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Original article

Satisfaction with botulinum toxin treatment: a cross-sectional survey of patients with cervical dystonia

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Abstract

Objective:
Botulinum toxin is widely utilized as a first-line therapy for cervical dystonia (CD). Numerous studies have demonstrated the efficacy and safety of this treatment, but little data exist on patient satisfaction. To address this question, a structured patient survey was conducted in Germany, France, the US, and Canada ($n = 136$ patients with CD).

Methods:
Specific information was collected on the patients' current and prior botulinum toxin treatment cycles and their overall quality-of-life (including completion of the Cervical Dystonia Impact Profile-58 [CDIP-58]).

Results:
Patients rated the mean onset of action for their previous injection as 3.8 days, with peak effect at 3.6 weeks and a decline in effects at 9.5 weeks. While most patients were satisfied with their current therapy, only 50.7% were very satisfied, 42.6% were somewhat satisfied, and 6.6% not at all satisfied with their current therapy. Patient satisfaction was lowest just prior to injection and highest at the time of peak effect. Approximately 45% of patients reported that they would prefer a treatment cycle of $\leq$10 weeks. The mean patient rating of current state of health was above 50 on a visual analog scale from 0 (low) to 100 (high). CDIP-58 results indicated that patients continued to have symptoms on all domains.

Conclusions:
Botulinum toxin is generally very effective for the treatment of CD. However, this survey indicates that patient satisfaction typically declines prior to re-injection, and many patients may prefer an injection interval of less than the standard 12 weeks. While the survey was based on subjective patient recollections, and the degree to which patient satisfaction is attributable to the control of neurological symptoms remains unclear, prospective studies are clearly warranted to confirm the time course of patient satisfaction and to determine the optimal treatment parameters with botulinum toxins.

Introduction

Cervical dystonia (CD) is a common and lifelong focal dystonia[1] in which remissions are rare beyond the first year[2,3]. CD can significantly impact a patient's quality-of-life, not only due to neurological symptoms and pain, but also with respect to mental and emotional health, role limitations, and social function. In these respects, the negative impact on quality-of-life has been shown to be significant for patients with CD[2,4,5].

Treatment of CD with botulinum toxin type A or B effectively reduces symptoms, is well tolerated, and improves quality-of-life[6–11].

Nevertheless, some patients experience re-emergence of symptoms as the previous dose begins to wear off and before a new dose can be administered. In spite of this symptom re-emergence, concerns about potential immunologically mediated resistance to botulinum toxin with long-term treatment has resulted in a standard of treating with the lowest effective dose at inter-dose intervals of at least 12 weeks[7]. This dosing schedule could lead to reduced patient satisfaction during the latter part of the dosing cycle, as patients may have to tolerate symptoms until the next injection can be administered. In this study, structured interviews were conducted to characterize patient satisfaction with the current standard-of-care botulinum toxin type A (hereafter referred to as botulinum toxin) dosing regimens for symptomatic control in patients with CD.

Methods

Patient selection and study design

In this cross-sectional study, structured patient interviews took place in four countries (Germany, France, the US, and Canada) and lasted ~25 min each. All interviews were conducted by clinically experienced interviewers familiar with in the injection of botulinum toxin for the treatment of CD and native speakers of the local language. It was anticipated that the same interviewer would conduct all interviews in any one country. To be included in the survey, patients had to have undergone two complete treatment sessions with either abobotulinumtoxinA (Dysport; a registered trademark of Ipsen Limited, Slough, UK) or onabotulinumtoxinA (Botox; a registered trademark of Allergan, Inc., Irvine, CA). Patients receiving botulinum toxin injections at less than 10-week intervals were excluded. Patients were interviewed during specific time frames with regard to their most recent injection: (1) 7–8 weeks after their last injection or (2) 9–10 weeks after their last injection. Based on clinical experience, it was considered that these time frames would have allowed a sufficient time for the botulinum toxin injections to confer peak clinical effects. Information on patient demographics, disease characteristics, and previous treatment with botulinum toxin was collected.

Evaluation of treatment

The survey questionnaire was refined following pilot interviews in all four countries (see Appendix for final questionnaire used for this survey). The questionnaire was used to collect and evaluate the following information regarding the most recent botulinum toxin injection cycle: (1) general impression; (2) intervals between botulinum toxin injections; and (3) perceived time of onset of drug effect, peak effect, and waning effect of the last full treatment cycle. The following information was collected and evaluated regarding the current injection: (1) satisfaction with therapy at different stages of the treatment cycle (current, strongest effect, right before last injection), as measured using a visual analog scale (VAS) scale, where 1–3 was 'not at all satisfied', 4–7 was 'somewhat satisfied', and 8–10 was 'very satisfied'; (2) preference for a re-injection of botulinum toxin on the day of interview, as measured using a VAS scale, where 1–3 was 'not at all', 4–7 was 'somewhat', and 8–10 was 'very much'; and (3) preferred interval, in weeks, for receiving botulinum toxin injections. The survey questionnaire was also used to assess quality-of-life, based on general subjective ratings of current state of health as well as assessments of the impact of CD on specific aspects of patients' lives. Patients rated their current state of health on a VAS scale, with 0 being worst possible state of health and 100 being best possible state of health. The use of this subjective scale was intended to ensure that results reflected the patients' own perspectives. The Cervical Dystonia Impact Profile-58 (CDIP-58) was administered to determine the impact of CD on patients' lives[12,13]. The CDIP-58 is a validated scale and measures the impact of CD on eight sub-scales (head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning)[12,13].

Statistical methodology

Descriptive statistics were used to summarize all survey data collected in this study. It was planned that each CDIP-58 measure would be modeled using a two-way analysis of variance (ANOVA) with main effect terms for time since the previous injection session (weeks 7–8 vs weeks 9–10) and country. A time-by-country interaction term was also included in the model. If the time was significant, then the interaction term in the model would further ascertain whether the effect of the time varied significantly by country. However, none of the main effects or the interaction terms were found to be significant in any of the models and, therefore, results are described for the whole population.

Results

One hundred and thirty-six patients (50 males, 86 females) who had CD and were currently being treated with either abobotulinumtoxinA or onabotulinumtoxinA injections were interviewed. Demographic and baseline disease-related characteristics are shown in Table 1. The mean time since diagnosis of CD at the time of the survey was 92.9 months (standard deviation [SD] 86.2). Patients had been receiving injections of abobotulinumtoxinA or

Table 1. Demographic and baseline disease characteristics.

Characteristic	Patients ($n=136$)
Female, *n* (%)	86 (63.2)
Age, years, *n* (%)	
18–35	16 (11.8)
36–55	54 (39.7)
56–75	54 (39.7)
76–85	12 (8.8)
>85	0
Duration of CD, months, mean (SD)	92.9 (86.2)
Number of months receiving botulinum toxin, mean (SD)	45.3 (48.0)
Other chronic disease being medically managed, *n* (%)	62 (45.6)

CD, cervical dystonia; SD, standard deviation.

onabotulinumtoxinA for a mean (SD) of 45.3 (48.0) months. More than half of the patients in this survey had co-morbid chronic diseases requiring medical management, the most common being hypertension (54%), diabetes (20%), arthrosis (19%), and cardiac diseases (12%; more than one condition could be reported in an individual patient).

Evaluation of treatment

Treatment intervals

The mean (SD) treatment interval between injections was 14 (3.7) weeks. Patients usually received botulinum toxin treatment at intervals of every 9–10 weeks (4.4%; technically protocol violators), every 11–12 weeks (42.7%), every 13–14 weeks (27.2%), every 15–16 weeks (10.3%), or >17 weeks (15.4%). Patients were asked if they had received an explanation from their physician regarding the treatment interval and, if so, what the explanation was. For the patients who received a reason for the treatment interval chosen by their physician, the following explanations were provided: need to avoid formation of antibodies ($n=15$); you just shouldn't give it more often ($n=13$); risk of side-effects with shorter intervals ($n=13$); individual state of the patient ($n=10$); this is standard procedure ($n=8$); this injection interval is the most successful ($n=5$); decrease of efficacy – shorter interval needed ($n=5$); other ($n=5$), and according to the state of approval ($n=1$). Reasons were not mutually exclusive (i.e., more than one reason may have been provided).

Last injection cycle

Patients were asked to recall the onset, peak, and decline of effects of their most recent injection. The estimated mean (SD) onset of action was 3.8 (2.7) days, mean (SD) peak effect was 3.6 (2.5) weeks, and mean (SD) declining effect was 9.5 (4.4) weeks.

Table 2. Information regarding current injection cycle.

Satisfaction VAS	Current therapy ($n=136$)	Just prior to last injection ($n=102$)[a]	Peak effect of therapy ($n=102$)[a]
Not satisfied at all (1–3 on VAS), *n* (%)	9 (6.6)	40 (39.2)	0
Somewhat satisfied (4–7 on VAS), *n* (%)	58 (42.6)	48 (47.1)	17 (16.7)
Very satisfied (8–10 on VAS), *n* (%)	69 (50.7)	14 (13.7)	73 (71.6)
Mean (SD)	7.1 (2.23)	4.5 (2.25)	8.7 (1.27)

[a]Data missing for 34 patients.
VAS, visual analog scale.

Table 3. Preferred injection intervals.

Preferred treatment interval	Patients ($n=134$)
<7 weeks, *n* (%)	11 (8.2)
7–8 weeks, *n* (%)	21 (15.7)
9–10 weeks, *n* (%)	30 (22.4)
11–12 weeks, *n* (%)	43 (32.1)
13–14 weeks, *n* (%)	2 (1.5)
15–16 weeks, *n* (%)	7 (5.2)
17–18 weeks, *n* (%)	0
19–20 weeks, *n* (%)	1 (0.8)
>20 weeks, *n* (%)	19 (14.2)
Mean (standard deviation)	12.9 (8.3)
Median	11.0

Current injection cycle

Patients were asked how satisfied they were with their current therapy (Table 2). Most patients were either somewhat satisfied (42.6%) or very satisfied (50.7%), while 6.6% were not satisfied at all. When asked about their satisfaction with therapy just prior to the last injection, 39.2% of patients were not satisfied at all, 47.1% were somewhat satisfied, and only 13.7% were very satisfied. At the peak of therapy effect, 71.6% of patients were very satisfied and 16.7% were somewhat satisfied.

Just over half of the patients stated that they would prefer to have a re-injection on the day of the interview if they were given a choice (31.6% somewhat and 22.1% very much). However, when patients were asked specifically about their preference for injection intervals, the median was higher and ranged from 10 weeks to 12 weeks (Table 3). Interestingly, 62 patients (45.6%) said they would prefer injection cycles of ≤10 weeks.

Current state of health

Patients rated their current state of health on a VAS scale, with 0 being worst possible state of health and 100 being best possible state of health on the day of the interview.

Table 4. Cervical Dystonia Impact Profile-58 transformed scores.

Domain variable	Mean (SD), Range of scores 0–100
Head and neck	47.7 (27.1)
Pain and discomfort	47.7 (29.3)
Sleep	41.5 (31.3)
Upper limb activity	37.9 (26.3)
Walking	25.6 (27.3)
Annoyance	39.3 (28.4)
Mood	31.3 (28.1)
Psychological functioning	31.7 (26.4)

The overall mean (SD) rating for all patients was 62.4 (18.6).

Disease impact (CDIP-58)

Mean ratings on the eight domains of the CDIP-58 are shown in Table 4. For most of the domains, scores were near the middle of the range, indicating that patients continued to have symptoms.

Discussion

Cervical dystonia has a considerable negative impact on quality-of-life, affecting physical, social, and emotional domains[14]. Treatment with botulinum toxin has been found to be safe and effective in this population[8,9,15] and to improve quality-of-life[16,17]. This structured patient survey was conducted to determine the level of patient satisfaction with botulinum toxin treatment. While most patients were satisfied with their current therapy, only 50.7% were very satisfied, 42.6% were somewhat satisfied, and 6.6% not at all satisfied with their current therapy. Satisfaction was lowest just prior to the next injection—when the effects of the previous dose were diminishing—and highest at the time of peak effect. Approximately 45% of patients reported that they would prefer a treatment cycle of $\leq$10 weeks. This is likely due to the re-emergence of symptoms prior to the end of the standard 12-week injection interval, a notion supported by CDIP-58 results showing that patients had symptoms on all domains at the time of the interviews (7–10 weeks after the prior injection session).

Patient satisfaction in this detail is rarely reported in short-term, double-blind, placebo-controlled clinical trials of botulinum toxin treatment for CD. This is likely due to the short-term nature of the trials, as single injections are unlikely to have an immediate impact on patient satisfaction. Even in longer-term studies, patient satisfaction with treatment is not typically measured pro-actively; instead, satisfaction is assumed to correlate with treatment response[6,18]. In this study, patients were questioned specifically about their satisfaction with treatment. While in general patients were very satisfied with their botulinum toxin treatment, satisfaction was somewhat dependent upon the timing of the assessment with regard to the injection cycle; ratings of satisfaction were highest at the time of peak therapeutic peak effect and lower immediately prior to the next injection. Nevertheless, there were no differences between weeks 7–8 and weeks 9–10 on any measure. It will be important for future studies to analyze the time course of changes in patient satisfaction more finely as it relates to peak and trough effects of the injections.

The findings of this study suggest that many patients would prefer a shorter interval between botulinum toxin treatments. Nevertheless, most physicians adhere to the standard of no less than 12 weeks between injections, in large part out of concern over the development of neutralizing antibodies to botulinum toxin. Greene *et al.*[19] were one of the first groups to characterize and make recommendations in an effort to minimize the likelihood of developing botulinum toxin resistance. Eight of the 76 patients evaluated (10.5%) in that study developed resistance to botulinum toxin. Patients with resistance had a shorter period of time between injections (8.8 weeks vs 11.4 weeks), a greater number of booster injections (30% vs 18%), and a higher dose administered over a 3-month period (311 Units vs 258 Units) than those who did not develop resistance. Consequently, Greene *et al.* recommended that botulinum toxin be injected as infrequently as possible ('ideally, no more frequently than every 3 months and certainly no more frequently than every 4 weeks'). However, it is important to note that most patients were treated with the original botulinum toxin formulation from Allergan (Lot 79–11) in that study[19]. Further study is required to better understand the relationship between shorter dosing intervals and development of neutralizing antibodies using newer formulations of botulinum toxin (including incobotulinumtoxinA, which is a botulinum neurotoxin type A free of complexing proteins [also called accessory proteins] and has a lower bacterial protein load than either abobotulinumtoxinA or onabotulinumtoxinA). If evidence supports the use of shorter injection intervals with such newer formulations, this may potentially improve patient satisfaction and become the new standard of care.

It is important to consider some of the limitations of this patient survey and patient surveys in general. First, patient responses are based upon recollection and are not or cannot be checked by a treating clinician or by objective scales. Second, this survey excluded patients with injection intervals less than 10 weeks. Although there are few patients who are re-injected in less than 10 weeks, it may have offered a different perspective regarding injection interval preferences. Third, it remains unclear whether and to what extent satisfaction with treatment is related

to control of neurological symptoms, and what contribution is made by other effects of CD on quality-of-life. Further prospective study is required to fully understand the life-cycle of patients' satisfaction with botulinum toxin treatment.

Conclusions

The results of this patient survey indicate that patient satisfaction with botulinum toxin injections generally follow the onset, peak, and trough of efficacy; patients are most satisfied when the effect of treatment is at its peak, and less satisfied when it is at its nadir. These findings, coupled with the number of patients who indicated that they would prefer a short dosing interval, suggest that more research is needed to determine the optimal treatment parameters with botulinum toxins.

Transparency

Declaration of funding
This study was sponsored by Merz Pharmaceuticals, LLC.

Declaration of financial/other relationships
K.S. is a part-time employee of Merz Pharmaceuticals, LLC, is a consultant for Boehringer Ingelheim, Ipsen, Merz Pharmaceuticals, Nupath, Synosia Therapeutics, and Teva, has been a speaker for Boehringer Ingelheim, Ipsen, Merz Pharmaceuticals, and Teva, and has received grants from Acadia Pharmaceuticals, Boehringer Ingelheim, Impax Pharmaceuticals, Phytopharm, and Synosia Therapeutics. R.R. has been a consultant to, participated in advisory boards for, or received research support from Allergan, Boston Scientific, Lundbeck, Merz Pharmaceuticals, Neuronova, and the National Parkinson Foundation. B.O. is an employee of Merz Pharmaceuticals, LLC. All authors contributed to the writing of the first draft of the manuscript, subsequent review and critique, and all authors approved the final draft prior to submission.

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References

1. Dauer WT, Burke RE, Greene P, et al. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. Brain 1998;121:547-60
2. Jahanshahi M, Marsden CD. A longitudinal follow-up study of depression, disability, and body concept in torticollis. Behav Neurol 1990;3:233-46
3. Claypool DW, Duane DD, Ilstrup DM, et al. Epidemiology and outcome of cervical dystonia (spasmodic torticollis) in Rochester, Minnesota. Mov Disord 1995;10:608-14
4. Jahanshahi M. Psychosocial factors and depression in torticollis. J Psychosom Res 1991;35:493-507
5. Jahanshahi M, Marsden CD. Body concept, disability, and depression in patients with spasmodic torticollis. Behav Neurol 1990;3:117-31
6. Hsiung GY, Das SK, Ranawaya R, et al. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Mov Disord 2002;17:1288-93
7. Swope D, Barbano R. Treatment recommendations and practical applications of botulinum toxin treatment of cervical dystonia. Neurol Clin 2008; 26(1 Suppl):54-65
8. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev 2005:CD003633
9. Benecke R, Jost WH, Kanovsky P, et al. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology 2005; 64:1949-51
10. Ferreira JJ, Costa J, Coelho M, et al. The management of cervical dystonia. Expert Opin Pharmacother 2007;8:129-40
11. Brashear A. Botulinum toxin type A in the treatment of patients with cervical dystonia. Biologics 2009;3:1-7
12. Cano SJ, Hobart JC, Edwards M, et al. CDIP-58 can measure the impact of botulinum toxin treatment in cervical dystonia. Neurology 2006;67:2230-2
13. Cano SJ, Warner TT, Linacre JM, et al. Capturing the true burden of dystonia on patients: the Cervical Dystonia Impact Profile (CDIP-58). Neurology 2004;63:1629-33
14. Gudex CM, Hawthorne MR, Butler AG, et al. Effect of dystonia and botulinum toxin treatment on health-related quality of life. Mov Disord 1998;13:941-6
15. Brashear A. The botulinum toxins in the treatment of cervical dystonia. Semin Neurol 2001;21:85-90
16. Skogseid IM, Roislien J, Claussen B, et al. Long-term botulinum toxin treatment increases employment rate in patients with cervical dystonia. Mov Disord 2005;20:1604-9
17. Molho ES, Agarwal N, Regan K, et al. Effect of cervical dystonia on employment: a retrospective analysis of the ability of treatment to restore premorbid employment status. Mov Disord 2009;24:1384-7
18. Skogseid IM, Kerty E. The course of cervical dystonia and patient satisfaction with long-term botulinum toxin A treatment. Eur J Neurol 2005;12:163-70
19. Greene P, Fahn S, Diamond B. Development of resistance to botulinum toxin type A in patients with torticollis. Mov Disord 1994;9:213-7

