Clinical outcomes of Botox injections for chronic temporomandibular disorders: do we understand how Botox works on muscle, pain, and the brain?


Abstract. The main objective of this retrospective review was to analyze the clinical outcomes following the use of botulinum toxin (onabotulinumtoxinA, Botox) injections to relieve the symptoms of chronic temporomandibular disorders (TMD). Seventy-one patients with a diagnosis of TMD (according to the RDC/TMD international consortium) associated with or without bruxism and refractory to conventional treatment (e.g. oral appliances, physiotherapy, etc.) received Botox injections into the temporals and masseter muscles. Subjective responses to Botox were categorized as ‘beneficial’ or ‘not beneficial’, as patient-reported outcomes based on the subjective reduction in pain and/or improvement in function. Fifty-five of the 71 subjects (77%) reported beneficial effects with Botox. Subjects with a concomitant bruxism diagnosis reported significant improvement over subjects without bruxism (87% vs. 67%; P = 0.042). Subjects with stress-related psychiatric comorbidities and bruxism had a significantly higher benefit than those with stress-related psychiatric comorbidities alone (P = 0.027). Patients reported less improvement if the time between the initial Botox injection and follow-up was less than an average of 5 weeks, compared to an average follow-up of 5–10 weeks (P = 0.009). The subgroup TMD diagnosis and time interval post-injection are important predictors of patient-reported beneficial outcomes.

Key words: temporomandibular joint; Botox; chronic pain; bruxism; post-traumatic stress disorder; anxiety.

Accepted for publication 4 November 2016
Available online 28 November 2016
During the second part of the 1990s, botulinum toxin injections (onabotulinumtoxinA, Botox) were introduced as a treatment for temporomandibular disorders (TMD). At that time, it was appreciated that patients with acute, subacute, or chronic TMD pain derived relief from this novel approach. This was encouraging because similar to many other chronic functional pain syndromes, TMD has the potential to become centralized, leading to symptoms that are beyond the control of traditional interventions. Overall, our lack of understanding of the centralization process has contributed to a deficit of effective treatments that are available for chronic pain patients; this can result in severe debilitation and have significant negative effects on various measures of quality of life for those individuals suffering with chronic pain. The current approaches and treatment responses for TMD problems in general are quite different, especially if therapeutic effects are considered for acute versus chronic pain. Thus, it is imperative to identify new therapeutic strategies to treat both the acute and chronic TMD patient.

Fortunately, Botox injections may play a valuable role in such a desired treatment approach.

It is commonly understood that Botox exerts a therapeutic effect through well-described molecular actions at the neuromuscular junction. A local paralytic effect is produced via inhibition of acetylcholine release, and this synaptic blockade has been taken advantage of to successfully treat a wide number of clinical problems, including movement disorders, focal hyperhidrosis, rhytids, urological pain syndromes, and migraines. Utilizing Botox to treat both acute and chronic centralized TMD pain is a logical extension of its clinical usefulness, although the exact mechanisms of how this might occur have yet to be completely elucidated.

The objective of this study was to analyze the retrospective clinical outcomes following the use of onabotulinumtoxinA (Botox) to relieve the symptoms of chronic TMD. In addition, attention is called to open questions regarding the timing, duration, and location of action of therapeutic Botox injections.

### Materials and methods

#### Subjects

US military veterans treated at the TMD clinic of the San Francisco Veterans Affairs Health Care System, San Francisco (SFVA) between 2002 and 2013 were included in this study. The diagnosis of TMD was made in accordance with the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). Subject data were obtained from the computerized patient record system (CPRS) from consecutive standardized encounters for each patient. From an initial group of 151 patients treated for TMD problems, 71 patients without any benefit from conventional treatment (psychological support, splint therapy, physiotherapeutic support) after 6 weeks were included in the study. Their demographic characteristics are shown in Table 1.

It was also determined whether or not there was a history of (1) a previously established stress-related psychiatric diagnosis, as noted in the medical record, (2) masticatory muscle fibromyalgia for more than 6 months, as noted in the medical record; (3) bruxism, by patient self-report and clinical examination.

Subjective responses to Botox (Allergan Inc., Dublin, Ireland) were categorized as ‘beneficial’ or ‘not beneficial’, based on a documented reduction in pain and/or improvement in function, as a patient-reported outcome after 5 and 10 weeks of post-treatment follow-up. No adverse events after Botox injections were recorded in the patient electronic health records. No patient dropouts were recorded. Responses were measured for statistical significance using a $\chi^2$ test ($P < 0.05$ deemed significant). The Institutional Review Board approved this retrospective clinical review and specified that there be no contact with the subjects; however, informed consent was obtained from each subject who received Botox treatment. Adverse events were monitored and included: evidence of distant or contiguous spread of Botox, systemic effects such as difficulty with respiration, injection site discomfort or infection, and allergic reaction.

#### Intervention

All subjects received a one-time treatment with a total of 100 units of Botox, which was reconstituted with sterile saline (100 units/4 ml of sterile saline). The Botox was injected into the bilateral temporals and masseter muscles. Three points were injected along the inferior portion of the masseter and two points along the anterior–superior portion of the temporals. Ten units of Botox were delivered to each point using a 5-ml syringe and a 23-gauge needle. The injection technique involved inserting the needle into the soft tissue until bone was encountered and then the needle was withdrawn approximately 2–4 mm so that the tip was in the muscle, at which time the liquid was injected.

#### Statistical analysis

Subjective responses to Botox were identified by a review of the medical records and categorized as beneficial or not beneficial as a patient-reported outcome. A

---

### Table 1. Descriptive characteristics of the population treated with Botox injections ($N = 71$).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$n$ (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (64.8)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (35.2)</td>
</tr>
<tr>
<td><strong>Age, years, mean ± SD (range)</strong></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>30–39</td>
<td>15 (21.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>16 (22.5)</td>
</tr>
<tr>
<td>50–59</td>
<td>20 (28.2)</td>
</tr>
<tr>
<td>60–69</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>70–79</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>80–89</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><strong>Comorbidities, $n$ (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Bruxism</td>
<td>38 (53.5)</td>
</tr>
<tr>
<td>Stress-related psychiatric comorbidities</td>
<td>37 (52.1)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>DJD other than TMJ</td>
<td>29 (40.8)</td>
</tr>
<tr>
<td>DJD other than TMJ + fibromyalgia</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td><strong>Presenting symptoms, $n$ (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Joint pain only</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>Myofascial pain only, including those presenting with temporal headache</td>
<td>27 (38.0)</td>
</tr>
<tr>
<td>Joint pain + myofascial pain</td>
<td>37 (52.1)</td>
</tr>
</tbody>
</table>

SD, standard deviation; DJD, degenerative joint disease; TMJ, temporomandibular joint.
beneficial response was defined as a documented subjective improvement in function (improved jaw movements) or decrease in pain, whereas a non-beneficial response was defined as no improvement in function or decrease in pain, or a worsening of symptoms.

The subjects’ responses to Botox were analyzed relative to comorbidities and TMD sub-diagnoses, which were jointly referred to as ‘associated factors’, in order to investigate the therapeutic role of Botox under these variables. The associated factors were grouped as follows: (1) presence of bruxism; (2) the origin of symptoms, which included pain stemming from joint, muscle, or both; (3) systemic risk factors; (4) time-sensitive analysis of subjective responses to Botox; (5) established diagnosis of a stress-related psychiatric comorbidity.

Results

Subjects

Demographic group characteristics are shown in Table 1. The subjects had a mean age of 45.8 years and were predominantly male (64.8%). More than half of the subjects had one or more established psychiatric diagnoses (Table 2). Bruxism (n = 38, 53.5%) was detected in more than half of the subjects through clinical findings and patient self-report, as documented in the CPRS. The majority of the subjects complained of having pain originating from both the joints and muscles of mastication (n = 37, 52.1%), while isolated pain from the joint only (n = 7, 9.9%) and from the muscles only (n = 27, 38.0%) was found in a minority of the subjects.

Associated systemic risk factors included fibromyalgia and degenerative joint disease, which were found in 14.1% (n = 10) and 40.8% (n = 29) of the subjects, respectively.

Many subjects had a past medical history that included various established psychiatric diagnoses (n = 39, 54.9%); some subjects presented with multiple diagnoses. Thirty-seven patients (52.1%) had stress-related psychiatric comorbidities, which included depression, post-traumatic stress disorder (PTSD), anxiety, and adjustment disorder (Table 2). Taken together, these stress-related psychiatric comorbidities are the most frequently diagnosed mental disorders among veterans around the country.20–22 The remaining psychiatric diagnoses are less commonly observed.

Effects of Botox and associated factors

Bruxism

The subject group with bruxism was compared to the subject group without bruxism. Subjects with a history positive for bruxism were significantly more likely to benefit from Botox compared to those without bruxism (P = 0.042) (Table 3).

Presenting symptoms

Subject groups with myofascial pain only, joint pain only, or both myofascial and joint pain, all reported subjective improvements from Botox. When each group was compared against the others, there was a trend towards the joint pain only group benefiting more from Botox compared to the other two groups. However, this was not statistically significant, most likely due to the small sample size (P = 0.47).

Systemic risk factors

In an effort to determine whether Botox had a differential effect on patients with degeneration in one or more joints other than the temporomandibular joint (TMJ), or a history of fibromyalgia, or both, these subject groups were compared to observe the effects of Botox on TMD-associated pain. There was no statistically significant difference in response between patients with degenerative joint disease in joints other than the TMJ and those without (P = 0.38). Among patients with and without fibromyalgia, patients benefitted as well, but again there was no statistically significant difference (P = 0.27). Lastly, for patients with dual diagnoses of degenerative joint disease and fibromyalgia compared to those without dual diagnoses, there was no statistically significant difference in benefit (P = 0.46). Thus, all groups benefitted from Botox, but no distinct difference was found among these systemic risk factors.

Time-sensitive analysis of subjective responses to Botox

The interval between the initial Botox treatment and the follow-up appointment is shown in Fig. 1. The results are informative: at an interval of 5 weeks or less, the subjects were less likely to observe an improvement in their TMD pain, whereas subjects who were queried between 5 and 10 weeks after Botox were more likely to report an improvement (N = 71; P = 0.009).

Stress-related psychiatric comorbidities and bruxism

The majority of the patients with a diagnosis of stress-related psychiatric comorbidities also had bruxism (59.5%). As illustrated

Table 3. Effect of Botox on bruxism (P = 0.042).

<table>
<thead>
<tr>
<th></th>
<th>Beneficial, n (%)</th>
<th>Not beneficial, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruxism</td>
<td>33 (87)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>No bruxism</td>
<td>22 (67)</td>
<td>11 (33)</td>
</tr>
</tbody>
</table>

Fig. 1. Interval between Botox and follow-up in weeks.
in Table 4, while both groups of patients benefitted from Botox therapy, those patients with stress-related psychiatric comorbidities who also had bruxism showed a significantly greater benefit compared to those with stress-related psychiatric comorbidities but without bruxism ($P = 0.027$).

Discussion

Botox treatment for TMD patients is still controversial. The development of a clear consensus on the benefits of this treatment modality is still in progress. At this point, however, existing randomized clinical trials (RCTs) fail to demonstrate that Botox treatment is superior to other conventional therapeutic options, despite years of clinical experience that suggests it is. Contributing to this lack of consensus is that pain is a very subjective measurement and difficult to standardize within individuals and between groups, which often leads to inconclusive study results. Therefore, to reach a final conclusion, an RCT will have to take into account specific TMD subgroups, and importantly, the psychosocial component of TMD should not be ignored, as chronic pain is quite often derived from or exacerbated by psychological factors. In the current study, the interplay between psychology and pain is well expressed in the patient cohort. All of the subjects were US military veterans; such subjects have often suffered traumatic experiences resulting in a complicated psychological history that can affect emotional and pain processing. This provides us with an opportunity to better understand how Botox works in patients with TMD in the setting of altered emotional states and how best to devise appropriate treatment strategies for them going forward.

No patient withdrew from the clinical protocol; all of the subjects attended the dental clinic regularly for follow-up visits. The retrospective clinical findings showed that a significant proportion of these TMD patients who were resistant to conventional treatments reported the Botox treatment to be beneficial (77.5% of patients). Moreover, if they had a history of bruxism they were more likely to benefit from Botox compared to those patients who did not have bruxism. This is consistent with existing studies that have also shown the therapeutic role of Botox in alleviating the effects of bruxism in the general population. The possibility that the therapeutic effect observed in patients who received Botox was due to a placebo effect could not be ruled out. This is a limitation of the study that could be overcome with a well-designed, controlled, and timed double-blinded RCT.

Given the robust comprehensive health history that follows the patient throughout the national Veterans Affairs system, it was possible to accurately derive correlations between patient medical comorbidities and their TMD status. This is particularly relevant given the known association between psychiatric conditions and TMD, as mentioned above. This association is especially strong between PTSD and masticatory muscle disorder (MMD). According to Schiffman and Ohrbach, MMD is a diagnostic subset of TMD and is defined by myofascial pain as a response to reflexive contraction per se or underlying clinical problems like parafunctional habits, joint disease, or inflammation.

The present study contributes to the understanding we have regarding the indications for Botox injections in TMD patients in general and this patient cohort specifically. The data demonstrate that chronic pain patients with comorbid stress-related psychiatric conditions and bruxism are the subgroup most likely to benefit from Botox injections. Further, in this sample, the majority of the patients with a diagnosis of stress-related psychiatric comorbidities also had bruxism (39.5%) and these patients showed a greater benefit from Botox treatment, in terms of patient-reported outcomes, than patients who had stress-related psychiatric comorbidities and TMD without bruxism. This finding is not surprising, as many studies have demonstrated a strong association between stress-related psychosocial conditions and masticatory hyperactivity. This suggests that there is a possible relationship between TMD and certain psychiatric disorders such as PTSD. Indeed, there is literature that supports the idea that chronic pain and PTSD share common neuroanatomical and neurochemical pathways.

The delayed recognition or cognition of the beneficial effects of Botox could be an important gateway into gaining a greater understanding of the central mechanisms and psychology of pain.

Funding

No support or funding from any source was received for this clinical review.

Competing interests

None of the authors report a conflict of interest.
Ethical approval

Institutional Review Board of the University of California San Francisco, California, USA.

Patient consent

Not required.

References


35. XM. Involvement of NMDA receptor mechanisms in jaw electromyographic activity and plasma extravasation induced by inflammatory irritant application to temporomandibular joint region of rats. Pain 1996;68:169–78.


Outcomes of Botox injections for chronic TMDs

Address:
Stephen T. Connelly
Department of Veterans Affairs Medical Center
Dental Service (160)
4150 Clement St.
San Francisco
CA 94121
USA
Tel: +1 415 221 4810x5821;
Fax: +1 415 750 6603
E-mail: stephen.connelly2@va.gov