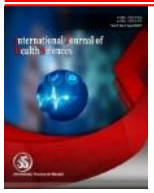

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The Efficacy of Botulinum Toxin Injections and Orofacial Myofunctional Therapy on Orofacial Disorders: A Systematic Review of Clinical Studies

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Abstract

Background: Botulinum toxin injections are widely used in the orofacial region for cosmetic and therapeutic purposes. Recently, interest has grown in combining Botulinum toxin A injection with facial exercises to enhance or sustain aesthetic and functional outcomes. **Objective:** To examine the efficacy of Botulinum toxin injections with facial exercise on orofacial disorders. **Methods:** A comprehensive electronic literature search was conducted across databases. Studies were screened for eligibility, and reviewers independently assessed quality and bias. **Results:** An electronic search of databases up until Feb 2026 revealed 164,916 Articles. Seven studies met the inclusion criteria, including four RCTs and three prospective clinical studies conducted in a hospital-based setting. Different Botulinum toxins have been used in these studies. Two studies used Onabotulinumtoxin A, two used botulinum toxin (Dysport), and two RCTs used botulinum A toxin (Botox). Additionally, the presented studies performed various myofunctional therapies. **Conclusion:** The current evidence suggests that facial exercise following Botulinum toxin A injections may enhance treatment outcomes in the orofacial area by sustaining muscle tone and prolonging aesthetic benefits. Further research with larger sample sizes and standardized protocols must establish the effectiveness and best practices of this combined approach.

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Contents

1 Introduction

The orofacial region, comprising the muscles of the face and jaw, plays a critical role in facial expressions, speech, mastication, and aesthetics. Dysfunction in this area, whether due to neurological conditions, trauma, or aesthetic concerns, can significantly impact an individual's quality of life. Treatment modalities, including botulinum toxin (BoNT) injections and facial exercises, have been developed to address these issues. Both approaches have gained widespread attention for their therapeutic and cosmetic benefits (Small, 2014; Hong, 2023; Altuhafy et al., 2023). Botulinum toxin, a neurotoxin derived from *Clostridium botulinum*, has been widely used for medical and aesthetic purposes. In the orofacial region, it has proven effective in treating conditions such as bruxism, temporomandibular joint (TMJ) disorders, hemifacial spasms, and facial dystonia (Serrera-Figallo et al., 2020; Altuhafy et al., 2022). Among many other uses, Botulinum neurotoxin type A (BoNT/A) has been widely used for medical and aesthetic purposes in the facial area, such as frown lines between the eyes, necklines, myofascial pain, bruxism, migraines, dystonia, hemifacial spasms, facial palsy, blepharospasm, and strabismus (Small, 2014; Hong, 2023; Altuhafy et al., 2023; Serrera-Figallo et al., 2020). By temporarily inhibiting muscle contraction, BoNT/A provides relief from muscular hyperactivity and associated pain while also offering aesthetic improvements in cases of facial wrinkles (Hong, 2023; Altuhafy et al., 2023; La Fleur & Adams, 2020; Kalladka et al., 2021). BoNT/A has been effectively used to treat a variety of orofacial conditions, including muscle hyperactivity disorders, TMJ pain, hemifacial spasms, and bruxism, as well as to reduce the appearance of wrinkles (Altuhafy et al., 2023; Romero-Reyes et al., 2023; Delcanho et al., 2022). Its efficacy in reducing muscle activity and providing pain relief has made it a preferred treatment for many patients with orofacial dysfunction. On the other hand, facial exercises aim to strengthen the orofacial muscles through repetitive movements. Proponents argue that these exercises can enhance facial tone, improve symmetry, and provide rehabilitative benefits following conditions such as facial nerve paralysis (Pereira et al., 2011; Lee et al., 2015). Facial exercises have been employed in both therapeutic and cosmetic contexts, but their efficacy, especially in comparison to interventions like BoNT, remains a subject of ongoing research (Pereira et al., 2011; Shimada et al., 2019; Altuhafy et al., 2024).

Combining BoNT/A and facial exercises in the orofacial area has garnered growing interest among clinicians for its potential to optimize both aesthetic outcomes and therapeutic benefits. When combined with botulinum toxin, facial exercises may help counterbalance the toxin's muscle-relaxing effects, potentially promoting long-term muscle tone and joint functionality improvements (La Fleur & Adams, 2020; Altuhafy et al., 2024; Sari et al., 2024). For example, in managing TMJ disorders and bruxism, studies suggest that the combined approach of Botulinum toxin and exercises can reduce hyperactivity in the masseter muscles while preserving overall facial strength and joint mobility (Altuhafy et al., 2023; La Fleur & Adams, 2020; Shimada et al., 2019). This integrative approach is especially beneficial in cases requiring muscle relaxation and active toning or rehabilitation. In patients recovering from facial paralysis, for instance, Botulinum toxin can reduce unwanted muscular contractions, while targeted exercises can stimulate weakened muscles, helping to restore facial symmetry and functionality (Pereira et al., 2011; Lee et al., 2015). Thus, combining BoNT/A with facial exercises may provide a more comprehensive solution for patients seeking aesthetic enhancement, pain relief, or rehabilitation of orofacial muscles. Further research on this combination is needed to establish optimized protocols and clarify its long-term benefits in orofacial therapy and aesthetics [6, 14, 15]. Despite

the widespread use of both botulinum toxin and facial exercises, the comparative effectiveness of these interventions in treating orofacial conditions has yet to be conclusively established. While BoNT/A offers immediate and localized muscle relaxation, facial exercises may provide long-term functional improvement through muscle strengthening. This systematic review aims to evaluate the effectiveness of BoNT/A and facial exercises for orofacial disorders, providing a robust evidence base. By synthesizing the findings of these studies, the review will offer insight into the comparative benefits, limitations, and potential applications of these interventions.

2 Materials and Methods

Reporting format

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). This study's protocol was registered with PROSPERO (Registration number CRD42024613574). Due to the high heterogeneity in the studies, a meta-analysis was not performed.

Focused Question

The focused question was, "Is combined Botulinum toxin A injections with facial exercises effective in managing **orofacial disorders**"?

Patients, Interventions, Control, Outcome (PICO)

The present systematic review included randomized controlled clinical trials comparing the effectiveness of treating patients with a combined BoNT/A and facial exercise protocol compared with each treatment used individually and other conventional therapies, based on the following Participants- Interventions-Comparisons-Outcome-Study design (PICOS) approach: (P): patients undergoing BoNT/A injections, (I): Facial Exercise OR Orofacial myofunctional therapy with or after BoNT/A, (C): Non-facial exercise or other treatment, (O): Management of orofacial disorders and improvement of mandibular function, (S): Randomized controlled clinical trials and prospective studies.

Search strategy and data extraction

An electronic search was conducted according to PRISMA guidelines, and databases including PubMed, Cochrane Library, Medline, Web of Science, and Embase were searched until Feb 2026. As a first step, studies were independently searched by two authors using a combination of the following keywords based on Medical Subject Headings: (1) Botulinum toxin injection, (2) Botox, (3) Botulinum neurotoxin injection and facial exercise, (4) myofunctional therapy (5) orofacial pain disorders, (6) adults, (7) pain, (8) discomfort. Specific vital languages were merged using Boolean operators (OR and AND) to broaden the results. Subsequently, two authors (MA, AR) assessed the titles and abstracts of the studies identified using the aforementioned tools, and the texts of pertinent studies were independently evaluated. Additionally, reference lists of relevant original studies and review articles were manually searched to identify potentially overlooked studies in the initial phase by two authors (AR, MA). Any discrepancies were addressed through discussion with a third author (JK). All the information from the included studies was synthesized by tabulating the data according to (a) study design, b) c) study outcomes. In addition, a quality assessment was performed.

Risk of bias assessment

Two authors (MA, AR) independently assessed the risk of bias (RoB) of included studies using the revised Cochrane risk-of-bias tool for randomized trials (Higgins et al., 2019). The ROBINS-I tool was used for assessing the risk of bias in non-randomized studies of interventions (Sterne et al., 2016). Any disagreements were resolved through discussion with a third author (JK). The data were organized into evidence tables, and a descriptive analysis was performed to highlight the characteristics of the included studies.

3 Results and Discussions

3.1 Results

Study selection

An electronic search of indexed databases (PubMed, Cochrane Library, Scopus, Web of Science, and Embase) up to Feb 2026 yielded 164,916 studies. After removing duplicates, 719 studies remained. Four studies were added for screening after a hand search of the references. After reading the titles and abstracts, 11 studies underwent full-text assessment for eligibility, and four were excluded. A total of 7 RCTs were included in the present systematic review for qualitative analysis and processed for data extraction (Figure 1, Tables 1 and 2).

General characteristics of the included studies

The included studies were four RCTs and three prospective studies that were conducted in a hospital-based setting between 2011 and 2024 (Lee et al., 2015; Sari et al., 2024; Pitakpatapee et al., 2021; PO'Reilly et al., 2012; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015). The number of participants in the included studies ranged from 8 to 51, and their ages ranged from 36.11 to 65.1 (±11.8) years. Five studies (Lee et al., 2015; PO'Reilly et al., 2012; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015) included both male and female patients and two studies (Sari et al., 2024; Pitakpatapee et al., 2021) did not report the gender. The intervention consisted of combined therapy of BoNT/A injection and facial exercise or facial exercises following the injection, and the control group consisted of only the BoNT/A injection protocol or saline injection with Electromyography Biofeedback (EMG) (Pourmomeny et al., 2015). The study duration ranged from 3 to 24 months. A total of 3 studies mentioned the source of funding (Lee et al., 2015; Pitakpatapee et al., 2021; PO'Reilly et al., 2012) (Table 3).

General characteristics of the Intervention

All the included studies report various facial disorders, including blepharospasm, hemifacial spasm, aberrant facial nerve regeneration, benign essential blepharospasm, Bell's palsy with herpes zoster oticus, and facial synkinesis (Lee et al., 2015; Sari et al., 2024; Pitakpatapee et al., 2021; PO'Reilly et al., 2012; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015). Different BoNT/A have been used in the studies. Two studies used Onabotulinumtoxin A (Sari et al., 2024; Pitakpatapee et al., 2021), 2 studies used botulinum toxin (Dysport) (Guarda-Nardini et al., 2012; Pourmomeny et al., 2015), 2 RCTs used botulinum A toxin (Botox) (Lee et al., 2015; Azuma et al., 2012), whereas 1 study mentioned only botulinum toxin-A without specifying it (PO'Reilly et al., 2012). Variability was noted among the studies, including the volume, the target injection area for BoNT/A, and the needle size. Five studies used BoNT/A injections with volumes ranging from 1.5 to 500 units (Lee et al., 2015; Sari et al., 2024; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015), whereas two studies did not report the volume, needle gauge, or injection site [15, 19]. Various target areas are mentioned in the presented studies. In one study, BoNT/A was injected into the movement of muscles innervated by the facial muscles symmetrically (Sari et al., 2024). In another study, the BoNT/A injected in the periocular and perioral areas included the zygomaticus major and minor muscles, prominent hypertrophic regions on the contralateral side, Deep furrows, and creases caused by facial muscular hyperkinesis or atrophy (Lee et al., 2015). A study done by Azuma et al. (2012), showed that BoNT/A injections were used around the upper and lower eyelids in the ipsilateral orbicularis oculi muscle. Moreover, a study by Guarda-Nardini et al. (2012), reported that BoNT/A injection (Dysport) was performed by asking patients to clench their jaws to identify the target muscle. Then, multiple injections were given in the more prominent areas of the muscles, with each injection covering, on average, a 2 cm skin surface over the target muscle tissue. A five-injection minimum with a reverse pyramid pattern was performed in the masseter muscles, and a chessboard pattern was used for the temporalis muscles. Multiple BoNT/A injections in the temporalis and masseter muscles. A study by Pourmomeny et al. (2015), found that the injection sites were orbicularis oculi, orbicularis oris, zygomatic major, levator labii superioris, and depressor labii inferiors. Regarding the needle gauge, 2 studies reported a 27-gauge needle (Lee et al., 2015; Azuma et al., 2012), and 2 reported using a 30-gauge needle (Guarda-Nardini et al., 2012; Pourmomeny et al., 2015). Two studies by PO'Reilly et al. (2012) and Pitakpatapee et al. (2021) did not report the needle size. The presented studies included various facial exercises, including the study by Sari et al. (2024), which reported that the patient was

advised to lift eyelids as much as possible to create wrinkles on the forehead, each movement for 5 seconds, to repeat each movement 10 times with a 10-second break every day, 3 times a week for 1 week (Sari et al., 2024). The study by PO'Reilly et al. (2012), reported that participants were instructed to make a motion consisting of forcefully screwing up their faces as tightly as possible for 2 seconds, then stretching them as wide as possible for 2 seconds. Hence, the jaw is maximally open, the mouth aperture is as big as possible, and the eyebrows are maximally elevated. Then, patients will perform five full-face squeeze motions, then relax for 15 seconds. This constitutes a cycle. Cycles are repeated until 5 minutes have elapsed. If the patient finds this problematic after 5 minutes, they should increase the interval between squeezing phases (PO'Reilly et al., 2012). Another study by Pitakpatapee et al. (2021), reported a video-guided program that included 7 minutes of active and passive facial muscle squeezing of the muscles usually affected by HFS immediately after BTX-A injection. Meanwhile, a study by Lee et al. (2015), reported using the half-mirror biofeedback exercise, 30 min per day for 2 years. In the study by Azuma et al. (2012), Patients were instructed to keep their eyes open symmetrically during three designated mouth movements: pursing one's lips, baring one's teeth, and puffing out one's cheeks while looking into a mirror for 30 minutes per day for 10 months (Azuma et al., 2012). In the study by Guarda-Nardini et al. (2012), deep digital pressure is applied to specific coordination points defined by the method and selected based on a precise clinical examination, as indicated by the fascial manipulation guidelines. Therapists use their elbows, knuckles, or fingertips to exert pressure on the muscle areas; each patient underwent three50 (±1) min sessions of fascial manipulation weekly for a total of 150 (±50) min over a two- to four-week span (Guarda-Nardini et al., 2012). A study done by Pourmomeny et al. (2015), reported that rehabilitation included stretching the muscles of the affected side and EMG biofeedback using an EB Neuro-MYTO II instrument, which has two channels (one for voluntary and the other for involuntary movement), three times a week for four months (Tables 4 and 5).

General characteristics of outcome variables

The presented studies used different assessment tools to evaluate the effect of combining BoNT/A with facial exercise on orofacial disorders compared to other treatments. The study by Sari et al. (2024), reported that the HSGS and Jankovic scales were used to evaluate the effect of BoNT/A injection with facial exercise compared to BoNT/A injection without any additional Activity. The study noted that Facial self-exercise following the BoNT/A application may extend the effectiveness of botulinum toxin treatment in subjects with HFS and BFS (P = .008) (Sari et al., 2024). PO'Reilly et al. (2012) evaluated the effect of BoNT/A injection with facial exercise compared to BoNT/A injection alone and reported that 5-minute video recordings were reviewed and scored by one masked investigator, Pre-treatment Questionnaire, Post-treatment Questionnaire, and Post-treatment Telephone Questionnaire. This study suggested a possible trend towards an increased efficacy of BoNT/A, with facial muscle squeezing post-BTX treatment (p = 0.367) (PO'Reilly et al., 2012). Also, the study by Pitakpatapee et al. (2021), evaluated the effect of the combined facial exercise with BoNT/A injection to BoNT/A alone and used these tools: HFS-30 and the hemifacial spasm score, Physician-Assessed Samsung Medical Center (SMC) severity grading scale. The authors concluded that a combination of a novel facial exercise protocol and BoNT/A injection showed a promising benefit for adult patients with HFS (Pitakpatapee et al., 2021). The study by Lee et al. (2015), evaluated patients who received BoNT/A injection with facial biofeedback rehabilitation using a mirror, and compared it with no treatment; the Sunnybrook (SB) facial nerve grading system was used. This facial rehabilitation strategy, consisting of three injections of BoNT/A and half-mirror biofeedback exercises, proceeds over 2 years and offers a long-lasting cure for facial synkinesis, facial symmetry, and improved facial aesthetics. In the study performed by Azuma et al. (2012), DVgate Still software and Adobe Photoshop images, % of eye-opening) were used. The findings demonstrate that facial biofeedback rehabilitation with a mirror after a single dose of BoNT/A is a long-lasting treatment for established facial synkinesis in patients with chronic facial palsy, compared with no prior BoNT/A injection ($P < 0.05$). The study by Guarda-Nardini et al. (2012) assessed maximum pain levels (VAS ratings) and jaw range of motion in millimeters, and the data were consistent with the current literature, suggesting that several conservative therapeutic approaches may be helpful for patients with TMD-related symptoms ($P<0.05$). Pourmomeny et al. (2015), The study used the Photoshop assessment and FGS and reported that Biofeedback therapy is as effective as the combination of biofeedback and BoNT/A in reducing synkinesis and restoring facial symmetry in Bell's palsy, compared with saline injection with EMG ($P>0.05$) (Table 6).

Risk of bias of included studies

RoB for Randomized controlled trials

The Cochrane Collaboration's RoB tool was used for the RCT studies. The randomization sequence generation and allocation clearance were low in the four RCT studies (Lee et al., 2015; Sari et al., 2024; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015). Blinding of Participants and Personnel and Blinding of Outcome Assessment were high in the three studies (Lee et al., 2015; Sari et al., 2024; Azuma et al., 2012; Guarda-Nardini et al., 2012). In the study by Pourmomeny et al. (2015), The Blinding of Participants and Personnel was low, and the Blinding of Outcome Assessment was high. Moreover, the Incomplete Outcome Data was high in one study only [14], and some concerns were raised in the other three RCT studies [15, 21, 22]. Additionally, the Selective Reporting was low in all four studies (Lee et al., 2015; Sari et al., 2024; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015). Other Biases were some concerns in all four studies (Lee et al., 2015; Sari et al., 2024; Azuma et al., 2012; Guarda-Nardini et al., 2012; Pourmomeny et al., 2015). Overall, the risk of bias was high in three studies (Sari et al., 2024; Pitakpatapee et al., 2021; Guarda-Nardini et al., 2012), and some concerns in one study, only done by Pourmomeny et al. (2015). **(**Table 7 and figures 2,3).

RoB for non-randomized controlled trials

Three studies were prospective, and the Cochrane Collaboration's RoB tool was used. For instance, in the two studies by PO'Reilly et al. (2012) and Azuma et al. (2012). The biases were due to confounding, Biases in the selection of participants in the study, Biases in the classification of interventions, and biases due to deviations from intended interventions, which were low. The Biases due to confounding, Biases in the selection of participants in the study, and Biases in the Classification of interventions were serious in one study by Lee et al. (2015). The Bias due to deviations from intended interventions was moderate in the same study (Lee et al., 2015). However, the Bias due to missing data, Bias in the measurement of the outcome, Bias in the selection of the reported result, and Overall risk of bias judgment were moderate in all three studies (Lee et al., 2015; PO'Reilly et al., 2012; Azuma et al., 2012) (Table 8 and figures 4,5).

3.2 Discussions

Orofacial pain disorders are common, significantly debilitating conditions that occur more frequently in women than in men. Typically, the initial treatment approach is conservative and traditional, involving pharmacological or non-pharmacological methods (Altuhafy et al., 2023; Ferrillo et al., 2022). First-line treatments often include non-invasive treatments or therapies, such as occlusal splints, physical therapy, facial exercises, stress management, and cognitive-behavioral therapy (CBT), which address muscular imbalances and psychosocial factors contributing to pain. Pharmacological interventions, such as nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antidepressants, and anticonvulsants, are commonly used to manage pain and reduce inflammation. Additionally, heat or cold therapy and ultrasound are employed to alleviate discomfort and enhance healing (Ferrillo et al., 2022). The choice of treatment depends on the specific type and severity of the orofacial pain disorder. There is a growing emphasis on multimodal, patient-centered approaches to optimize relief and function.

Botulinum toxin A is emerging as a very potent and valuable clinical tool for TMD's diagnostic and therapeutic care (Altuhafy et al., 2023). It provides significant relief from TMD pain and reduces the intensity, frequency, and duration (Delcanho et al., 2022). Bruxism, clenching, subluxation, masseteric hypertrophy, recurrent dislocation of the temporomandibular joint, oromandibular dystonia, and chronic myogenous orofacial pain trigger point injections are various applications that can be successfully treated with botulinum toxin (Altuhafy et al., 2023; Delcanho et al., 2022). More recently, data from studies have suggested a possible trend toward an increased efficacy of BoNT/A with facial exercises. Guarda-Nardini et al. (2012) indicated that the gathered data fit well with the current literature. They suggested several conservative therapeutic approaches may be helpful for patients with TMD-related symptoms. Future studies on larger samples over a longer follow-up were needed to identify tailored treatment strategies. Pourmomeny et al. (2015), demonstrated that biofeedback therapy is as effective as the combination of biofeedback and BTX in reducing synkinesis and recovery of facial symmetry in Bell's palsy. Although BoNT/A injections have shown

remarkable results within a few days concerning the disappearance of facial synkinesis, the temporary nature of the therapeutic benefit of facial sequelae treatment with botulinum toxin is a severe disadvantage (Mazlout et al., 2012; Yoelin et al., 2018).

Facial exercises are gaining recognition as a noninvasive treatment option for orofacial pain disorders, such as temporomandibular disorders (TMD), facial nerve dysfunction, and others affecting the muscles and joints of the face and jaw (Zhang et al., 2021). One of the primary benefits of facial exercises is their ability to reduce muscle tension and improve strength. Stretching and strengthening exercises work to relax tense muscles and enhance the function of weaker ones, restoring balance in facial muscle activity. This reduces pain and improves coordination and symmetry, especially in cases of facial nerve dysfunction, such as Bell's palsy or facial synkinesis (Bednarczyk et al., 2024; von Piekartz et al., 2024). Combining facial exercises with Btx injections offers a synergistic approach to managing orofacial pain disorders, leveraging the strengths of both treatments to provide more comprehensive relief (PO'Reilly et al., 2012). Most of the previous studies examining the therapeutic effect of botulinum toxin injection for facial sequelae have shown remarkable results in the disappearance of facial synkinesis within a few days (Yoelin et al., 2018). Still, the effect lasts only 3-5 months. In addition, many reports on the impact of facial exercise on facial sequelae have been proven to have low-quality evidence by systematic reviews (Ainsworth & Kraft, 1995). To prolong the effect of the botulinum toxin, this therapy was combined with mirror biofeedback exercises (Sari et al., 2024). The combination of mirror biofeedback exercise and botulinum toxin A offers many synergistic advantages. During the period when botulinum toxin A is effective, patients can train their defective facial muscles with mirror exercises (Sari et al., 2024). Benign essential blepharospasm (BEB), Hemifacial spasm (HFS), and aberrant facial nerve regeneration (AFNR) represent common forms of facial dystonia (Ainsworth & Kraft, 1995). In Europe, the prevalence of BEB has been reported as 36 per million. However, estimates have varied (Mazlout et al., 2012; Ainsworth & Kraft, 1995). The exact cause of BEB is unclear, and current treatments aim to control symptoms. Botulinum toxin A injections are the mainstay of treatment for many forms of facial dystonia and have numerous other applications. Due to the temporary nature of its effect and the regular injections required, it is a costly and time-consuming intervention (Mazlout et al., 2012). PO'Reilly et al. (2012) performed a study to address whether voluntary muscle squeezing post-BoNT/A treatment with increased neuronal activity translates into noticeable patient benefits in practice. They concluded that although statistical significance was not achievable, this study suggested a possible trend toward an increased efficacy of BoNT/A, with facial muscle squeezing post-BTX treatment (PO'Reilly et al., 2012). Pitakpatapee et al. (2021) concluded that a combination of a novel facial exercise protocol and BoNT/A injection showed a promising benefit for adult patients with HFS. Orthodontic devices, such as splints or mouthguards, are often prescribed to address bruxism, correct jaw alignment, and reduce joint strain. In more severe cases, surgical interventions may be considered. These include arthrocentesis or arthroscopy for temporomandibular joint (TMJ) disorders and nerve decompression surgery for conditions involving neuralgia. Complementary and alternative therapies, such as acupuncture and biofeedback, are also employed in some cases to provide additional pain relief and improve patient outcomes.

The primary strength of this systematic review is its incorporation of randomized controlled trials (RCTs), which represent a high standard of evidence for evaluating clinical interventions. Also, including participants from both genders and varying age groups allows researchers to explore potential subgroup differences, such as gender-specific or age-related variations in treatment efficacy, side effects, or outcomes. The studies are better positioned to account for possible differences in response to interventions or treatments that may arise due to biological, hormonal, or age-related factors. This can provide deeper insights into personalized treatment strategies and improve the quality of evidence supporting clinical decisions. However, the variability across these RCTs posed significant challenges for synthesizing data quantitatively through meta-analysis. Methodological inconsistencies among the included studies were a notable limitation. Specifically, there were substantial differences in the diagnostic classifications used, encompassing a wide range of conditions such as hemifacial spasm, blepharospasm, aberrant facial nerve regeneration (AFNR), benign essential blepharospasm, unilateral facial palsy, Bell's palsy, facial synkinesis, and herpes zoster oticus. Additionally, there was no uniformity in the diagnostic criteria employed, with some studies relying on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) while others utilized alternative frameworks. Beyond diagnostic variability, the studies displayed inconsistencies in the intervention protocols. These included differences in the application methods of botulinum toxin, variations in facial exercise

regimens, and discrepancies in the specific facial regions targeted for treatment. Furthermore, heterogeneity extended to the intervals used for assessing parameters, the types of parameters measured, the duration of follow-up periods, and the statistical methods applied for group comparisons. Such variability hindered the ability to draw robust and generalizable conclusions from the reviewed data.

The limited statistical power of the included RCTs further complicated the interpretation of intergroup differences. Among the four RCTs analyzed, the overall risk of bias was assessed as high in three studies (Sari et al., 2024; Pitakpatapee et al., 2021; Guarda-Nardini et al., 2012). The remaining study, conducted by Pourmomeny et al. (2015), was judged to have "some concerns" regarding bias. While three RCTs were prospective in design, they exhibited moderate risks in several domains. This included bias due to missing data, bias in the measurement of outcomes, bias in the selection of reported results, and the overall risk of bias assessment (Lee et al., 2015; PO'Reilly et al., 2012; Azuma et al., 2012). A critical methodological shortcoming was the lack of power analysis for sample size estimation in all the included RCTs. This omission raises concerns about the potential for Type II errors, where real differences between treatment groups may have been missed due to insufficient statistical power. Such limitations highlight the need for caution when interpreting the statistical findings of these studies, as the absence of adequately powered samples undermines the reliability of the reported results.

This Systematic review aimed to reassess the effectiveness of combining BoNT/A injections with facial exercises for managing orofacial pain disorders by analyzing previous research and comparing the outcomes with placebo and other conventional treatments. The findings will guide practitioners in treating TMDs, hemifacial spasm, blepharospasm, AFNR, benign essential blepharospasm, unilateral facial palsy, Bell's palsy, and facial synkinesis. Results indicate that BoNT/A injections combined with facial exercises can significantly reduce pain levels, though effects on secondary outcomes vary. This treatment approach offers disadvantages as it is non-invasive, reversible, has fewer side effects, and may also positively impact the psychological and emotional aspects of orofacial conditions. Consequently, this review underscores the potential of Botulinum toxin A and facial exercises as an effective treatment for different orofacial conditions or disorders. Despite these promising findings, additional studies with more extended follow-up periods and standardized protocols for Botox and facial exercises are needed to draw stronger, more definitive conclusions regarding the efficacy of this combined treatment approach.

4 Conclusion

This review underscores the potential of BoNT/A and facial exercises as effective treatments for different orofacial conditions or disorders. Despite these promising findings, additional studies with more extended follow-up periods and standardized protocols for Botulinum toxin A and facial exercises are needed to draw stronger, more definitive conclusions regarding the efficacy of this combined treatment approach.

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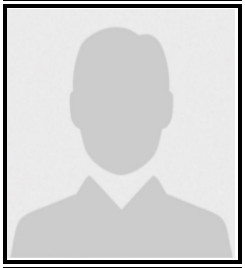
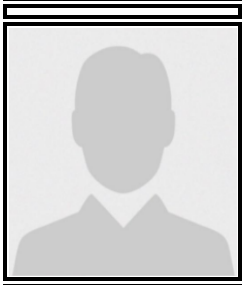
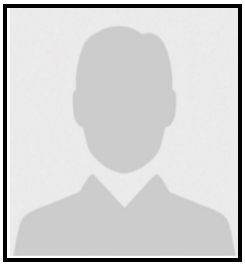
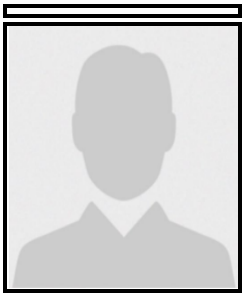
Biography of Authors

	**Maryam R Altuhafy BDS, MSD** Assistant Professor of Clinical Dentistry, Orofacial Pain and TMJD Eastman Institute for Oral Health, Rochester, NY, USA. Phone: +1 (585) 733-1059 Email: Maryam_Altuhafy@urmc.rochester.edu ORCID: 0000-0001-7025-5728
	**Alfred Ravikumar BDS, MS** Resident, Orofacial Pain and TMJD Rochester, NY, USA. Phone: +1 (585) 733-1059 Email: Alfred_Ravikumar@urmc.rochester.edu
	**Mayaf Altuhafy BDS** High Diplomate in Restorative Dentistry, Dubai, UAE Phone: +971 564730347 Email: Mayafaltuhafy@gmail.com
	**Junad Khan DDS, MSD, MPH, PhD** Director and Associate Professor, Orofacial Pain and TMJD Eastman Institute for Oral Health 625 Elmwood Avenue Rochester, NY, USA. Phone: +1 (201) 238- 4248 Email: Junad_khan@urmc.rochester.edu ORCID: 0000-0002-3107-6118

APPENDIX

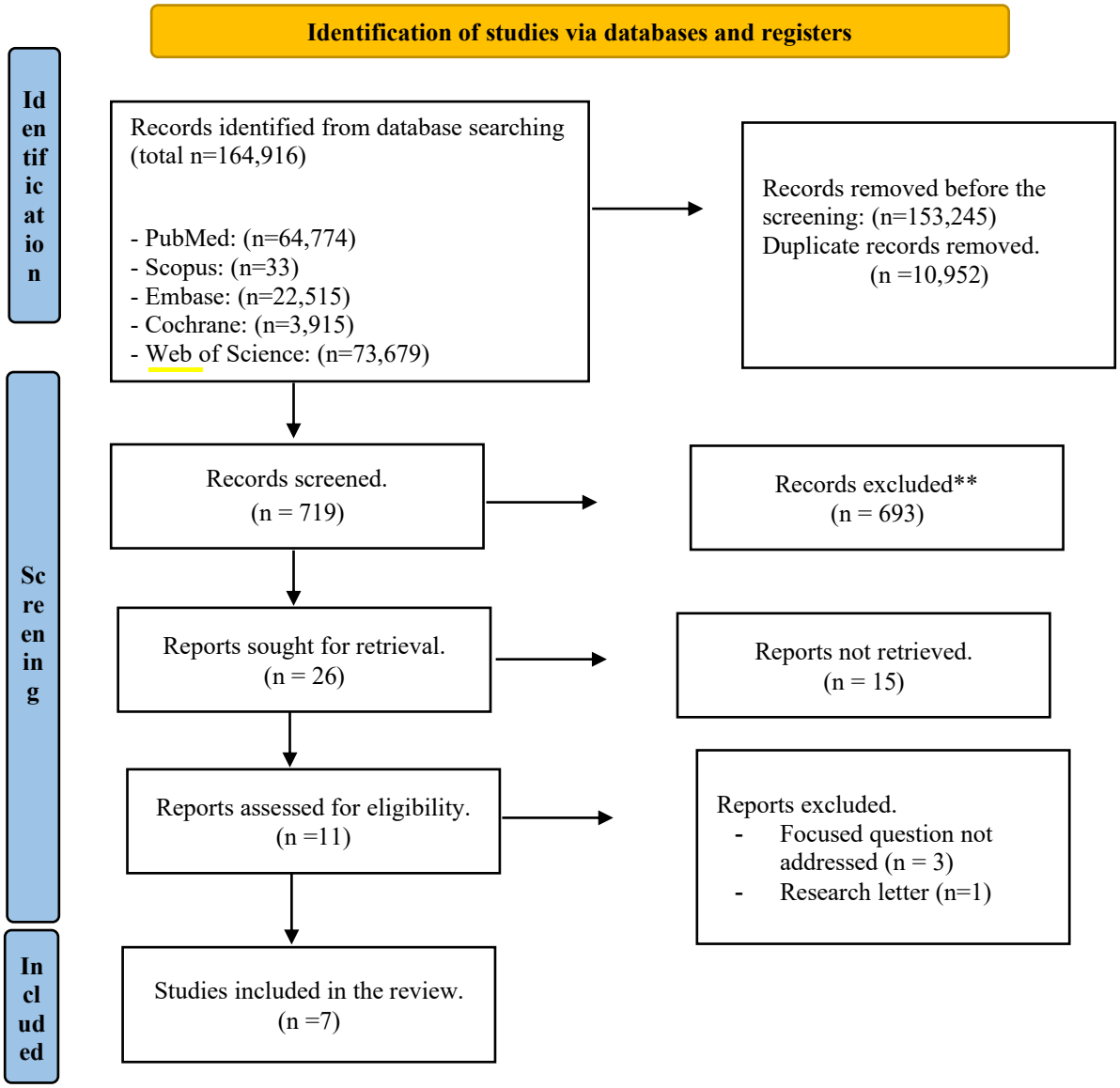


Figure 1. Flow chart of included studies

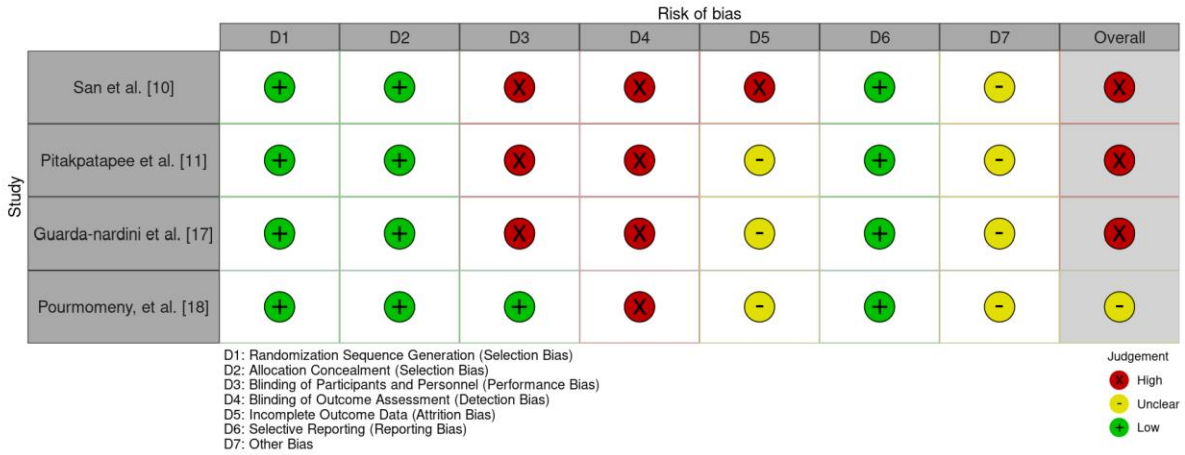


Figure 2. Traffic light Plot for ROB of RCT studies

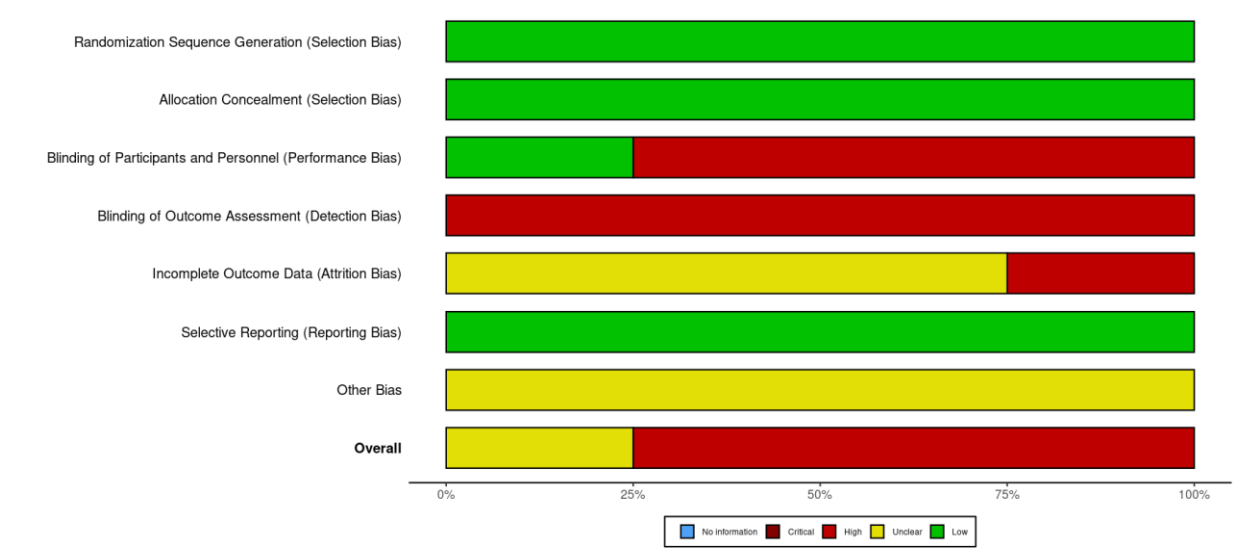


Figure 3. Summary Plot for ROB of RCT studies

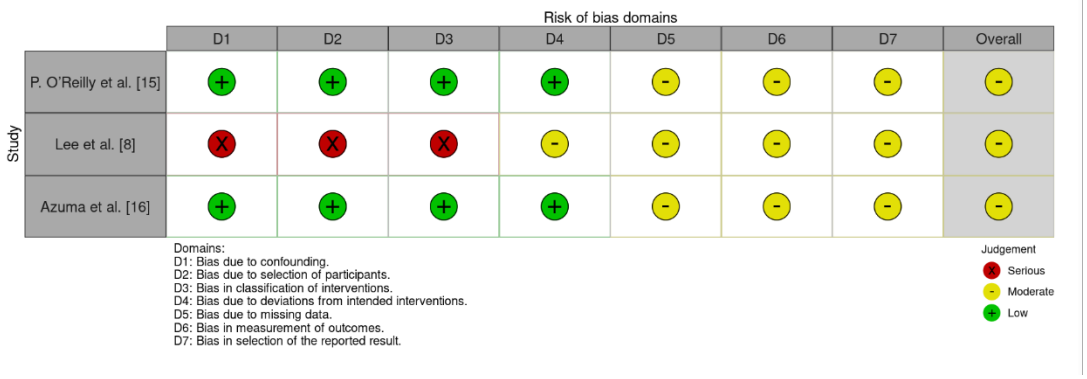


Figure 4. Traffic light Plot for ROB of Non-RCT studies

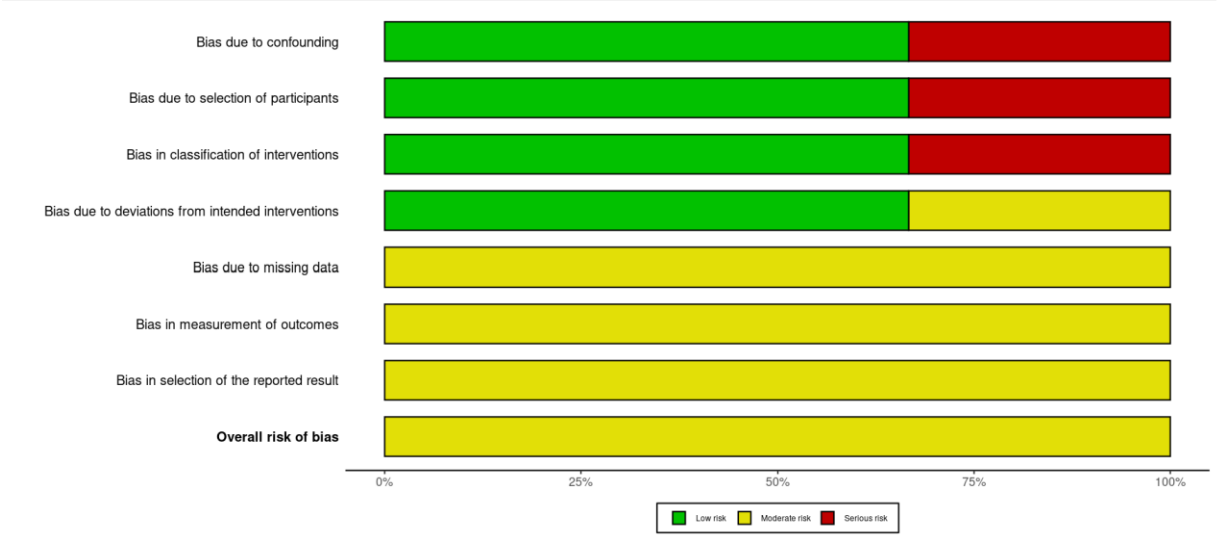


Figure 5. Summary Plot for ROB of Non-RCT studies

Table 1. Search strategy for electronic databases

Database Search	Keywords	Results
PubMed	(myofunctional therapy MeSH Terms]) OR facial exercises [Title/Abstract]) AND (((((((Botulinum neurotoxin MeSH Terms]) OR Botulinum neurotoxin injection [Title/Abstract]) OR Botox injection [Title/Abstract]) OR myofunctional therapy [Title/Abstract]) AND orofacial disorders Title/Abstract]) OR facial exercise AND pain [Title/Abstract]) OR discomfort [Title/Abstract]).	64,774
Embase	('facial exercise' OR (facial AND ('exercise'/exp OR exercise))) AND 'botulinum neurotoxin injection' OR 'muscle training'/exp OR 'muscle training'	22,515
Scopus	Botulinum AND toxin AND facial AND exercises AND facial AND disorders	33
Web of Science	("Botulinum neurotoxin injection ") AND (‘‘myofunctional therapy’’) AND (“Pain”) OR (“Discomfort”)	73,679
Cochrane	(‘‘Botulinum toxin A injection’’) OR (‘‘Botulinum neurotoxin injection’’) OR (‘‘adults’’) OR (‘‘orofacial disorders’’) OR (‘‘discomfort’’)	3,915

Table 2. List of excluded studies at full-text review with reasons for exclusion

Reference	Reasons for the Exclusion
Alam et al. (2007) PMID: 30617028	Research letter
Keen et al. (2002) PMID: 8016257	Focused question not addressed.
Akulov et al. (2002) PMID: 28991664	Focused question not addressed
Graboski et al. (2011) PMID: 16202527	Focused question not addressed.

Table 3. General Characteristics of Included Studies

Author /Year	Country	Funding	Study Design	Participants	Mean Age	Gender M/F	Control	Intervention	Duration of Study
San et al./ 2024 [14]	Turkey	NR	RCT	51(51)	Group 1 58.81 ± 11.48 Group 2 59.79 ± 11.66	NR	BoNT injection, without any additional Activity	BoNT injection, With exercise	3 months
P. O'Reilly et al. /2012 [19]	United Kingdom	Research grant - QVH from Allergan Inc.	Prospective double cross-over	26(26)	65.1 (±11.8) years	Male-11 Female-15	BoNT injection, without any additional Activity in 1st treatment visit and 3rd treatment visit. Although squeezing exercises were given in the 2nd treatment visit	BoNT injection, with additional intensive facial exercises given in 1st treatment visit and 3rd treatment visit. Although no exercises were given in the 2nd treatment visit	9 months
Pitakpatapee et al. /2020 [15]	Thailand	Siriraj Medical Research Center	RCT -pilot, assessor-blinded, single-centered, randomized	42(38)	NR	NR	BTX-A injection alone	Combined facial exercise with BTX-A injection	8 months
Lee et al. /2014 [11]	Republic of Korea	Research Foundation of Inje University.	Prospective	17(17)	49.3 ±5.1 years).	Male-7 Female-10	Pretreatment – No Botulinum toxin injection with facial biofeedback rehabilitation with a mirror	Botulinum toxin injection with facial biofeedback rehabilitation with a mirror	24 months
Azuma et al /2011 [20]	Japan	NR	Prospective	8(8)	65.0 years	Male-7 Female-6	Pretreatment – No Botulinum toxin injection with facial biofeedback rehabilitation with a mirror	Post-treatment - Botulinum toxin injection with facial biofeedback rehabilitation with a mirror	10 months
Guarda-nardini et al.	Italy	NR	RCT	30(30)	Group A 47.7 (14.3)	Male-8 Female-22	No treatment	Facial manipulation exercises	3 months

Author /Year	Country	Funding	Study Design	Participants	Mean Age	Gender M/F	Control	Intervention	Duration of Study
/2012 [21]					Group B 43.2 (13.9)			after Btx injection	
Pourmomeny AA, et al /2015 [22]	Iran	NR	RCT	34(34)	Group A 36.11 Group B 39.11	Group A-Male-5 Female-12 Group B-Male-1 Female-16	Saline Injection with EMG	Botulinum toxin injection with EMG	4 months

RCT-Randomized Control Trial, BTX-Botulinum Toxin, EMG-Electromyography Biofeedback, NR-Not reported.

Table 4. Characteristics of Botulinum toxin A

Author	Diagnosis	Type of Botulinum toxin A	Volume	The target area of Botulinum toxin Injection	Size of the needle
San et al.[14]	HFS BFS	Onabotilinumtoxin A (BoNTA)	HFS- 15 to 30 units BFS- 30 to 40 units	Movement of muscles which are innervated by facial muscles symmetrically	NR
P. O'Reilly et al. [19]	AFNR, BEB, or hemifacial spasm (HFS)	Botulinum toxin-A	NR	NR	NR
Pitakpatapee et al. [15]	HFS	Onabotulinumtoxin A	NR	NR	NR
Lee et al. [11]	Unilateral facial palsy	Botulinum toxin A (Botoxâ; Allergan Incorporated, Irvine, CA, USA)	1.5 to 3 U,	The periocular and perioral areas included the zygomaticus major and minor muscle, Prominent hypertrophic regions on the contralateral side, Deep furrows, and creases caused by facial muscular hyperkinesis or atrophy.	27-Gauge
Azuma et al. [20]	Bell palsy and 5 with herpes zoster oticus	Botulinum A toxin (Botox; GlaxoSmithKline, Middlesex, UK	15 units	Ipsilateral orbicularis oculi muscle, Around the upper and lower eyelid	27-Gauge
Guarda-nardini et al. [21]	Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) diagnosis of myofascial pain	Botulinum toxin (Dysport, Ipsen, Ltd., UK)	150U of botulinum toxin (was injected per each treated side	Patients were asked to clench their jaws to identify the muscle to be injected properly. Then, multiple injections were given in the more prominent area of the muscles, with an injection covering, on average, a two cm skin surface over the target muscle tissue. A five-	30-Gauge

Author	Diagnosis	Type of Botulinum toxin A	Volume	The target area of Botulinum toxin Injection	Size of the needle
				injection minimum with a reverse pyramid pattern was performed in the masseter muscles, and a chessboard pattern was used for the temporalis muscles. Multiple botulin toxin injections in the temporalis and masseter muscles	
Pourmomeny AA, et al. [22]	Bell's Palsy, facial synkinesis	Botulinum toxin -A (Dysport)	BTX-A including 500 units were diluted with normal saline (2.5ml)	Injection sites were orbicularis oculi, orbicularis oris, zygomatic major, levator labii superioris, and depressor labii inferiors	30-Guage

BFS = blepharospasm, HFS = hemifacial spasm, AFNR- aberrant facial nerve regeneration, BEB-benign essential blepharospasm, NR-Not reported.

Table 5. Characteristics of Facial Exercises

Author	Diagnosis	Exercise	Duration
San et al. [14]	HFS BFS	Lift eyelids as much as possible to create wrinkles on the forehead 2. Frown 3 Close your eyes tight 4. Try to open your eyes as your eyelids closed 5. Squeeze your nose wings 6. Bring your upper lip forward 7. Pretend to whistle 8. Puff up by pulling your lower lip forward 9. Smile 10. Stretch your lips diagonally to your teeth. Pull the corners of the lips to the sides.	Each movement for 5 seconds, repeat each movement 10 times with a 10-second break every day, 3 times a week for 1 week.
P. O'Reilly et al. [19]	AFNR, BEB, or hemifacial spasm (HFS)	A motion consists of forcefully screwing up the face as tightly as possible for 2 seconds, then stretching it as wide as possible for 2 seconds so the jaw is maximally open, the mouth aperture is as big as possible, and the eyebrows are maximally elevated. • Patients conduct 5 squeeze motions of the whole face and then relax for 15 seconds. This constitutes a cycle. • Cycles are repeated until 5 minutes have elapsed. • If the patient is finding this difficult towards the end of 5 minutes, they are advised to increase the time interval between squeeze phases.	5 minutes after their first and third treatment, whereas after their second treatment, they were asked to rest in a seated position for 5 minutes and instructed not to talk or perform any voluntary movements of their face.
Pitakpatapee et al. [15]	HFS	The active and passive facial muscle squeezing of the muscles usually affected by HFS is performed once immediately after BTX-A injection by a video-guided program.	7 min performed immediately after BTX-A injection by a video-guided program.
Lee et al. [11]	unilateral facial palsy	Patients started the newly developed rehabilitation method (half-mirror biofeedback exercise). They were instructed to look at the lens of a camera and concentrate on three designated eye movements (eyelid closure with minimal effort, eyelid closure with maximal effort, and look at over), three mouth movements (say "e," "o," and	30 minutes per day for 2 years

Author	Diagnosis	Exercise	Duration
		blowing a balloon), and a gross facial picture at rest.	
Azuma et al. [20]	Bell palsy and 5 with herpes zoster oticus	Patients were instructed to keep their eyes open symmetrically during 3 designated mouth movements: pursuing one's lip /u:/, baring one's teeth /, and puffing out one's cheeks /: while looking into a mirror.	30 minutes per day for 10 months
Guarda-nardini et al.[21]	Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) diagnosis of myofascial pain	Deep digital pressure is exerted over specific Centers of Coordination points defined by the method and selected according to a precise clinical examination, as indicated by Fascial Manipulation guidelines. Therapists use their elbows, knuckles, or fingertips to exert pressure on the muscle areas.	Each patient underwent three (±1) 50-minute sessions of Facial Manipulation every week for 150 (±50) minutes over two to four weeks.
Pourmomeny AA, et al. [22]	Bell's Palsy, facial synkinesis	Rehabilitation included stretching the muscles of the affected side and EMG biofeedback using an EB Neuro-MYTO II instrument, which has two channels (one for voluntary movement and the other for involuntary movement).	Three times a week for 4 months

BFS = blepharospasm, HFS = hemifacial spasm, AFNR- aberrant facial nerve regeneration, BEB-benign essential blepharospasm, EMG -electromyography biofeedback, NR-Not reported.

Table 6. Outcome and Statistical Analysis

Author	Assessment	P-Value	Outcome
San et al.[14]	HSGS and Jankovic scales (Jan -F, Jan-S)	JAN-S (P = 0.008) JAN-F (P =0 .027)	Facial self-exercise following the application of botulinum toxin may extend the effectiveness of the treatment in subjects with HFS and BFS.
P. O'Reilly et al. [19]	5-minute video recordings were reviewed and scored by 1 masked investigator (JR), Pre-treatment Questionnaire, Post-treatment Questionnaires, Post-treatment Telephone Questionnaire	P= 0.367	Increased efficacy of botulinum toxin-A, with facial muscle squeezing post-BTX treatment.
Pitakpatapee et al.[15]	HFS-30, Hemifacial Spasm Score Physician-assessed Samsung Medical Center (SMC) severity grading scale	NR	A combination of a novel facial exercise protocol and BTX-A injection showed a promising benefit for adult patients with HFS, and a confirmatory RCT is feasible.
Lee et al. [11]	Sunnybrook (SB) facial nerve grading systems	NR	This facial rehabilitation strategy, consisting of three injections of botulinum toxin and half-mirror biofeedback exercises, proceeds over two years and offers a long-lasting cure for facial synkinesis and symmetry and improved facial aesthetics.
Azuma et al. [20]	DVgate Still software, Adobe Photoshop images, % of eye-opening),	P < 0.05	Findings demonstrate that facial biofeedback rehabilitation with a mirror after administration of a single dose of botulinum A toxin is a long-lasting treatment of established facial synkinesis in patients with chronic facial palsy.
Guarda-nardini et al. [21]	Maximum pain levels (VAS ratings) and jaw range of motion in millimeters were assessed.	P<0.05	The data that was gathered fit well with the current literature, suggesting that several conservative therapeutic approaches may be helpful in patients with TMD-related symptoms. Future studies on larger samples over a longer follow-up are needed to identify tailored treatment strategies.
Pourmomeny AA, et al. [22]	Photoshop assessment and FGS	P>0.05	Biofeedback therapy is as effective as the combination of biofeedback and BTX in reducing synkinesis and recovery of facial symmetry in Bell's palsy.

HSGS = hemifacial spasm grading scale, JAN-F = Jankovic scale-frequency, JAN-S = Jankovic scale-severity, FGS-facial grading system

Table 7. Risk of Bias assessment across individual studies using the Cochrane Risk of Bias Tool for randomized clinical trials.

Author \ Domains	Pre-intervention domains		At-intervention domain	Post-intervention domains				The overall risk of bias judgment
	Bias due to confounding	Bias in the selection of participants for the study	Bias in the Classification of Interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in the measurement of the outcome	Bias in the selection of the reported result	
P. O'Reilly et al. [19]	Low	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Lee et al. [11]	Serious	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate
Azuma et al. [20]	Low	Low	Low	Low	Moderate	Moderate	Moderate	Moderate

Table 8. Risk of Bias assessment across individual studies using the Cochrane Risk of Bias Tool for randomized clinical trials.

Author	Randomization Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias	Overall
San et al. [14]	Low	Low	High	High	High	Low	Some concerns	High
Pitakpatapee et al. [15]	Low	Low	High	High	Some concerns	Low	Some concerns	High
Guarda-nardini et al. [21]	Low	Low	High	High	Some concerns	Low	Some concerns	High
Pourmomeny et al. [22]	Low	Low	Low	High	Some concerns	Low	Some concerns	Some concerns