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Severity and Impact of Xerostomia in Patients Treated with Botulinum Toxin Type B for Cervical Dystonia: Observations on the Quality of Life of Patients with Xerostomia

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ABSTRACT

Background: Although dry mouth (xerostomia) has been reported with botulinum toxin type B used as treatment for cervical dystonia, the impact of this adverse effect (AE) on patients' activities of daily living (ADLs) has not been assessed.

Objective: The aim of this study was to examine the severity, duration, and impact of xerostomia in patients with cervical dystonia who reported this AE in routine clinical practice following treatment with botulinum toxin type B.

Methods: In this uncontrolled study, investigators at 5 study centers across the United States retrospectively identified patients who were diagnosed with cervical dystonia and had received ≥1 treatment with botulinum toxin type B injection and who had reported xerostomia, based on patients' charts. These patients were mailed a survey that included questions about their treatment history, disease severity, and xerostomia (severity, onset, duration, change with subsequent injections, and effects on dental and oral health), as well as an 8-item Patient Benefit Questionnaire (PBQ), which was designed to assess the impact of xerostomia symptoms on patients' ADLs.

Results: A total of 45 patients received a mean of 2.91 injections with botulinum toxin type B (mean dose per injection, 11,958 U), with a total of 131 injections. The mean severity of patient-rated xerostomia following the first injection of botulinum toxin type B was 3.88 on a scale of 1 (mild) to 5 (severe), and this rating did not change for patients who received subsequent injections (mean, 3.76). Following a typical injection of botulinum toxin type B, xerostomia

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began a mean (SD) of 4.82 (3.32) days later and persisted for a mean (SD) duration of 5.56 (3.57) weeks. The overall mean score on the 10-point PBQ prior to botulinum toxin treatment was 8.89, which decreased to 5.42 following botulinum toxin type B injection (lower scores indicate more severe xerostomia).

Conclusions: This study of patients with cervical dystonia suggests that patients who experience xerostomia following treatment with botulinum toxin type B injection, on average, rate their symptoms as moderate to severe and exhibit reduced scores on the PBQ—a questionnaire on which lower scores indicate greater negative impact of xerostomia on patients' ADLs. (*Curr Ther Res Clin Exp.* 2004;65:161–171)

Key words: xerostomia, botulinum toxin, patient benefit questionnaire.

INTRODUCTION

Cervical dystonia is a syndrome of involuntary contractions of the neck and/or shoulder muscles that results in abnormal postures and movements. Historically, this disorder was treated with oral anticholinergics, but these drugs were often accompanied by inadequate efficacy and/or unacceptable adverse effects (AEs).[1,2] Since the mid-1980s, botulinum toxin type A has been the primary treatment for this disorder, improving head position and associated pain.[3,4] In a randomized, controlled trial,[5] botulinum toxin type A was found to produce greater improvement in head position with fewer AEs than the anticholinergic trihexyphenidyl hydrochloride in patients with cervical dystonia. In 2000, a botulinum neurotoxin product based on the B serotype that also significantly improves the symptoms of cervical dystonia was introduced in many European countries and the United States.[6,7]

Acceptable tolerability has been reported with the A and B serotypes in the treatment of cervical dystonia.[3–7] However, according to a MEDLINE search (key terms, *botulinum toxin type A*, *botulinum toxin type B*, *cervical dystonia*, *torticollis*, *comparison*, *BOTOX®*,* and *MYOBLOC®*,† a growing amount of research and experience suggests that the specific AE profiles of these 2 preparations differ somewhat,[8] although no published, controlled studies have directly compared these botulinum neurotoxins in the treatment of cervical dystonia. In particular, xerostomia, or dry mouth, is one of the most common AEs with type B in the treatment of cervical dystonia, occurring in 17 of 39 patients (43.6%) treated with 10,000 U in a double-blind trial[6] and in 21 of 24 patients (87.5%) treated with a mean of 11,310 U in an open-label trial.[8] In contrast, xerostomia is rarely reported in patients treated with botulinum toxin type A.[4,8] The AE profiles appear to differ, even in both botulinum toxin formu-

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lations that contain the A serotype,[9,10] suggesting the importance of factors other than serotype.

In 3 randomized, placebo-controlled trials,[6,7,11] the incidence of xerostomia in patients treated with botulinum toxin type B for cervical dystonia ranged from 24% to 44% with the 10,000-U dose versus 3% with placebo. Although xerostomia was the most commonly reported AE in these trials, the impact of this AE on patients' activities of daily living (ADLs) has not been assessed. The severity of xerostomia has been specifically reported in only 1 published trial,[8] with 10 of 21 patients (47.6%) experiencing severe xerostomia. A 6% rate of severe xerostomia was documented in unpublished data pooled from several controlled and uncontrolled studies that included 570 patients.[12]

Because cervical dystonia is a chronic disorder that tends to require treatment over the course of many years,[13,14] it is important to determine whether xerostomia with botulinum toxin type B is merely a bothersome AE that tends to improve with repeated injections or whether it causes more severe and pervasive problems. Therefore, the present study was undertaken to examine the severity, duration, and impact of xerostomia in patients with cervical dystonia who reported this AE in routine clinical practice following treatment with botulinum toxin type B.

PATIENTS AND METHODS

In this uncontrolled study, investigators at 5 study centers across the United States retrospectively identified patients who were diagnosed with cervical dystonia and had received ≥1 treatment with botulinum toxin type B IM injection* that resulted in xerostomia, based on patients' charts. For these patients to be eligible, they could not have been using any other treatments known to cause xerostomia and must have been free from conditions that could impair or enhance recall of AEs (eg, dementia, hyperchondriasis); these criteria were also determined by the physician based on patient charts. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. Women of childbearing age were required to use an effective method of birth control throughout the study.

Patients at each site who met these criteria were sent a treatment satisfaction survey form in the mail, which they were asked to complete and mail to a central location (Center for Outcomes Research, Chapel Hill, North Carolina). The survey included the 8-item Patient Benefit Questionnaire[15] (PBQ) designed to assess the impact of xerostomia symptoms on patients' quality of life (QOL), with possible scores on each of the 8 items ranging from 1 (extreme symptoms) to 10 (no symptoms). The reliability and validity of this questionnaire have been established in a study of patients with parotid-sparing head and neck

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cancer.[15] In addition to the PBQ, patients were asked about disease severity and treatment history and satisfaction with botulinum toxin therapy (rated on a scale of 1 [very dissatisfied] to 7 [very satisfied]), and the following features of their xerostomia: severity (rated on a 5-point scale; 1 = mild, 3 = moderate, 5 = severe), time of onset, duration, frequency, change with repeated injections, and effects on dental and oral health. Patients were also asked to check other AEs they experienced with botulinum toxin type B from a list of 12 AEs (headache, neck pain, stiff neck, back pain, sore muscles, pain, difficulty swallowing, nausea, infections, flulike symptoms, dizziness, blurred vision).

Data on botulinum toxin preparations and doses injected were obtained from patients' charts. In addition, physicians rated the severity of each patient's cervical dystonia when left untreated and following treatment with botulinum toxin on a scale of 1 (mild) to 5 (severe). The protocol was approved by appropriate local institutional review boards (IRBs), and IRB procedures for obtaining informed consent were followed.

RESULTS

Physicians identified a total of 74 patients who had received botulinum toxin type B injections for cervical dystonia, based on chart reviews. Five of these patients did not meet the inclusion criteria, and surveys were mailed to the remaining 69 patients. At the time of this analysis (June 2003), 45 patients had returned their surveys, for a response rate of 65.2%.

A summary of patient disease history and botulinum toxin type B treatment is shown in the **table**. Most patients had fairly severe disease, as indicated by mean scores >4 on a 5-point scale, as rated by physicians and patients. Patients received a mean (SD) of 2.91 (1.86) injections with botulinum toxin type B, with a total of 131 injections. The mean dose of botulinum toxin type B was 11,958 U, and increased from a mean (SD) of 9131 (4328) U on the first treatment (44 patients [97.8%]) to 12,679 (3477) U on the fifth treatment (14 patients [31.1%]) (**Figure 1**).

The mean (SD) severity of patient-rated xerostomia following the first injection of botulinum toxin type B was 3.88 (1.31) on a scale of 1 (mild) to 5 (severe), and this rating did not change for patients who received subsequent injections (mean [SD], 3.76 [1.13]). Although 12 patients (26.7%) reported that their xerostomia symptoms gradually improved following subsequent injections with botulinum toxin type B, 16 (35.6%) reported that symptoms did not change, and 3 (6.7%) reported that symptoms became worse. Following a typical injection of botulinum toxin type B, patients reported that their xerostomia began at a mean (SD) of 4.82 (3.32) days after the first dose of botulinum toxin type B and persisted for a mean (SD) duration of 5.56 (3.57) weeks (range, 1–12 weeks).

Following treatment with botulinum toxin type B, patients reported lower scores on every item on the PBQ (**Figure 2**). The overall mean (SD) PBQ score

Table. History of treatment of cervical dystonia with botulinum toxin type B (N = 45).

History Parameter	Value
Year symptoms of cervical dystonia began	
Mean	1986
Range	1958–2001
Year physician diagnosed cervical dystonia	
Mean	1991
Range	1958–2001
Patient-rated severity of cervical dystonia symptoms*	
Mean (SD)	4.10 (0.79)
Range	2–5
Physician-rated severity of cervical dystonia symptoms left untreated*	
Mean (SD)	4.56 (0.62)
Range	3–5
Physician-rated severity of cervical dystonia symptoms treated with type B*	
Mean (SD)	2.55 (1.02)
Range	1–5
No. of type B treatments	
Mean (SD)	2.91 (1.86)
Range	1–7

*Severity scale: 1 = mild, 2 = slightly moderate, 3 = moderate; 4 = slightly severe, 5 = severe.

reported by patients under normal conditions (ie, without botulinum toxin treatment) was 8.89 (2.16), which decreased to 5.42 (1.99) following botulinum toxin type B treatment (lower scores indicate more severe xerostomia).

On the treatment satisfaction scale, patients reported being dissatisfied on average with the xerostomia symptoms associated with botulinum toxin type B and somewhat dissatisfied with its AEs in general (**Figure 3**). Patients rated the effectiveness of treatment between neutral and somewhat dissatisfied.

When patients were asked whether they had noticed any changes in dental or oral health, 10 of 45 patients (22.2%) reported a sour taste, 8 (17.8) reported bad breath, 6 (13.3%) reported sore gums, 3 (6.7%) reported more infections in their mouths, 2 (4.4%) reported bleeding, and 2 (4.4%) reported more cavities. To relieve xerostomia, most patients (37 [82.2%]) reported drinking fluids often between meals and 31 (68.9%) carried fluids with them wherever they went.

On the AE symptom checklist, 26 patients (57.8%) reported having difficulty swallowing; other AEs reported included neck pain (21 patients [46.7%]), sore muscles (20 [44.4%]), stiff neck (17 [37.8%]), pain (15 [33.3%]), headache (13 [28.9%]), blurred vision (11 [24.4%]), dizziness (10 [22.2%]), upset stomach (10 [22.2%]), nausea (6 [13.3%]), flulike symptoms (5 [11.1%]), and infections (1 [2.2%]).

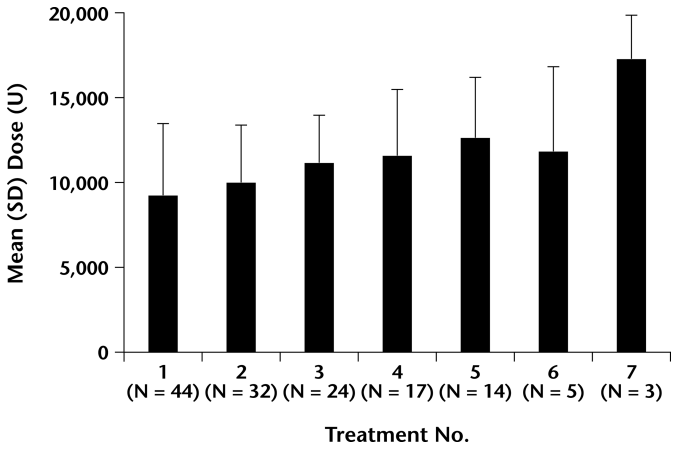

Figure 1. Mean (SD) doses of botulinum toxin type B across multiple treatments.

DISCUSSION

In the present study, the severity of xerostomia associated with botulinum toxin type B was consistently rated between moderate and severe and lasted a mean duration of ~6 weeks. Xerostomia following botulinum toxin type B resulted in a 39.0% reduction in PBQ scores compared with off-treatment scores, and no clear trend of amelioration of xerostomia was observed with repeated treatments. Lifestyle changes, such as frequent fluid intake between meals and carrying extra fluids, were also prevalent.

Results of the present study are in general agreement with those of Dressler and Benecke,[8] who found that 87.5% of 24 patients with cervical dystonia reported xerostomia, which was rated as severe in 10 patients (41.7%). In addition, the mean dose of botulinum toxin type B used in the aforementioned study was 11,310 U, which is similar to the mean dose of 11,958 U in the present study.

These dosage data suggest that, in routine clinical practice, botulinum toxin type B is being used at higher doses than were studied in the pivotal clinical trials (2500–10,000 U).[6,7,11] Thus, the AE data obtained in controlled studies with doses of 2500 and 5000 U may not be entirely applicable to clinical practice. As shown in Figure 1, an apparent increase in dosages was observed over time in the present study, although the numbers of patients at each injection were not the same, with only a few patients having received 6 or 7 injections. Additional long-term studies are needed to confirm the apparent dose increases over time and to determine whether these may be due to secondary nonresponsiveness or to other causes.

Xerostomia often indicates reduced salivary flow.[16] Saliva not only lubricates food, but also permits clear speech, maintains nonirritating pH levels, prevents

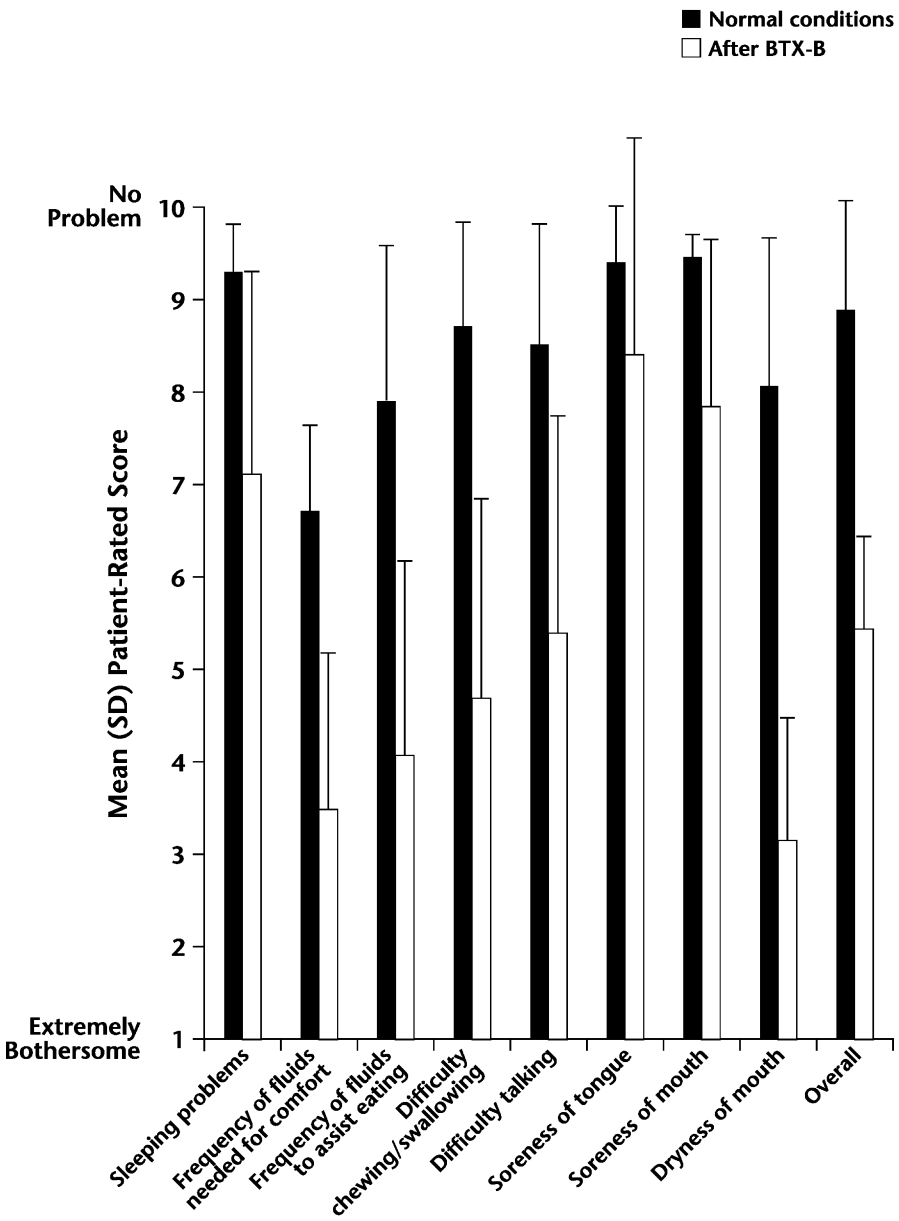

Figure 2. Mean (SD) patient-rated scores for each of the 8 items on the Patient Benefit Questionnaire under normal conditions and after botulinum toxin type B (BTX-B) treatment. Scale ranges from 1 (extremely bothersome) to 10 (no problem).

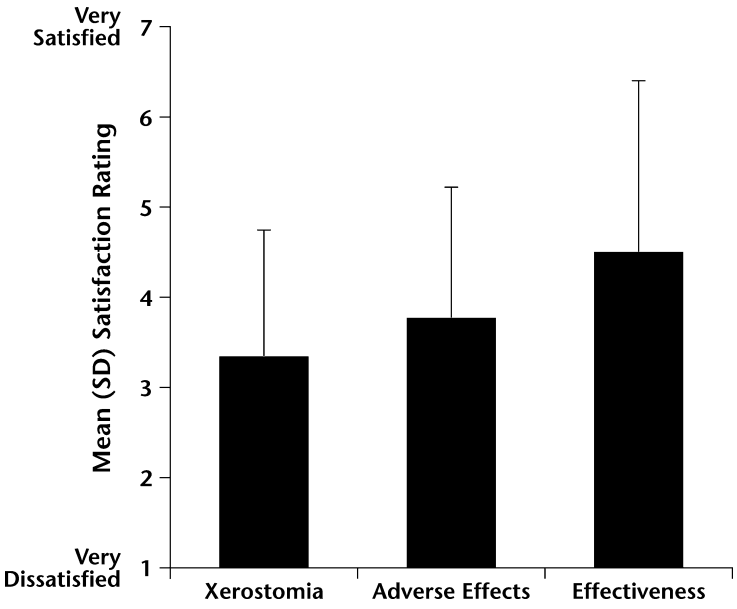

Figure 3. Mean (SD) patient-rated satisfaction with the xerostomia, adverse effects, and effectiveness associated with botulinum toxin type B treatment. Scale ranges from 1 (very dissatisfied) to 7 (very satisfied).

dehydration of the oral mucous membranes, maintains dental integrity, and helps initiate digestion.[17,18] Patients with salivary hypofunction show increases in potentially harmful microorganisms that can increase dental decay and oral candidiasis.[17] Patients in the present study indicated an increased need for fluids as well as difficulty chewing, swallowing, and talking, as rated on the PBQ. These ratings indicate that salivary flow was likely reduced by botulinum toxin type B, which may have potential long-term consequences in patients who receive this therapy repeatedly. Pilocarpine hydrochloride* tablets, which increase salivary flow, have been found to improve xerostomia in patients with several other diseases, such as radiation-induced xerostomia and Sjögren's syndrome[19,20]; these tablets may also be beneficial for the treatment of xerostomia associated with botulinum toxin type B, but no published studies have examined this.

Xerostomia is a common complication of radiation therapy for head and neck cancer[21] and is one of the major causes of reduced QOL in these patients.[22] In 1 study,[23] patients with head or neck cancer responded to the same PBQ used in the present study. Patients in that study showed a mean score of

*Trademark: Salagen® (MGI PHARMA, Inc., Minneapolis, Minnesota).

8.6 at baseline and a mean score of 5.5 following 7 weeks of radiation therapy. In comparison, mean scores on this measure for patients in the present study were 8.89 and 5.42, respectively. This comparison highlights the significance of xerostomia for cervical dystonia patients.

Because botulinum toxin type B is injected locally into affected neck and shoulder muscles for the treatment of cervical dystonia,[6,7] its tendency to cause xerostomia—presumably an effect on parasympathetic neurons that innervate the salivary glands—suggests systemic transport of the toxin,[8] although diffusion cannot be ruled out as a possible mechanism.

Systemic distribution is also suggested by findings of xerostomia with botulinum toxin type B for the treatment of other indications. In a study of 10 patients who received botulinum toxin type B for upper-limb spasticity, 9 patients (90.0%) reported xerostomia at week 4.[24] In a study of 31 patients being treated with botulinum toxin type B for postwhiplash headaches, 12 (38.7%) reported xerostomia.[25] In the present study, 11 of 45 patients (24.4%) also reported blurred vision, which is further suggestive of systemic toxin distribution, given the physical distance of the ocular system from the neck and shoulder injection sites in the present study.

The present study has several limitations. The study design was uncontrolled and depended on patients' recollections of xerostomia. In addition, patients who may have had mild xerostomia or who were not bothered by their xerostomia symptoms may not have reported them to their physicians. Thus, the present results apply only to the population of patients who reported xerostomia following botulinum toxin type B treatment. In controlled trials,[6,7,11] the percentage of patients with cervical dystonia reporting xerostomia following treatment with botulinum toxin type B ranged from 24% to 44% versus 3% with placebo.

CONCLUSIONS

This study of patients with cervical dystonia suggests that patients who experience xerostomia following treatment with botulinum toxin type B injection, on average, rate their symptoms as moderate to severe and exhibit reduced scores on the PBQ—a questionnaire on which lower scores indicate greater negative impact of xerostomia on patients' ADLs. Future studies are needed to confirm and extend these results, which, it is hoped, will raise awareness of this nontrivial AE.

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