



TITLE: Botulinum Toxin A for the Treatment of Trigeminal Neuralgia and Temporomandibular Joint Dysfunction: A Review of the Clinical-Effectiveness

DATE: 04 August 2009

CONTEXT AND POLICY ISSUES:

Temporomandibular joint dysfunction (TMD) is a musculoskeletal and rheumatologic disorder of the temporomandibular joint, which may result in jaw deformities, malocclusion, inflammation, and compression of the bilaminar tissue, with pain and dysfunction being the most prominent clinical features.¹ Trigeminal neuralgia (TN) is a disorder caused by proximal compression of trigeminal nerve root, which may bring about electric shock-like pain that occurs with or without stimulation.²

For patients with TMD, current treatment options include occlusal therapies and use of pharmacologics such as non-steroidal anti-inflammatory drugs, corticosteroids, antidepressants, muscle relaxants, sedative-hypnotics, and capsaicin.¹ Current recommended treatment options for patients with TN include the use of carbamazepine, with additional pharmacologic approaches such as baclofen, phenytoin, gabapentin, clonazepam, and valproic acid.² Neurosurgical options for TN include glycerol instillation or balloon compression of the gasserian ganglion, or ablative procedures.³

Botulinum toxin is a neurotoxin that inhibits the release of the neurotransmitter acetylcholine at the neuromuscular junction.⁴ Botulinum toxin A is currently available in Canada as Botox, and Botox Cosmetic by Allergan Inc.,⁵⁻⁷ and Xeomin by Merz Pharmaceuticals.⁸ Botulinum toxin A is currently indicated for a variety of neuromuscular disorders in Canada, including focal spasticity, blepharospasm, strabismus, and cervical dystonia.⁵ Based on its neuromuscular effects, botulinum toxin A has been proposed as an analgesic, suggesting potential benefits for the management of TN and TMD.⁴

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In Canada, botulinum toxin A is not currently indicated for the management of TN and TMD. To better guide potential off-label coverage decisions, information is required on the clinical benefits and harm of botulinum toxin A when used for the management of TN and TMD.

RESEARCH QUESTION:

What is the clinical-effectiveness of botulinum toxin A for the treatment of trigeminal neuralgia (TN) and temporomandibular joint dysfunction (TMD)?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including Medline and Embase on the OVID platform, The Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and July, 2009. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), controlled clinical trials, and observational studies.

SUMMARY OF FINDINGS:

For TMD, no relevant health technology assessments were identified. Two relevant systematic reviews^{4,9} and one observational study¹⁰ were identified in the literature search. Each systematic review identified one RCT relevant to TMD. No other relevant RCTs, controlled clinical trials, or observational studies were identified from the literature search.

For TN, no relevant health technology assessments, RCTs, or controlled clinical trials were identified. Three observational studies¹¹⁻¹³ specific to TN were identified in the literature search.

A summary of the target populations, interventions, comparators, methodologies, and clinical findings for included studies are provided below.

Health technology assessments

No relevant literature identified.

Systematic reviews and meta-analyses

Sycha et al.⁴ (2004) conducted a systematic review that assessed the analgesic efficacy and safety of botulinum toxins versus other medicines, placebo, or no treatment in acute or chronic rare head and neck pain syndromes. The authors described searching three databases up to May 2003 and, in addition, handsearching was conducted to identify additional papers of interest. Field experts were also contacted to identify potentially relevant studies. Two reviewers independently selected articles. Disagreements were resolved by discussion with a third reviewer. Included study quality was assessed using Jahad et al.'s Quality Assessment Scale. This scale rates the methodological quality of RCTs, with a score of one indicating low quality, and a score of five indicating high quality. Data extraction was performed independently by two reviewers.

The authors included 18 trials (RCTs or quasi-randomized controlled trials) which investigated the analgesic effects of botulinum toxins as monotherapy or add-on treatment, with pain assessment as the primary or secondary outcome. Patients were included regardless of age, sex, or severity of condition. All commercially available preparations of botulinum A were considered, regardless of routes of administration.

Of the 18 trials included, one RCT evaluated the use of botulinum toxin for TMD (Nixdorf et al., 2002). None of the trials included patients with TN. The Nixdorf et al. RCT was a 24-week cross-over trial that included 15 patients who were diagnosed with TMD for more than six months. The authors of this systematic review did not describe what intervention was received by the control group. The time of the cross-over and the washout period were not reported. Participation was restricted to females without inflammatory temporomandibular joint pathology or disc displacement. It was unclear whether 100 mouse units (MU) or 150 MU of botulinum toxin A (Botox) was used. Pain was assessed based on the visual analogue scale (VAS).

The authors of this systematic review provided mean and standard deviation VAS values for the intervention group and control group at week eight. No other values for the 24 week study were reported. Ten of the patients were included in the analysis at eight weeks and there was a mean change of 19 (SD = 31) in the experimental group compared to a mean change of 1 (SD=23) for the control group. The VAS scale used was not explained, but it can be assumed it was on a 100 point scale. No statistical testing or further discussion of the results was reported. Two patients from the treatment group were lost to follow up due to zygomaticular major paralysis, and three patients were lost because of pain escalation. The authors did not report whether these three patients were from the intervention group, control group, or a combination of both groups. The number of adverse events was not reported, however, it was stated that there was a high rate of paralysis, injection pain, and asymmetrical smile in the experimental group and a high rate of injection pain in the control group.

The authors of this systematic review reported that the Nixdorf et al. RCT was of high quality (given a four out of five on the Jadad scale) and did not provide evidence that administering botulinum toxin A to patients with TMD statistically significantly changed pain intensity scores. Sycha et al. reported that due to the lack of evidence, they were unable to draw any conclusions on the efficacy or harm of botulinum toxin A on TN or TMD.

Ihde et al.⁹ (2007) conducted a systematic review to determine if botulinum toxin A was safe and effective in treating patients with cervical dystonia and maxillofacial conditions. The authors classified TMD as a maxillofacial condition. TN was not investigated in this study.

The authors searched for systematic reviews or RCTs that treated patients with TMD. Case series and case reports were not included. The quality of this systematic review was unclear due to the lack of methodological details reported; such as, number of reviewers or quality assessment of the included study.

One RCT (von Lindern et al., 2003) on TMD was included. This RCT compared botulinum toxin A (Botox) to saline in patients with chronic facial pain associated with masticatory hyperactivity. A total of 90 patients were enrolled. Patient inclusion and exclusion criteria and demographic data such as medical history, mean age, and female to male ratio were not reported. A dose of 35 MU of botulinum toxin A was injected into masticatory muscles of the intervention group (n = 60), while the control group received saline injections (n = 30). Patients were evaluated for local

facial pain symptoms based on VAS, with lower scores indicating less pain. No further information on the VAS was reported. Patients were followed up at four weeks post-injection.

The authors of the systematic review reported improvement in local facial pain symptoms in 91% of treatment group, with a statistically significant improvement in mean VAS scores (3.2 for the intervention group versus 0.4 in the control group, $p < 0.01$). Patients with greater initial pain (> 6.5 points on the VAS) showed a greater improvement than those with less initial pain (< 3.5 on the VAS). No p values were reported. It was unclear whether patients from this subgroup analysis were from the control group, the intervention group, or both. Adverse events in this study were described as being relatively mild and transient, with dysphagia and temporary paralysis of the muscles effecting facial expressions occurring in one patient from the intervention group.

Ihde et al. concluded that a single RCT does not provide firm evidence for the efficacy and safety of botulinum toxin A for the treatment of TMD, and more randomized trials should be performed.

Observational studies

Turk et al.¹² (2005) reported findings of a single arm study investigating the effectiveness of botulinum toxin A for patients in an outpatient neurology clinic. Patients had TN for at least six months, were refractory to antiepileptic medications, had no surgical interventions, and differed in pain localizations (e.g., left side or right side). A total of eight patients (six females, two males) were enrolled. Authors reported patients' mean age at entry to be 57.1 ± 10.1 years (not reported whether SD or SE), with a mean duration of disease at 1.6 ± 1.1 years (not reported whether SD or SE) on average.

A total of two doses of botulinum toxin A were injected on the side of the TN of each patient, 50 units (U) were administered above the zygomatic arch and 50 U below the zygomatic arch. Patients did not receive any medications after receiving the injection. Pain severity was assessed through VAS at baseline, and again after one week, two months, and six months post treatment. No additional information on the VAS was reported. Patients recorded the frequency and intensity of the pain they experienced each day at bedtime.

The authors reported statistically significant reductions of pain between baseline and each follow-up period, based on VAS scores. The mean score at baseline was 4.00 compared to 2.88 at week one ($p = 0.011$), 1.94 at month two ($p = 0.011$), and 1.19 at month six ($p = 0.011$). Patient-reported pain frequency was a mean of 4.00 at baseline compared to 2.88 at week one ($p = 0.012$), 1.81 at month two ($p = 0.012$), and 1.25 at month six ($p = 0.012$); these differences were also statistically significant. Decreases in pain were recorded within hours to days after injection and a significant decrease in pain intensity and frequency occurred within a mean and SD of 3.2 ± 2.0 days. Further information, such as ranges of VAS scores, was not reported. No serious adverse events were recorded, although the authors only reported adverse events thought to be related to treatment. One patient developed dysesthesia for one week on the injection side of cheek and another patient reported difficulty in chewing for three to four days on the injected side.

The authors concluded that while botulinum toxin A reduced pain in cases of refractory TN in this study, the results were preliminary and were based on a small sample size. The authors also stated that larger studies were required to establish clinical-effectiveness of botulinum toxin A for TN.

Zúñiga et al.¹¹ (2008) reported findings of a single arm study to evaluate the analgesic effects of botulinum toxin A (Botox) for the management of TN. Enrolled patients were diagnosed with idiopathic TN, had undergone previously unsuccessful drug treatments, were candidates for surgery, and had varying trigger zones and nerve branches affected. A total of 12 patients (seven female, five male) were enrolled. Patients' mean age at entry was 58.5 years (range 28 years to 91 years), with mean duration of disease at 6.2 years (range 0.5 years to 12 years). Prior to the intervention, nine patients were receiving carbamazepine (400 mg to 1,200 mg) and two received oxcarbazepine (600 mg to 1,200 mg) for at least three months, while one patient had not received any pharmacological treatment prior to the study.

Administered botulinum toxin A doses varied between 25 U and 50 U and were injected in trigger zones. Patients were evaluated for analgesic effects pre- and post-injection based on VAS, and were evaluated on the number of painful paroxysms pre- and post-intervention. Measurements were taken once weekly for eight weeks. No additional information was reported on the VAS used.

The authors reported a reduction of cumulative mean VAS scores (8.83 at baseline compared to 4.08 at week eight, with SD of 1.19 and 4.44, respectively) and a reduction in mean cumulative number of paroxysms (23.42 at baseline compared to 12.4 at week eight, with SD of 13.5 and 8.6,7 respectively). It was not reported whether these differences were statistically significant. In 10 patients, trigger zones disappeared within the first two weeks. Although not reported in the findings, the authors stated that motor benefits of the intervention lasted between three to six months and that pain recurred in most patients after 60 days. No adverse events were reported, however, two patients failed to respond, and one patient suffered from transient facial asymmetry.

The authors concluded that while botulinum toxin A could be useful in management of TN, further double-blind studies with sufficient numbers of patients are required to validate the clinical-effectiveness of botulinum toxin A for TN.

Piovesan et al.¹³ (2004) described findings of a single arm study to determine the minimum dose of botulinum toxin A required for TN treatment and to investigate the duration of its effect. Enrolled patients fulfilled the criteria of International Headache Society (2003 version) for having TN. A total of 13 patients (nine female, four male) were enrolled. The four male patients' mean age and SD at entry was 67.75 ± 6.6 years with a mean and SD duration of disease at 10.25 ± 6.95 years. The nine female patients' mean and SD age at entry was 59.22 ± 14.26 years with a mean and SD duration of disease of 8.22 ± 8.44 years. Twelve patients were taking carbamazepine, three were taking gabapentin, and one patient was taking codeine, lioresal, and oxcarbamazepine. Three patients had previous surgeries for TN.

Botulinum toxin A was injected into patients' facial subarea(s) according to individual patients' description of pain sites. Mean dose for all branches and all patients was reported to be 3.22 U/cm^2 . Patients were evaluated for pain intensity, number and distribution of paroxysmal attacks based on VAS, analgesic time effect, and use of analgesics pre- and post-intervention. Post-injection measurements were taken on days 10, 20, 30, and 60.

The authors reported statistically significantly reduced pain intensity and average pain area 10 days after the injection ($p = 0.006$). At day 20, pain relief reached its peak effect and was maintained on day 30. By day 60, the values were increasing which indicated less pain relief than reported on days 20 to 30 but patients were still experiencing pain reduction when

compared to baseline. The authors reported a reduction of analgesic use in all 13 patients, with four patients becoming medications free post-intervention, and the remaining nine patients reduced medication use by more than 50%. The authors did not indicate when analgesic was measured. The authors also did not report adverse events for the duration of the study.

The authors concluded that while botulinum toxin A could be an efficient treatment for TN, a placebo-controlled clinical trial would be needed to confirm these findings.

Karacalar et al.¹⁰ (2005) published the findings of a single arm study that investigated the effects of botulinum A toxin in decreasing pain and increasing functional range of motion in patients with Temporomandibular Joint Disk Disfigurement. This condition can be interpreted as TMD based on comparing the Karacalar et al.'s description of the condition with the common clinical features of TMD of pain, limitation of mandibular movement, and temporomandibular joint sounds as presented by Harrison's Principles of Internal Medicine 17th Edition.¹⁴

Enrolled patients had anterior disk displacement (ADD) without osseous changes. ADD diagnosis was based on presence of clicking or locking of temporomandibular joint, pain, and difficulty opening the mouth based on magnetic resonance imaging (MRI) findings. A total of 26 patients (18 female, eight male) were enrolled. Patients' mean and SD age was 28.5 ± 10.2 years (range 19 years to 58 years).

A total of 25 U of botulinum toxin A was injected at two points into the masseter muscle, and three points into the temporalis muscle. The lateral pterygoid muscle was also injected in all patients, but authors did not describe the dose. The other masticatory muscles were injected in nine patients. Authors did not describe the reason(s) for these nine patients receiving additional injections, and did not describe the dose. Patients were evaluated for pain of the temporomandibular joint using VAS (no further information reported on the VAS), mouth opening, jaw clicking, and subjective functional dysfunction (e.g., drinking, eating, talking). Patients were instructed to take note of any adverse events and were advised not to take any form of drug therapy (including analgesics) throughout the study without consulting the authors first. However, the authors did not report whether patients took drug therapies throughout the study. Measurements were taken in two-week intervals, for an average follow-up period of three months.

The authors reported a statistically significant decrease in VAS scores of the right joint from 3 to 1 based on visual interpretation of the authors' graph ($p = 0.0019$). Pain scores of left joint also statistically significantly decreased from 4 to 1 based on visual interpretation of the authors' graph of the VAS results ($p = 0.0000$). A statistically significant increase in mouth opening, from 37 to 41, was reported based on visual interpretation of the graph ($p = 0.002$). However, it was not possible to clearly identify exact timing of the post-injection observations. Functional dysfunction decreased from 3.0 to 0.8 based on visual interpretation of the authors' graph, which was not a statistically significant result ($p = 0.065$). Clicking of the left joint was statistically significantly reduced ($p = 0.001$). The authors stated that clinical-effectiveness was witnessed within the first week and at two months, and that post-injection values returned to pre-injection values within three months in all but two patients. The authors did not report pre- and post-intervention clicking values, or values for clicking of the right joint. No adverse events were reported, but the authors stated that two patients' condition worsened, one patient showed no improvement, and two patients did have improvement with mouth opening.

The authors concluded that in patients with temporomandibular disk displacement botulinum toxin A may be an effective treatment, although definitive conclusions could not yet be made.

Limitations

There are several limitations in this HTIS report.

- **Methods:** Several limitations to the methodology of this HTIS report exist, including, English language articles only were included, articles had to be peer-reviewed and published between 2004 and July, 2009, hand searching to retrieve additional articles was not conducted, and a limited grey literature search was conducted. These limitations may have affected the content of the summary of findings and the conclusions of this report.
- **Contents of findings:** While two systematic reviews were identified, each included only one RCT. Authors of both systematic reviews concluded that there was insufficient evidence to draw conclusions regarding the clinical benefit and harm of botulinum toxin A in the treatment of TMD and TN. No other relevant RCTs were identified by literature searches. The four observational studies retrieved through the literature search had no comparator group and involved small sample sizes. Thus, causality cannot be ascertained and there can be a higher risk of bias in the study results and conclusions non-randomized, non-comparative studies.
- **Diversity amongst intervention groups:** While all included systematic reviews and single arm studies pertained to patients with either TMN or TN, there was diversity in definition TMN of TN used by these studies. Patients were recruited under different criteria, and differed in terms of severity of disease, and age. Where use of co-interventions such as drug therapies and surgical procedures were present, confounding factors negatively affected the level of confidence of study results.
- **Heterogeneity of interventions:** The dosing, injection site(s), and type of botulinum toxin A used varied across studies; further work is needed to determine the optimal approach.
- **Differences in outcome measures:** Most studies performed pain assessment using VAS as an outcome. However, not all authors described the scales used. Some studies also incorporated functional outcomes as a measurement, and further work is needed to evaluate their significance in the context of the clinical-effectiveness of botulinum toxin A.
- **Variety in length of study:** Follow-up times of included studies were varied and generally short, ranging from four weeks to six months post injection. Therefore, the longer term (greater than six months) clinical-effectiveness and safety of single or multiple doses of botulinum toxin A in the treatment of TN and TMD were not assessed.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

There is a lack of high quality evidence pertaining to the assessment of clinical benefit and harm of botulinum toxin A for the treatment of TN and TMD. Two RCTs along with four small observational studies were identified both through selected systematic reviews and literature search.

Included studies¹¹⁻¹³ described in this review suggested that, for TN, botulinum toxin A might be beneficial in pain reduction for some patients. Across all relevant studies identified, doses ranging from 6 U to 100 U per patient were used. Clinical responses were reported from minutes to days post-intervention, and there is some evidence that effectiveness is sustained for at least two months. None of the included studies reported serious adverse events, although some patients developed transient, but non life-threatening adverse events such as difficulty

chewing, dysesthesia, and transient facial asymmetry. Without larger and more rigorous studies, the aforementioned results are preliminary, and further research is needed before more definitive conclusions can be drawn. There was no evidence identified for the longer term clinical-effectiveness and safety of botulinum toxin A in the treatment of TN.

Included studies described in this review reported inconsistent findings for the potential benefit and safety of botulinum toxin A for the treatment of TMD. One systematic review⁹ and one single arm study¹⁰ suggested that botulinum toxin A can be effective for managing pain for patients with TMD, while another systematic review⁴ did not find evidence of botulinum toxin A providing significant differences in pain intensity reduction. None of the aforementioned studies provided definitive conclusions on the clinical benefit and harm of botulinum toxin A for TMD. There is no evidence on the effect of single or multiple treatments with botulinum toxin A over a long period of time for patients with TN.

Overall, there is some recent, lower-quality evidence to suggest that botulinum toxin A may provide short-term pain relief in some patients with TN and TMD. No recent evidence was found on the longer-term benefit and harm of botulinum toxin A for the treatment of TN and TMD. The lack of high-quality and longer-term evidence should be considered when determining coverage of botulinum toxin A for these indications.

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