Botulinum Toxin Type-A Improves Occupational Impairment Associated With Primary Axillary Hyperhidrosis and Results in High Levels of Satisfaction With Treatment

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INTRODUCTION

Primary axillary hyperhidrosis is associated with substantial occupational, physical, and emotional impairment, as well as considerable difficulties in personal relationships and potential social stigmatization.[1-5] The negative effects of primary axillary hyperhidrosis on health-related quality of life (HRQOL) as measured by the Dermatology Life Quality Index (DLQI) are similar to or greater than those reported for moderate to severe acne and psoriasis.[1,2,6-8]

Current treatment options include topical prescription antiperspirants (ie, aluminum chloride hexahydrate 10%–35%) and surgical approaches.[9] However, the effectiveness of each of these options varies and each is associated with adverse events and/or risks that may limit its use. The range of effectiveness of high-strength antiperspirants is difficult to interpret because published data use different measurements and often do not quantify baseline levels of sweating. At best, 68% of patients report an initial response of greater than 75% improvement in sweating.[10] Treatment with topical aluminum chloride, however, can be short-lived. In one study only 32% of patients who had initially responded to therapy reported sustained relief at 6 months and 68% of the original treated population opted for surgery at this time point.[11] Side effects of topical aluminum chloride treatment can include skin irritation and itching, particularly in the axillary region,[12] and treatment is often discontinued due to this irritation. In addition, long-term use can lead to atrophy of the eccrine gland's secretory cells in the axillary region.[13] In fact, this perhaps may be the mechanism by which aluminum chloride therapy functions.

Surgical approaches may involve excision of axillary tissue by several methods (eg, subcutaneous curettage, axillary liposuction) or endoscopic transthoracic sympathectomy (ETS). The limited data that report the effectiveness of sweat gland excision suggest that sweating is reduced by 25% to 38% when measured gravi-metrically[14] and to 40% to 46% of baseline when judged by patients.[15] Side effects with this treatment option can include wound infection, skin edge necrosis, slow healing, abscesses, and reduced shoulder mobility due to scarring.[9] ETS is generally not recommended to treat primary axillary hyperhidrosis[16,17] because of high rates of recurrence (up to 65% of patients)[16] and high rates of compensatory sweating (68% to 88% of patients).[18,19] In addition, potentially serious side effects such as pneumothorax, hemorrhage, Horner syndrome, nerve damage, cardiac effects, and even death limit its use.[16,18,20]

Botulinum toxin type A (BOTOX®, Allergan, Inc., Irvine, CA; BTX-A) is a breakthrough treatment for patients suffering from primary axillary hyperhidrosis in that it satisfies a previously unmet need for a highly effective and safe treatment for hyperhidrosis inadequately managed with topical agents but prior to irreversible surgical procedures. Intradermal injection of BTX-A results in a temporary chemodenervation of local sweat glands by blocking the release of the neurotransmitter acetylcholine. In clinical studies BTX-A rapidly and effectively reduces sweat production in patients with primary axillary hyperhidrosis.[3,21,22] Here we report an analysis of data from 3 studies conducted in different countries assessing the effects of BTX-A treatment on occupational and non-occupational impairment associated with primary axillary hyperhidrosis and patients' satisfaction with the treatment.

METHODS

Study design

This analysis is of data from 2 multi-center, double-blind, randomized, placebo-controlled, parallel-group studies (North American and European studies) and a 12-week multi-center open-label study (Canadian study). BTX-A was administered at 50 U or 75 U per axilla in the North American study and at 50 U per axilla in the European and Canadian studies (Table 1). The method of drug administration was similar among the 3 clinical studies. Briefly, Minor's iodine starch test was used to identify the hyperhidrotic areas. BTX-A, reconstituted with preservative-free saline, was then injected intradermally to 12–15 sites per axilla evenly spaced 1.5 cm apart. To confirm correct placement in the intradermal plane, physicians were instructed to obtain a visible wheal upon injection. Patients were monitored for potential side effects after the procedure.

Table 1. Study Populations and Doses in 3 Clinical Trials of BTX-A

	No. of patients		
Study	BTX-A 50 U/axilla	BTX-A 75 U/axilla	Placebo
North American (n = 322)	104	110	108
European (n = 320)	242	—	78
Canadian (n = 146)	146	—	—
Total	**492**	**110**	**186**

BTX-A, botulinum toxin type A; U, units

Key inclusion criteria

- Men or women, 18 years old or older, with persistent bilateral primary axillary hyperhidrosis
- Sweat production that interfered with activities of daily living, as assessed by subject history (European study) or as indicated by a score of 3 or 4 on the Hyperhidrosis Disease Severity Scale (range, 1–4; Table 2) (North American and Canadian studies)
- Gravimetric measurement of at least 50 mg of spontaneous sweat in each axilla over 5 minutes (European and North American studies)

Table 2. Hyperhidrosis Disease Severity Scale

How would you rate the severity of your hyperhidrosis?	Score
My underarm sweating is never noticeable and never interferes with my daily activities	1
My underarm sweating is tolerable but sometimes interferes with my daily activities	2
My underarm sweating is barely tolerable and frequently interferes with my daily activities	3
My underarm sweating is intolerable and always interferes with my daily activities	4

Key exclusion criteria

- Concurrent use of agents that might interfere with neuromuscular function
- Concurrent use of any other treatment for hyperhidrosis other than over-the-counter antiperspirants or deodorants
- Use of over-the-counter antiperspirants or deodorants within 24 hours of treatment (North American and Canadian studies only)
- Previous treatment with botulinum toxin of any serotype for hyperhidrosis (North American study), of any serotype for any reason (Canadian study), or within 4 months before study entry (European study)

Measures

Aspects of daily functioning, HRQOL, and experience with previous hyperhidrosis treatments were assessed by using the validated 41-item baseline module of the Hyperhidrosis Impact Questionnaire (HHIQ) and the 10-item follow-up module[23,24] (completed 4 weeks after treatment). In all 3 studies, patients were asked at baseline and at specified follow-up times to rate their satisfaction with or the limitations in their ability to perform their current work and non-work activities due to hyperhidrosis. Patients' satisfaction with the treatment was measured in the North American and European studies by using the following single item: Compared to treatments you have used before, how satisfied were you overall with this study treatment? Their satisfaction was measured in the Canadian study by comparing the answers at baseline and at week 4 to the single item: How satisfied are you with your current treatment for hyperhidrosis?

Statistical analyses

Data were expressed as the proportion of patients in each response category. The proportion of patients in each response category was calculated by using as the denominator the number of patients who answered each item. Data were dichotomized, and between-group comparisons were made by using the Fisher exact test (North American study), the chi-square test (European study), and the Mantel-Haenszel general association chi-square test (Canadian study). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 788 patients with primary axillary hyperhidrosis were enrolled in the 3 studies, 602 of whom were treated with intradermal injections of BTX-A 50 or 75 U per axilla and 186 with placebo. Demographics are presented in Table 3. Baseline demographics and disease characteristics were similar between the groups.

Table 3. Patient Demographics

	Study		
	North American	European	Canadian
White ethnicity	81%	98%	93%
Female sex	46%	54%	67%
Age, y, mean (range)	33 (18–69)	32 (17–74)	35 (18–73)

Occupational impairment

Patients treated with BTX-A reported less occupational dissatisfaction and work limitations due to hyperhidrosis at week 4 than at baseline (Figures 1 and 2).

Satisfaction with ability to perform work activities

- North American study: 27% (29/108), 19% (20/104), and 25% (26/104) of patients in the 50 U, 75 U, and placebo groups, respectively, were somewhat or very satisfied with their ability to perform their work activities in spite of hyperhidrosis at baseline, compared to 75% (76/101), 74% (71/96), and 37% (34/91) of patients at week 4
- European study: 19% (40/216) and 15% (11/71) of patients in the 50 U and placebo groups, respectively, were somewhat or very satisfied with their ability to perform their work activities in spite of hyperhidrosis at baseline, compared to 88% (57/65) and 22% (5/23) at week 4
- Canadian study: 8% (10/126) of patients were somewhat or very satisfied with their ability to perform their work activities at baseline, increasing to 89% (117/132) at week 4

Work limitations

- North American study: 36% (37/103), 39% (41/106), and 41% (42/103) of patients in the 50 U, 75 U, and placebo groups, respectively, were moderately to extremely limited at work at baseline, compared to 6% (6/95), 7% (7/99), and 28% (26/93) at week 4
- European study: 59% (134/229) and 54% (41/76) in the 50 U and placebo groups, respectively, were moderately to extremely limited at work at baseline, compared to 5% (10/221) and 38% (27/72) at week 4
- Canadian study: 79% (114/144) of patients were moderately to extremely limited at work at baseline, decreasing to 11% (15/141) at week 4

The improvements in work satisfaction and work limitations with BTX-A (50 U or 75 U) were statistically significant compared with placebo in the North American and European studies ($P \leq 0.001$) and compared with baseline in the Canadian study ($P < 0.001$).

Non-occupational impairment

Patients reported greater satisfaction in non-work activities at week 4 after treatment with BTX-A than at baseline (Figure 3).

- North American study: 12% (12/104), 11% (12/110), and 14% (15/104) of patients in the 50 U, 75 U, and placebo groups, respectively, were somewhat or very satisfied with their ability to perform their non-work activities in spite of hyperhidrosis at baseline, compared to 75% (72/96), 74% (75/101), and 30% (28/92) at week 4
- European study: 17% (36/217) and 8% (6/71) of patients in the 50 U and placebo groups, respectively, reported being somewhat or very satisfied with their ability to perform their non-work activities at baseline, increasing to 89% (76/85) and 28% (8/29) at week 4
- Canadian study: 6% (8/129) of patients were somewhat or very satisfied with their ability to perform their non-work activities at baseline, increasing to 89% (122/136) at week 4

The improvements in non-work activities with BTX-A (50 U or 75 U) were statistically significant compared with placebo in the North American and European studies ($P \leq 0.001$) and statistically significantly improved relative to baseline in the Canadian study ($P < 0.001$).

Treatment satisfaction

Since many patients with axillary hyperhidrosis are initially treated with topical aluminum chloride, we investigated patient experience with this treatment prior to enrolling into each study. Of the patients who had tried aluminum chloride therapy (North American, 15%; European, 33%; Canadian, 39%), 64% to 84% found it to be a poor or ineffective treatment (Figure 4).

Consistent with this finding, patients receiving BTX-A in each study reported greater satisfaction with BTX-A than with previous treatments they had received (European and North American studies). In the Canadian study, in which treatment satisfaction was assessed differently (compared with satisfaction with treatment at baseline), the majority of patients were more satisfied with BTX-A treatment than their treatment at baseline (Figure 5).

- North American study: 85% and 84% of patients treated with BTX-A 50 U and 75 U, respectively, vs 28% of those treated with placebo were much more satisfied with the study treatment than with their previous treatment
- European study: 95% of patients treated with BTX-A vs 32% of those treated with placebo were somewhat or much more satisfied with the study treatment than with their previous treatment
- Canadian study: 93% of patients were somewhat to very satisfied with the study treatment vs 15% at baseline

The observed high levels of satisfaction with BTX-A treatment for primary axillary hyperhidrosis were statistically significant compared with placebo in the North American and European studies ($P < 0.001$) and statistically significantly improved relative to baseline in the Canadian study ($P < 0.001$).

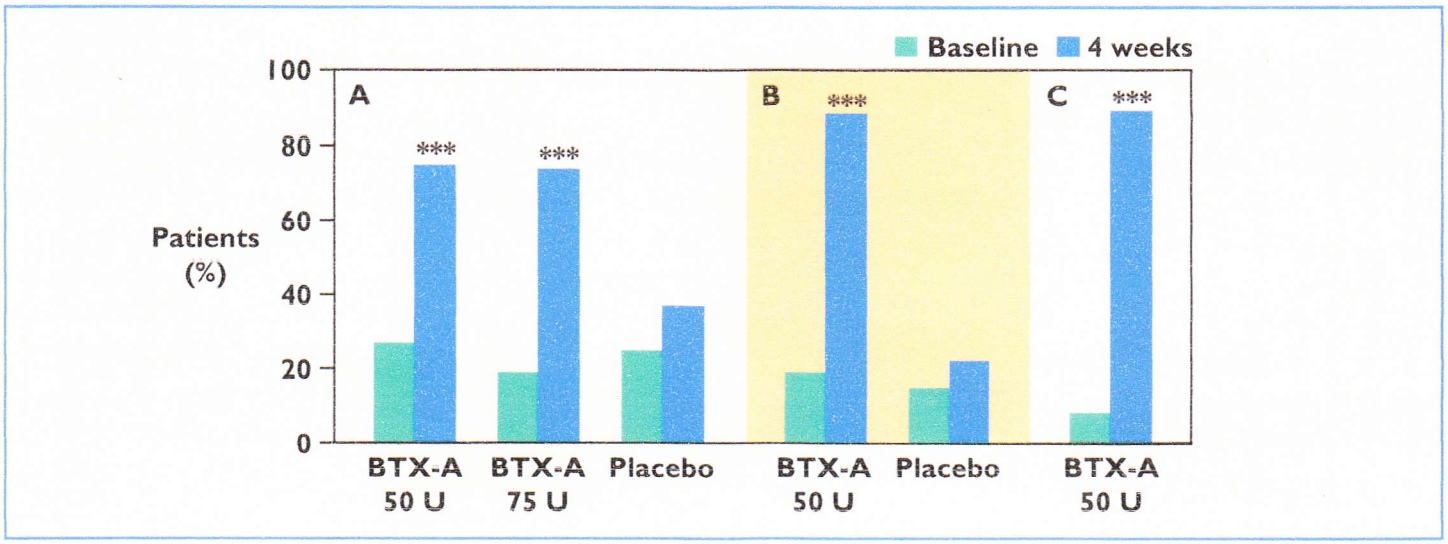

*Figure 1. Occupational impairment at baseline and after 4 weeks of treatment. Patients who were somewhat or very satisfied with their ability to perform work activities because of hyperhidrosis at baseline and at 4 weeks after treatment in the (A) North American study, (B) European study, and (C) Canadian study. ***P ≤ 0.001 vs placebo (A, B) or baseline (C).*

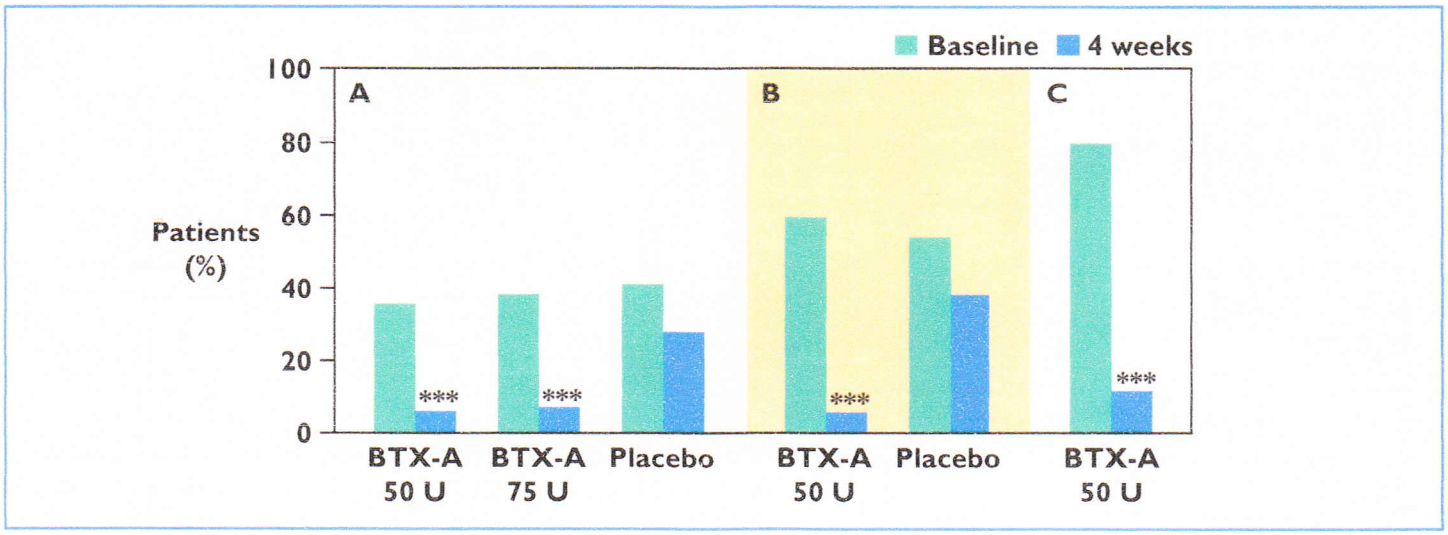

*Figure 2. Occupational impairment at baseline and after 4 weeks of treatment. Patients reporting moderate to extreme limitations at work at baseline and at 4 weeks after treatment in the (A) North American study, (B) European study, and (C) Canadian study. ***P ≤ 0.001 vs placebo (A, B) or baseline (C).*

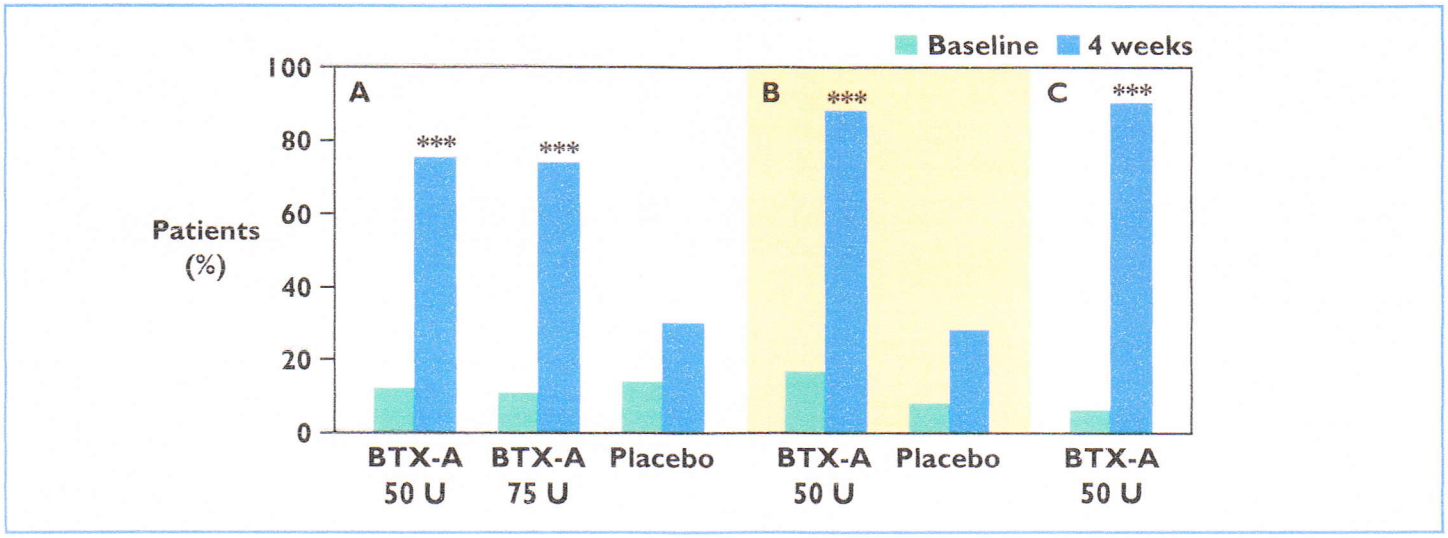

*Figure 3. Impairment in non-work activities at baseline and after 4 weeks of treatment. Patients who were somewhat or very satisfied with their ability to perform non-work activities because of hyperhidrosis at baseline and at 4 weeks after treatment in the (A) North American study, (B) European study and (C) Canadian study. ***P ≤ 0.001 vs placebo (A, B) or baseline (C).*

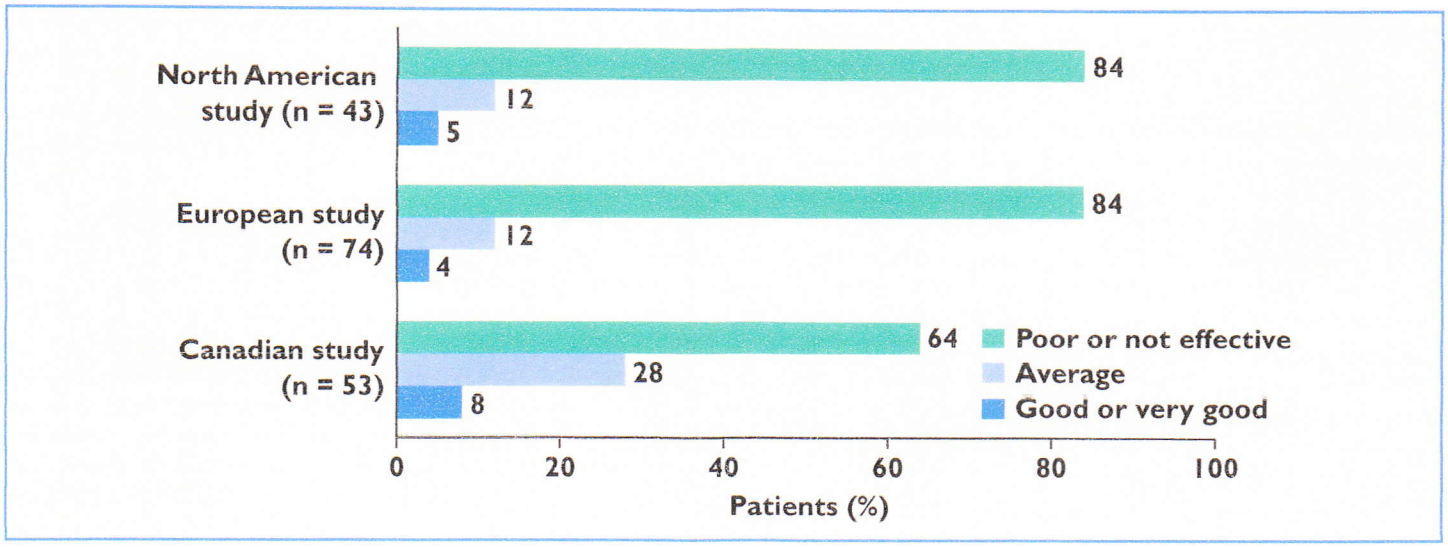

Figure 4. Patient ratings of their satisfaction with topical aluminum chloride therapy. Some proportions do not add to 100% because of rounding.

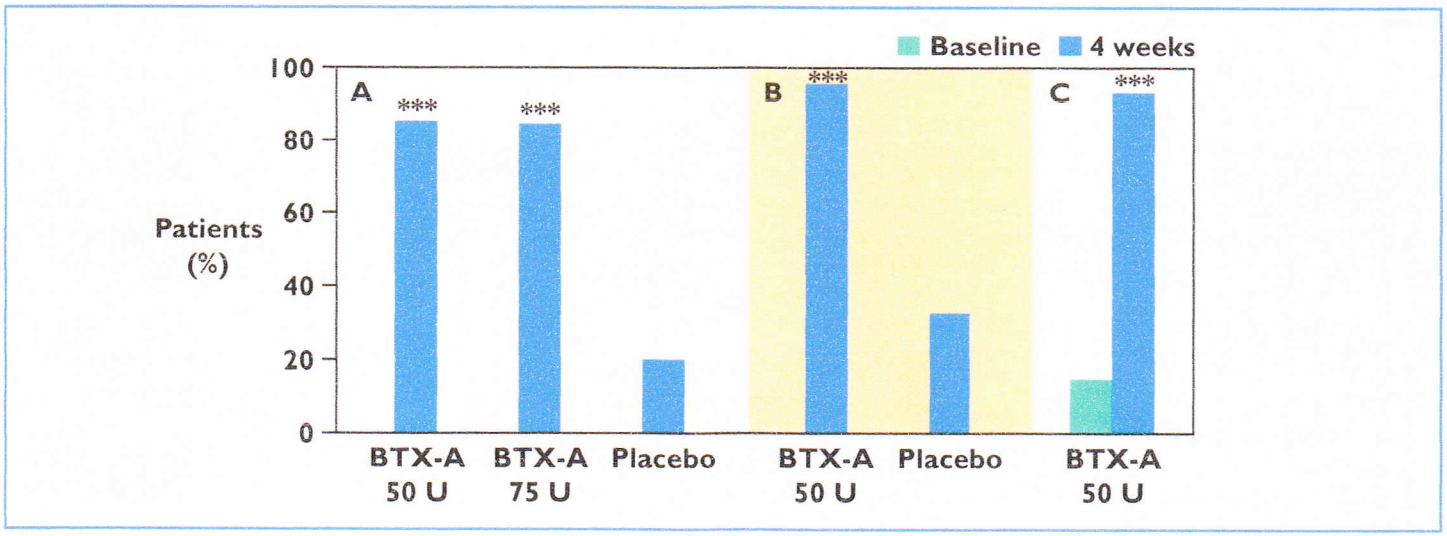

*Figure 5. Treatment satisfaction. Patients who were much more satisfied with their current treatment than with their previous treatments in the (A) North American study and (B) European study. Patients who were somewhat to very satisfied with their current treatment 4 weeks post-injection vs treatments they were receiving just prior to the study in the (C) Canadian study. ***P < 0.001 vs placebo (A, B) or baseline (C).*

CONCLUSIONS

As assessed in 3 large prospective studies, patients with primary axillary hyperhidrosis report substantial limitations and dissatisfaction with their ability to perform both work and non-work activities. Substantial and meaningful benefit can be achieved following BTX-A treatment in terms of minimizing such occupational impairment and increasing work productivity. Furthermore, BTX-A treatment for patients with primary axillary hyperhidrosis was associated with high levels of treatment satisfaction compared to previous treatment options. In view of the ignificant limitations of the currently available therapies, BTX-A appears to be a major advance in the treatment of primary axillary hyperhidrosis. Finally, it should be noted that the results presented are with the BOTOX® (Allergan, Inc., Irvine, CA) formulation of botulinum toxin type A and cannot be generalized to other botulinum toxin formulations or serotypes.

REFERENCES

1. Swartling C, Naver H, Lindberg M. Botulinum A toxin improves life quality in severe primary focal hyperhidrosis. Eur J Neurol. 2001;8:247-252.
2. Campanati A, Penna L, Gizzio T, et al. Quality-of-life assessment in patients with hyperhidrosis before and after treatment with botulinum toxin: results of an open-label study. Clin Ther. 2003;25:298-308.
3. Naumann M, Lowe NJ, Kumar CR, Hamm H. Botulinum toxin type A is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. Arch Dermatol. 2003;139:731-736.
4. Kowalski JW, Ravelo A, Glaser DA, Lowe, NJ. Quality-of-life effect of botulinum toxin type-A on patients with primary axillary hyperhidrosis: results from a North American clinical study population. Poster presented at: 62nd Annual Meeting of the American Academy of Dermatology; February 6-10, 2004; Washington, DC. Poster P196.
5. Hornberger J, Grimes K, Naumann M, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol. In press.
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210-216.
7. Tan SR, Solish N. Long-term efficacy and quality of life in the treatment of focal hyperhidrosis with botulinum toxin A. Dermatol Surg. 2002;28:495-499.
8. Naumann M, Hamm H, Spalding J, Kowalski J, Lee J. Comparing the quality of life effect of primary focal hyperhidrosis to other dermatological conditions as assessed by the Dermatology Life Quality Index (DLQI). Value in Health. 2003;6:242.Abstract.
9. Aktinis JL, Butler PE. Hyperhidrosis: a review of current management. Plast Reconstr Surg. 2002;110:222-228.
10. Benohanian A, Dansereau A, Bolduc C, Bloom E. Localized hyperhidrosis treated with aluminum chloride in a salicylic acid gel base. Int J Dermatol. 1998;37:701-708.
11. Rayner CR-W, Ritchie ID, Stark GP. Axillary hyperhidrosis: 20% aluminum chloride hexahydrate, and surgery. BMJ. 1980;280:1168.
12. Leung AK, Chan PY, Choi MC. Hyperhidrosis. Int J Dermatol. 1999; 38:561-567.
13. Hölzle E, Braun-Falco O. Structural changes in axillary eccrine glands following long-term treatment with aluminum chloride hexahydrate solution. Br J Dermatol. 1984;110:399-403.
14. Proebstle TM, Schneiders V, Knop J. Gravimetrically controlled efficacy of subcorial curettage: a prospective study for the treatment of axillary hyperhidrosis. Dermatol Surg. 2002;28:1022-1026.
15. Rompel R, Scholz S. Subcutaneous curettage vs injection of botulinum toxin A for treatment of axillary hyperhidrosis. J Eur Acad Dermatol Venereol. 2001;15:207-211.
16. Gossot D, Galetta D, Pascal A, et al. Long-term results of endoscopic thoracic sympathectomy for upper limb hyperhidrosis. Ann Thorac Surg. 2003;75:1075-1079.
17. Lello LEV, de Oliveira R, Szulc R, et al. Role of video-assisted thoracoscopic sympathectomy in the treatment of primary hyperhidrosis. Sao Paulo Med J. 2003;121:191-197.
18. Zacherl J, Huber ER, Imhof M, Plas EG, Herbst F, Fugger R. Long-term results of 630 thoracoscopic sympathectomies for primary hyperhidrosis: the Vienna experience. Eur J Surg Suppl. 1998;580:43-46.
19. Lin TS,Wang NP, Huang LC. Pitfalls and complication avoidance associated with transthoracic endoscopic sympathectomy for primary hyperhidrosis (analysis of 2200 cases). Int J Surg Investig. 2001;2:377-385.
20. Kawamata YT, Kawamata T, Omote K, et al. Endoscopic thoracic sympathectomy suppresses baroreflex control of heart rate in patients with essential hyperhidrosis. Anesth Analg. 2004;98:37-39.
21. Glaser DA, Lowe NJ, Eadie N, et al. 52-week prospective randomized, double-blind placebo-controlled safety and efficacy study of 2 dosages of botulinum toxin type-A treatment for primary axillary hyperhidrosis. Poster presented at: 56th Annual Meeting of the American Academy of Neurology; April 24-May 1, 2004; San Francisco, Calif. Poster P05.158.
22. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ. 2001;323:596-599.
23. Naumann M, Hamm H, Lowe NJ, on behalf of the BOTOX® Hyperhidrosis Clinical Study Group. Effect of botulinum toxin type A on quality of life measures in patients with excessive axillary sweating: a randomized controlled trial. Br J Dermatol. 2002;147.
24. Terle C, Hamm H, Naumann M, Roberts G, Kowalski J. Development, validity, and reliability of the Hyperhidrosis Impact Questionnaire (HHIQ). Qual Life Res. 2002;11:702. Abstract.

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