Action potentials are produced when strong impacts depolarize neurons. Khedr et al. (Khedr et al., 2005) showed a substantial improvement in pain with active TMS compared to a placebo.

rTMS was administered to S1/M1 and S2, and its effects were examined by Lindholm et al. in 2015. (Lindholm et al., 2015) The targeted cortical region employed by Lindholm et al. differs from the traditional site of stimulation used for pain treatment, which is another significant aspect that demands careful consideration (e.g., M1). According to Lindholm et al., a significant reduction in pain was observed when S2 was stimulated as opposed to S1/M1 and a placebo. (Lindholm et al., 2015) These are interesting findings because they contradict those of the early studies by Tsubokawa et al. (Tsubokawa et al., 1991), who claimed that motor cortex stimulation produced better results than stimulation of other brain areas in the treatment of deafferentation pain brought on by central nervous system lesions. At least in terms of pain research, the utilisation of S2 as a cortical rTMS target is unique.

Hagenacker et al.'s (Hagenacker et al., 2014) comparison of two distinct groups of M1-tDCS showed a substantial difference in pain alleviation. The protocol of their study differed significantly from the other studies mentioned in the literature; the differences noted were the use of self-administered tDCS, the use of a weak electrical current with an intensity of 1 mA, and a greater number of sessions.

4. Conclusion

CP is a complex and challenging condition bearing a significant impact on a patient's quality of life. The management of this condition typically involves a multidisciplinary approach, including medications, physical therapy, psychological support, and alternative therapies. With a comprehensive treatment plan and ongoing support, many patients with chronic orofacial pain can achieve significant improvements in their symptoms and overall well-being.

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