Botulinum Toxin as a Means for Relieving Temporomandibular Associated Pain in Adults: A Systematic Review

Matt Summers
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Abstract
Background: Temporomandibular joint disorder (TMJD) affects nearly 10 million people in the United States accounting for 17 million lost working days in 2001. Traditional conservative treatment for TMJD has limited benefit, which is why recent trials have studied the effects of botulinum toxin A on TMJD. Using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) the available evidence regarding the efficacy of botulinum toxin A for treating TMJD was evaluated.

Method: An exhaustive search of available medical literature was conducted using Medline, CINAHL, Evidence-Based Medicine Review Multifile and PubMed resulting in five randomized controlled trials limited to the English language, randomized controlled trials, and articles published since 2000 involving human subjects.

Results: This paper reviewed five studies and evaluated the three outcomes of pain resolution, jaw manipulation, and electromyography conduction using GRADE criteria. Three randomized controlled trials demonstrated reduction in electromyographic activity with the use of botulinum toxin A. Two randomized controlled trials concluded that botulinum toxin A can increase jaw manipulation without pain. Four out of five trials demonstrated improvement in TMJD pain with the use of botulinum toxin A.

Conclusion: The final GRADE for this systematic review was determined to be moderate. Although high grade studies need to be conducted, botulinum toxin A appears to be an effective alternative treatment for TMJD.

Keywords: botulinum, botulinum toxin A, joints, pain, facial pain, electromyography, masseter muscle, bruxism, masticatory muscles and orofacial pain.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
botulinum, botulinum toxin A, joints, pain, facial pain, electromyography, masseter muscle, bruxism, masticatory muscles and orofacial pain

Subject Categories
Medicine and Health Sciences

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Matthew Summers

A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science

Pacific University School of Physician Assistant Studies
May, 2011

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[Redacted for privacy]

Acknowledgements

[Redacted for privacy]
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INTRODUCTION

Background

Temporomandibular joint disorder (TMJD) is classified by acute or chronic musculoskeletal pain with malfunction of the masticatory system. Triggers include bruxism (teeth grinding), trauma or stress which causes persistent, unconscious, repetitive use of the masticator. Tending to affect women more than men, TMJD can manifest in both sexes and usually in the patient’s thirties and forties (Sheon 2011). According to the National Institute of Health (NIH 2011), ten million people suffer from chronic temporomandibular pain in the United States. Clinical symptoms tend to be unilateral, chronic pain in the muscles of mastication such as the masseter and temporalis that can radiate to ears, posterior cervical vertebrae, and temples. Often pain is associated with headache (Sheon 2011). It can be very debilitating to patients including as it does symptoms such as chronic jaw muscle stiffness, limited movement and locking of jaw, painful clicking to more severe problems such as upper and lower teeth misalignment (NIH 2011). Current TMJD treatment involves stabilizing splints, pain medication, restricting or limiting use of TMJ muscles by eating soft food, and physical therapy. At best, conservative therapy has limited results, for example NSAIDs and jaw exercises only reduces pain by 60% according to one study (Michelotti et al., 2004), whereas stabilizing splints proved of no benefit when compared with other therapy (Sheon 2011). Likewise physical therapy and soft food chewing often requires patient compliance for success.

Several studies have investigated the novel approach of using botulinum toxin A (Botox, BTX-A) for treating TMJD. Botulinum toxin prevents the release of
acetylcholine at neuromuscular junctions and autonomic synapses, effectively blocking
the transmission from nerve to muscle and reducing muscular activity (Current 2009).
Botulinum toxin injections have been successfully used in treating torticollis, hemiplegia
and joint pain (Comella 2011).

Purpose of the Study

The purpose of this paper is to perform a systematic review of the literature on
the use of botulinum toxin A as means of controlling TMJ associated pain using
the Grading of Recommendations Assessment, Development and Evaluation
(GRADE) tool developed by the GRADE Working Group Guyatt et al., 2008).

METHOD

An extensive review of the literature was conducted using the following
databases accessed through Pacific University Library: Medline, CINAHL, Evidence-
Based Medicine Review Multifile and PubMed. The following keywords were searched
individually and in combination: botulinum, botulinum toxin A, joints, pain, facial pain,
electromyography, masseter muscle, bruxism, masticatory muscles and orofacial pain.
The results were limited to the English language, randomized controlled trials, human
subjects and articles published since 2000. This resulted in 45 articles of which
duplicates, descriptive reviews and letters to the editor were excluded. This resulted in
five studies that met the inclusion and exclusion criteria and were included in the
systematic review.
RESULTS

Kurtoglu et al. (2008) conducted a randomized double-blind controlled study of 24 participants suffering from TMJ disorders with or without functional disc displacement, who were examined over the course of 14 and 28 day intervals. This study evaluated the effectiveness of botulinum toxin A for TMJD by injecting it into the left masseter muscle (LMR), right masseter muscle (RMR), right anterior temporal muscle (RTR) and left anterior temporal muscle (LTR). Using electromyogram (EMG) they recorded values with the jaw at rest, and measured maximum clenching at baseline, 14, and 28 days. While at rest, the study groups EMG results demonstrated a statistically significant difference over time ($p_{t} = .046$) and between baseline (day 0) and day 14 ($p_{0-14} = .034$) for the left masseter, whereas, the control group demonstrated an increase in EMG activity over time ($p_{0-14} = .076$). After 28 days, no difference was evident in the other EMG variables at rest position. With maximal clenching, the EMG values for the left masseter, RTC and LTC showed statistically significant differences in the BTX-A group ($p_{t} = .046$, $p_{t} = .028$, and $p_{t} = .028$, respectively) with no noted difference among the placebo groups. Based on this study’s results, the authors concluded that with BTX-A injection into the masticatory muscles, while clenching, the masseter muscle action potential may be reduced by 80% by day 14, and 25% by day 28 after the effects had dissipated with all subjects accounted during follow-up. The authors also noted significant differences between pain and psychological status in the study and placebo group during follow up at day 14 and 28. The authors suggested that the toxin concentration was inadequate and thus insufficient to affect the motor endplate. Faulty
preparation of the toxin and inadequate storage conditions may all have affected efficacy. The authors concluded that, first, the effect of BTX-A was related to localization and dosage, and second, patients with or without functional disc displacement, suffering from myofasical pain, could achieve a positive effect using BTX-A.

The next study reviewed was performed by Lee et al. (2010) who studied twelve subjects suffering from nocturnal bruxism. Six of the subjects were injected with botulinum toxin in bilateral masseters while the other six were injected with saline. Nocturnal electromyographic activity was recorded at four, eight, and 12 weeks after the initial injection. Exclusion criteria included TMJ disorders, pain in the orofacial region, insomnia, known botulinum toxin allergy, pregnancy, neuromuscular disease, bleeding disorders, antibiotic therapy use, pulmonary disease that produces coughing during sleep, or skin infections at the site of injection. A total of seven men and five women were included in this study, with mean ages of 25.0 ± 2.5 years for men and 24.8 ± 0.83 years for women. Subjects then responded using a symptom questionnaire. Lee et al. (2010) reported a decrease in EMG bruxism events when BTX-A was injected into the masseter muscle, but no statistical difference was recorded with injection into the temporoarils muscle despite three post injection times. The masseter-botulinum mean of 0.23 ± 0.29 was lower (p< 0.001) compared to the master-saline mean of 2.47 ± 1.23. The temporalis-botulinum mean of 2.22 ± 1.54 did not differ (p = 0.483) compared to the temporalis-saline mean of 1.85 ± 1.51. The authors concluded that bruxism events in the masseter muscle decreased significantly with the study group after the injection, whereas the temporalis muscle bruxism events did not differ among recording times. The authors concluded that using BTX-A injections in the masseter muscle reduced the number of
bruxism events while sleeping, attributed to muscle tone rather than direction from the central nervous system, therefore, BTX-A injections can be an effective treatment for nocturnal bruxism.

The next study reviewed was performed by Nixdorf et al. (2002) who studied the effects of BTX-A for the treatment of chronic moderate to severe jaw muscle pain in females. Out of 15, female subjects to enroll in the study, only 10 completed the 24 week trial. Using a 27 gauge, Teflon-coated needle attached to an audioamplified electromyographic (EMG) machine, confirmed placement within the targeted muscle group. Twenty five unit of BTX-A, were injected into the temporalis muscle while 50 units were injected into the masseter muscle, with three sites of injection per muscle. Comparison was made between normal saline and BTX-A compared in the study group. Exclusion criteria and treatment respectively included women that were pregnant or planning to be pregnant, breast feeding, taking aminoglycoside antibiotics, anticholinesterases and non-depolarizing or depolarizing muscle relaxants, or with neurological or bleeding disorders. Patients who had dental decay or were taking regular amounts of analgesics and had a history of TMJ surgery or trauma were also excluded. Information was recorded at baseline, eight, 16, and 24 weeks with crossover occurring at week 16 due to five patients dropping from the study as a result of inadequate pain control. The primary outcome measured by this study was “pain intensity and unpleasantness” based on a visual analogue scale (VAS) with 0mm being no pain and 100mm being the absolute maximum pain the patient could imagine. Additionally, this study looked at voluntary range of interincisal jaw opening without pain, and irrespective of pain, which was also measured using VAS. Positive treatment response was
designated as an opening of 6mm or greater. Secondary outcomes included palpation of tenderness recorded as either ‘yes’ or ‘no’ at twelve pre-determined sites; temporalis (anterior, middle, posterior), and masseter (posterior deep, anterior superficial, and inferior). Breakthrough analgesic medication of 500 mg acetaminophen was provided and each patient was asked not to take any supplemental analgesics. Results of this study indicated no significant difference between the two groups regarding pain intensity (p=0.10). In the BTX-A group a mean change of 19mm reduction in pain intensity (SD = 31) was noted compared to the 1 mm reduction in the placebo group (SD = 16). For pain unpleasantness the mean change was a 13mm reduction (SD = 23) for the BTX-A group and a 5mm reduction in the placebo group (SD=16), no significant difference was observed between either group (p=0.40). Regarding secondary outcomes, maximum opening without pain and irrespective of pain demonstrated a statistically significant change. In the placebo group, maximum opening improved by 10mm (SD =9) but remained constant at 0mm (SD11) in the BTX-A group (p=0.02). Jaw opening irrespective of pain improved by 5 mm (SD=7) in the placebo group, compared to the worsened 3mm (SD=5) in the BTX-A group (P=0.005). Muscle tender points before and after treatment did not significantly differ between either groups (p=0.91). Three follow up questions were asked at the end of the study ‘were the injections painful? Is treatment worth the trouble? Would you recommend treatment to a friend/family member with the same condition?’ demonstrated no significantly difference between groups (p = 0.64, 0.65, 0.67, respectively). The authors concluded that BTX-A was too costly (CDN $474.00 for a 100 U vial of BTX-A) and not effective enough to warrant treatment for
myogenous orofacial pain in female patients suffering from chronic pain of the muscles of mastication.

The next study reviewed was performed by von Lindern et al. (2003) who studied the effects of BTX-A injected into masticatory muscles for treatment of chronic facial pain associated with masticatory hyperactivity. In a randomized single blind placebo-controlled study with 90 patients, using a visual analog scale, patients reported for baseline pre injection, and post injection over 4 weeks. Enrollment criteria included patients who received conservative treatment (three months to a maximum of 34 months) involving occlusal splint therapy or relaxing techniques or massage. Indication for treatment was based on functional analysis of jaw movement, joint dysfunction, pain and muscle hyperactivity. Exclusion criteria included undefined pain syndromes with unclear patterns of radiation. An average of 35 units of Botox liquidated in 0.7 mL NaCl saline or 0.7 mL NaCl pure saline was injected on each side of muscle, given at maximum reported tenderness. Patients were asked to stop any other treatment for pain seven days prior to the first injection. Results demonstrated improvement in 55 cases (91%) in the verum group, with an overall improvement of 3.2 points on the visual analogue pain scale. In the saline group symptoms improved by 0.4 points on the VAS. This study then used a t-test and $x^2$ test which measure significant difference ($p < .01$) demonstrating a correlation between the pretreatment pain intensity on the VAS and improvement of local pain symptoms. Incidentally, patients that reported higher levels of pain (> 6.5 VAS) showed major improvement (>3.5, n = 26) compared to those who reported less pain (<6.5 VAS) who showed only minor improvement (<3.5, n=27). In 19 cases, the toxin subsided at approximately two months, pain symptoms would reoccur and a repeat
injection was administered. In the remaining patients, therapeutic effect lasted one to three months (throughout the observation period). Swallowing difficulty or temporary paralysis of a muscle related to facial expression were the only noted sided effects and only occurred in one patient, and subsided after four weeks. Temporary speech impairment or systemic botulism were not observed in this study. The authors concluded that botulinum toxin can be used for therapeutic application in patients suffering from chronic facial pain associated with masticatory hyperactivity.

The final study reviewed was conducted by Guarda-Nardini et al. (2008) who investigated the use of BTX-A to treat myofascial pain symptoms and to reduce muscle hyperactivity in bruxers in a RCT double blinded pilot study. Twenty patients clinically diagnosed with bruxism and myofascial pain were divided into the study group (10 patients treated with BTX-A) and the control group (10 patients treated with saline.) Each patient enrolled in the study had a clinical diagnosis of bruxism masticatory myofacial muscle pain. Using a validated set of screening-orientated clinical diagnostic criteria, the presence of bruxism was diagnosed. This allowed the study to focus on the clinical impact of BTX-A on the masticatory apparatus and to not focus on the pathophysiological disorder related to the central nervous system. Diagnosis of bruxism involved at least five nights a week of grinding/bruxin sounds during sleep in the last six months reported by spouse/bed partner and at least one of the following: report of morning masticatory muscle fatigue/pain; masseteric hypertrophy upon digital palpation; observation of tooth wear or shiny spots on restorations. Inclusion criteria were as follows: report of pain or ache in the jaw, face, preauricular area, temples, or inside the ear while jaw was at rest or during function; pain reported while palpation of three or
more of the following twenty muscle sites (right side and left side were counted as separate sites for each muscle: posterior temporalis, middle temporalis, anterior temporalis, origin of masseter, body of masseter, insertion of masseter, posterior mandibular region, submandibular region, lateral pterygoid area, and tendon of the temporalis.) Exclusion criteria included history of any treatment of bruxism and/or TMJD during six months prior to study; presence of neuromuscular pathologies preventing use of BTX-A, allergy or sensitivity to BTX-A. Treatment criteria involved 30 units of BTX-A injected into the masseter muscles and three injections of 20 units within the anterior temporalis muscles for a total of 100 units. Using anatomo-topographic and/or ultrasonographic control, injections were made at a single appointment, under the same maxillofacial surgeon. The study looked at the following; pain at rest and during chewing assessed by VAS; mastication efficiency assessed by VAS; maximum nonassisted and assisted mouth opening measured by , protrusive and laterotrusive movements measured by mm; functional limitation during usual jaw movements (0= absent, 1 = slight, 2= moderate, 3=intense, 4=severe); subjective efficacy of the treatment (0=poor, 1=slight, 2=moderate, 3=good, 4=excellent); and tolerance of treatment (0=poor, 1=slight, 2=moderate, 3=good, 4=excellent). Results were recorded at baseline, then one week, one month and six months.

Results based on descriptive analysis demonstrated a slight increase in the BTX-A group for maximum non-assisted and assisted mouth opening, protrusive and laterotrusive movements (mm) compared to the placebo group which was unaltered (non-assisted mouth opening: BTX-A baseline SD 8.74, 1 week 9.91, 1 month 9.61, 6 months of 7.63 compared to Placebo at baseline 9.40, 1 week 9.11, 1 month 7.63, and 6 months
of 9.11). Maximum assisted opening at baseline BTX-A SD 6.63, 1 week 8.52, 1 month 8.21, 6 months 7.04. Placebo maximum assisted opening SD at baseline 8.72, 1 week 8.21, 1 month 8.31, and 6 months 8.25. Protrusion BTX-A SD at baseline 3.53, 1 week 4.22, 1 month 3.77, 6 months 4.12; placebo baseline 1.55, week 1 1.78, 1 month 1.71 and 6 months 1.64. Right laterotrusion BTX-A baseline SD 2.03, 1 week 2.41, 1 month 2.46 and 6 months of 1.71; placebo at baseline 1.14, 1 week 1.49, 1 month 1.23, and 6 months of 1.60. Left laterotrusion BTX-A at baseline SD 2.33, 1 week 3.02, 1 month 3.16, and 6 months at 2.49; placebo at baseline 1.65, 1 week 1.35, 1 month 1.32, and 6 months at 1.40. Regarding symptoms, the botox group demonstrated a decrease in pain for chewing (BTX-A baseline SD 2.78, 1 week 3.05, 1 month 2.32 and 6 months 2.37; placebo baseline SD 2.92, 1 week 2.82, 1 month 2.71, 6 months 2.79) and while jaw at rest compared to the placebo group which demonstrated no change. Mastication and functional limitation with time, did change/differ in either group (BTX-A SD baseline 2.26, 1 week 2.38, 1 month 2.17, 6 months 1.90 compared to placebo SD baseline 1.63, 1 week 1.77, 1 month 1.32, 6 months 1.96). The BTX-A patients reported greater improvement with time and reported higher perception of treatment efficacy compared to the placebo group. Both groups reported tolerating the treatment well. Using a permutation test on the outcome variables defined as differences, the authors demonstrated significant differences between the BTX-A and placebo group in the parameters of pain improvement at chewing and patients perception of treatment effectiveness at six month follow up. No other significant differences between both groups were shown in the remaining outcome variables. The authors concluded BTX-A
was effective at reducing myofascial pain symptoms in bruxers, and that pilot data would need to be confirmed in a study with a larger sample size.

DISCUSSION

The purpose of this paper was to review current literature regarding the effectiveness of treating temporomandibular joint disorder with botulinum toxin A as an adjunct treatment to traditional therapy. Temporomandibular joint disorder affects 10 million people with some estimates suggesting up to 36 million people are in the United States (Hoffmann et al. 2011). Symptoms vary from mild jaw discomfort, jaw-joint pain and headaches to more chronic conditions such as intractable pain and severe jaw limitation and jaw function. In 2001, the Agency for Healthcare Research and Quality estimated that TMJD resulted in 17.8 million lost working days per year for every 100 million working adults in the United States and that financial cost are in the billions of dollars (Lewin 2001). Standard treatment for TMJD involves conservative symptomatic therapeutic modalities such as occlusal splints, physiotherapy, behavioral and physical treatments and medication. Issues such as patient compliance coupled with mild to moderate success in conservative treatment have lead to the exploration of more effective treatment for TMJD (Sheon 2011.) Botulinum toxin A has been successfully used to treat many pathologies involving increased muscle tone (Brin 1989) torticollis, hemiplegia and joint pain (Comella 2011). In the past ten years, more effective treatment has been needed and investigated for TMJD, specifically the use of botulinum toxin A.
Grading The Evidence:

GRADE stands for Grading of Recommendations Assessment, Development, and Evaluation, and is a system developed for evaluating research and grading recommendations in systematic reviews (Guyatt et al., 2008). Looking at a specific question as well as important outcomes, evidence is collected regarding that question. GRADE uses specific criteria for rating the quality of evidence which includes; risk of bias, study design, imprecision, inconsistency, directness and magnitude of effect (Guyatt et al. 2008). Using these criteria, the evidence is classified as high, moderate, low or very low according to the quality of the body of evidence. Using GRADE table findings are displayed in a succinct, informative manner (Appendix A, Table 1). Each outcome began as high as all studies involved were RCTs, and can only be downgraded, not upgraded using GRADE criteria. Each of the downgrading criteria is only worth one point.

Outcomes

The first outcome studied in this paper was electromyographic activity. Three papers were included in this category and each started with a high grade as all three papers were double-blind randomized controlled trials. Two points were deducted from this outcome based on study quality, as one study involved prodding with an EMG probe until the most sensitive area was found in the masseter and temporalis muscle on top of further injecting a total of 12 times during a treatment session. This lead to a significant confounder as pain resolution would begin simply by withholding treatment. The other deduction came from inadequate and subjective pain measurement. Each study was direct and precise and showed no evidence of publication bias, therefore, no additional
downgrading was required. A dose response was demonstrated in this outcome but could not be factored based on the GRADE criteria. Overall, for electromyographic activity this category received a moderate grade. Based on the articles reviewed, botulinum toxin A reduces electromyographic activity.

The next category included jaw manipulation such as mastication; studies that examined how well the jaw could move pre and post injection of botulinum toxin A. Two double-blind randomized controlled studies were included into this category with the final outcome being improvement of jaw manipulation without increased pain, or reduced pain with jaw manipulation. Both studies began with a high grade due to being RCTs. A deduction under precision was made with one study offering no confidence interval calculations and both studies having a small study population. A moderate grade was maintained throughout the rest of the categories, demonstrating study quality, consistency, and no evidence of publication bias. Based on this criteria, the overall GRADE of moderate was awarded to the outcome dealing with jaw manipulation. Using botulinum toxin A has a positive influence on jaw manipulation and reduction of pain associated with jaw manipulation.

The final category involved pain resolution with all five articles listed in this category. All five studies began with a high grade as all five studies were double blind randomized controlled trials. The body of evidence was downgraded due to poor study quality and consistency. A large magnitude of effect was demonstrated in pain resolution throughout this outcome as well as dose relationship, doses such as 30-50 units of botulinum toxin A proved to be therapeutic. You cannot upgrade an outcome under GRADE criteria of an RCT.
When looking at the quality of evidence as a whole, this systematic review found the GRADE outcome for overall evidence was moderate. Each randomized controlled trial evaluated the effectiveness of botulinum toxin A relating to TMJD, with four out of five studies demonstrating a positive outcome.

Study Limitations

The problem with the majority of these studies included small sample size. Kurtoglu (2008) for example, only having 24 participants, Lee (2010) 12 patients, Guarda-Nardini (2008) 20 patients, Nixdorf (2002) 15 patients, and von Lindern (2003) having 90 participants. Another limitation involved pain measurement, as some studies used visual analogue scales while others used EMG. Regardless, all trials measured pain differently whether using VAS, EMG, or patient subjective reporting. Even using EMG machines has its own drawbacks as seen in the Lee et al. (2010) study where patients were responsible for setting up EMG recording devices at home, with no way to gauge how these EMG machines were used by the patient, which may have lead to inadequate data gathering, causing inconsistency in numerical data.

Very few studies had adequate follow-up periods. Kurtoglu et al. (2008) study ended on day 28. Granted patients experienced a reduction in pain and improvement in psychological status. However, to truly measure the benefit of long term use of botulinum toxin A, further follow up is encouraged. Guarda-Nardini et al. (2008) continued to display benefits from botulinum toxin A for as long as 6 months, whereas, von Lindern et al. (2003), Lee et al. (2010) and Nixdorf (2002) limited their follow-up to three months and with the exception of Nixdorf, all proved to be experiencing benefit
from botulinum toxin treatment. It would be difficult to compare the results of follow up
given the lack of matching data between a three month and 6 month time period.

Nixdorf et al. (2002) demonstrated a confounding dilemma resulting from patients
receiving 12 injections during a treatment session as well as being subjected to further
prodding to locate sensitive areas of the muscle tissue via EMG electrodes, which may
have diminished their findings of pain relief. Discontinuation of injection and probe
placement would have ultimately felt more pleasant then continued needle introduction.
At week 16, five patients had dropped from the study due to inadequate pain control,
three from the BTX-A group and two from control leaving crossover in the remaining
portion of the trial. Of note, only Nixdorf et al. (2002) evaluated cost of therapy,
reporting $474 CDN for a 100 Unit Vial of BTX-A, calculating a profession fee of
$200.00 for a grand total therapy costing $1148.00.

Conclusions

Botulinum toxin A has been proven to be beneficial in treating various diseases.
Traditional treatment of TMJD offers limited benefit, thereby, requiring new treatment
options. This systematic review has reviewed current evidence regarding the efficacy of
botulinum toxin A as adjunct therapy for TMJD, and dubbed the quality of evidence as
moderate. Further testing would be encouraged perhaps involving a larger randomized
controlled trial. It would most likely demonstrate the effective nature of botulinum toxin
A for the treatment of TMJD. Issues such as cost, long term benefit of greater than 6
months requiring longer follow up, and scientific estimation of pain should be addressed
in the proposed much larger randomized controlled study, however overall the statistical
significance of botulinum toxin treatment would remain sound. When compared with cost of traditional conservative treatment, the clinical application of botulinum toxin may be of benefit to those suffering from chronic TMJD.
REFERENCES


## APPENDIX A

### Table 1: GRADE

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Starting grade</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Grade of Evidence for Outcome</th>
<th>Overall GRADE of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum Toxin A versus Saline</td>
<td>Electromyographic Activity</td>
<td>3 RCT</td>
<td>Reduced number of bruxism events in masseter muscles</td>
<td>High</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
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<td>Improvement in jaw manipulation without pain</td>
<td>High</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>Jaw manipulation /mastication efficiency</td>
<td>2 RCT</td>
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<td>Moderate</td>
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<tr>
<td></td>
<td>Pain Resolution</td>
<td>5 RCT</td>
<td>4 studies with pain resolution</td>
<td>High</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
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<td>1 study without pain resolution</td>
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### Overall GRADE of Evidence

- **Moderate**
- **Low**