

# A Double-Blind, Randomized, Comparative Study of Two Type A Botulinum Toxins in the Treatment of Primary Axillary Hyperhidrosis

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**BACKGROUND** Botulinum toxin (BTX) is an effective treatment for primary axillary hyperhidrosis. In this study we used two toxins not bioequivalent: BOTOX (Allergan, Inc.) and Dysport (Beaufour Ipsen Biotech).

**OBJECTIVE** The objective was to compare the efficacy, safety, and tolerability of BOTOX and Dysport in the treatment of primary axillary hyperhidrosis using a conversion factor of 1:3, respectively.

**METHODS** In a double-blind, randomized prospective study, 10 patients with primary axillary hyperhidrosis and sweat production exceeding 50 mg/minute received 50 U of BOTOX in one axilla and 150 U of Dysport in the other. We performed Minor's test and gravimetry at 0 days, at 15 days, and monthly for 1 year.

**RESULTS** No significant difference was observed in the sweating quantity at baseline. After 1 month all patients had achieved success for both axillae. The sweat rate was reduced by a mean of 97.7% for BOTOX and 99.4% for Dysport, without statistical difference. The duration of benefits was similar between both toxins, with a mean of 260 days for BOTOX and 290 days for Dysport, without statistical difference. The longest symptom-free interval was 12 months (5 patients, 55.6%).

**CONCLUSIONS** BOTOX and Dysport presented similar levels of safety and efficacy in the treatment of primary axillary hyperhidrosis when a conversion factor of 1:3 was used.

*Allergan Pharmaceuticals Ltd. and Laboratrios Biosintética Ltd./Beaufour Ipsen Biotech furnished their products BOTOX and Dysport but had no interference in the study.*

Primary axillary hyperhidrosis is a condition characterized by the presence of excessive sweat in axillary region induced by sympathetic hyperactivity.<sup>1,2</sup> The condition affects both the professional and the personal life of the individual, leading to serious social and psychological disablement.<sup>3</sup>

The use of classical treatments, such as aluminum salts and iontophoresis, often produce unsatisfactory results. Tranquilizers (oral sedatives) and anticholinergic drugs may be used as adjunctive treatments, but they may cause undesirable side effects. Surgery, such as endoscopic sympathectomy, is relatively

effective, although it carries the risk of pneumothorax, Horner's syndrome, and other complications, particularly compensatory sweating.<sup>3-6</sup>

The eccrine sweat glands are innervated by fibers from the sympathetic nervous system, in which acetylcholine is the main neurotransmitter. Botulinum toxin (BTX) acts mainly on the cholinergic synapses, inhibiting the release of acetylcholine.<sup>3,7,8</sup> Type A botulinum toxin (BTX-A) has been shown to be safe and effective in the treatment of localized hyperhidrosis, as showed in recent studies with intradermic injections of BTX-A into the axillary region.<sup>1,3,4,8-12</sup>

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There are currently three commercially available BTX-A in Brazil. We chose to use two nonbio-equivalent toxins of distinct origin: BOTOX (Allergan, Inc., Irvine, CA; 100 U per vial) and Dysport (Beaufour Ipsen, Paris, France; 500 U per vial). Previous research conducted on neurologic patients proposed a conversion factor between BOTOX and Dysport varying from 3 to 6.<sup>13,14</sup> A controlled double-blind study compared the performance of the two toxins BOTOX/Dysport, using a conversion factor of 1:4, in the treatment of palmar hyperhidrosis.<sup>13</sup> Odergren and colleagues<sup>15</sup> in a double-blind, randomized study of 73 patients with cervical dystonia, provided substantial evidence that 1 U of BOTOX is clinically equivalent to 3 U of Dysport.<sup>15</sup> This 1:3 equivalence ratio is supported by clinical studies in blepharospasm and hemifacial spasm<sup>16</sup> and also in spasmodic dysphonia.<sup>17</sup>

The aim of this double-blind, randomized, prospective study is to compare the efficacy, safety, and tolerability of BOTOX and Dysport in the treatment of axillary hyperhidrosis, using a conversion factor of 1:3. Few studies have attempted to establish an appropriate conversion factor between the two toxins.<sup>13,15,18</sup>

## Materials and Methods

### Patients

Ten patients (4 men and 6 women) aged between 19 and 56 years (mean age, 33.4 years) and presenting sweating greater or equal to 50 mg/minute by gravimetric measurements were included in the study. All the patients presented some degree of social and psychological restriction due to the increased sweating. Exclusion criteria were systemic diseases that cause hyperhidrosis, pregnant or lactating women, neuromuscular disease, use of aminoglycoside antibiotics in the previous 3 months, and those who received BTX applications in the past year. The study received the approval of the ethics committee, the study protocol conformed to the guidelines of the 1975 Declaration of Helsinki, and the patients signed consent forms.

### Study Format

The study followed a double-blind, randomized, comparative format. Each patient received 50 U of BOTOX in one axilla and 150 U of Dysport in the other, in a randomized manner according to the date of birth. The objective quantification of the quantity of sweat and Minor's test were performed immediately prior to application, 15 days after application, and at monthly intervals for the period of 12 months.

### Botulinum Toxin Injections

The vial of BOTOX with 100 U of BTX was diluted in 2 mL of 0.9% saline solution, obtaining a concentration of 50 U/mL. The vial of Dysport with 500 U of toxin was diluted in 3.32 mL of 0.9% saline solution, so that 50 U of BOTOX/mL would be equivalent to 150.6 U of Dysport/mL, with a conversion factor of 1:3.

After the Minor's test, borders of the hyperhidrotic area were marked and 20 equidistant points were distributed (1.5–2.0 cm) in each axilla. We used 0.5-mL syringes (BD Ultrafine II, Becton Dickinson, Franklin Lakes, NJ), with short 30-gauge needles, for the intradermic application, at an angle of 30° to the skin surface and a mean depth of 4 mm. Each axilla received 50 U of BOTOX or 150 U of Dysport during the same session, utilizing 2.5 U of BOTOX or 7.5 U of Dysport per point, corresponding to 0.1 mL of both dilutions.

### Evaluation of Sweating

Minor's test (iodine-starch test) was carried out to determine the area of sweating. Fifteen minutes prior to test, after drying of the axillae with gauze compresses, a 3% iodine tincture was painted over the axillae, followed by the application of corn starch powder (Maisena). The presence of sweating was indicated by the dark blue color.

Minor's tests photographic documentation and quantitative gravimetry are effected before applica-

tion, 15 days after, and every month over the period of 12 months. All the tests were performed in a room with constant temperature at 24°C. The objective quantification of the sweat was achieved with the gravimetry. A filter paper (Melitta traditional 102 Celupa Ltda, Avaré-São Paulo, Brazil) was previously weighed on a high-precision laboratory scale (Kern 822, Gottl, Kern & Sohn, Albstadt-Ebingen, Germany). The paper was then inserted into the axillary cavity for exactly 1 minute and weighed again, so indicating the rate of sweat secretion per minute.

### **Evaluation of Tolerability**

To evaluate the possible side effects, patients answered a complete questionnaire at each consultation. At Day 0, 15 patients were questioned regarding the presence of (1) pain in the area of the injections, (2) bruising, (3) reduction in muscular force in the shoulder girdle and upper members, and (4) compensatory sweating in other sites. At subsequent evaluations, questionnaire only inquired regarding reduction in muscular force in the shoulder girdle and upper members and compensatory sweating in other sites.

### **Statistical Analysis**

All the statistical analyses were performed according to the intention-to-treat principle. Continuous measures were compared using nonparametric paired (Wilcoxon and Friedman) and unpaired (Mann-Whitney) tests. Statistical analyses were two sided, and with an alpha error of 0.05. Statistica software (Version 5.1, 1997, Statsoft, Tulsa, OK) was used for all analyses. The percentage change in sweat production was assessed by analysis of variance with repeated measure in one factor.

## **Results**

### **Comparison of the Baseline Values**

Of the 10 patients included in the study, only 9 completed the 12 months of follow-up, with 1 patient giving up for unknown reasons after the second

consultation. Therefore, the calculation base of all the statistical tests was a casuistry of 9 patients.

No significant difference was observed in the sweating quantity at baseline between the axillae that received BOTOX and Dysport. The number of points and the volume of the solution injected were identical in the two groups.

### **Objective Evaluation of Sweating**

The sweat production, as measured by gravimetric assessment, was summarized for both the right and the left axillae. The percentage change at Month 1 compared with sweating quantity at baseline was determined for all patients.

Patients were classified as a treatment success if they had a reduction in sweat production as measured by gravimetric assessment of 50% or more at Month 1. After 1 month all patients had achieved success for both sides. The sweat rate was significantly reduced by a mean of 97.7% for BOTOX (from  $321.1 \pm 188.6$  to  $10.4 \pm 17.6$  mg/min) and 99.4% for Dysport (from  $311.7 \pm 216.7$  to  $3.9 \pm 11.7$  mg/min), without statistical difference (Figure 1).

Three months after the beginning of treatment, two patients showed a sweat production higher than 50%. In one patient relapses were observed in both sides (BOTOX and Dysport), and in the other one only BOTOX side was relapsed (see Figure 1). The duration of BTX injection benefits observed was similar between BOTOX and Dysport, with a mean of 260 days for BOTOX (range, 90–360 days) and 290 days for Dysport (range, 90–360 days), without significant statistical difference (Figure 2). The longest symptom-free interval recorded up to the present was 12 months (5 patients, 55.6%) and 7 months (1 patient). Three patients reported recurrence of sweating of both axillae between 3 and 5 months (see Figure 1). At Month 4 we observed a treatment success of 77.8% for the BOTOX side and 88.9% for the Dysport side, without statistical difference between both axillae.

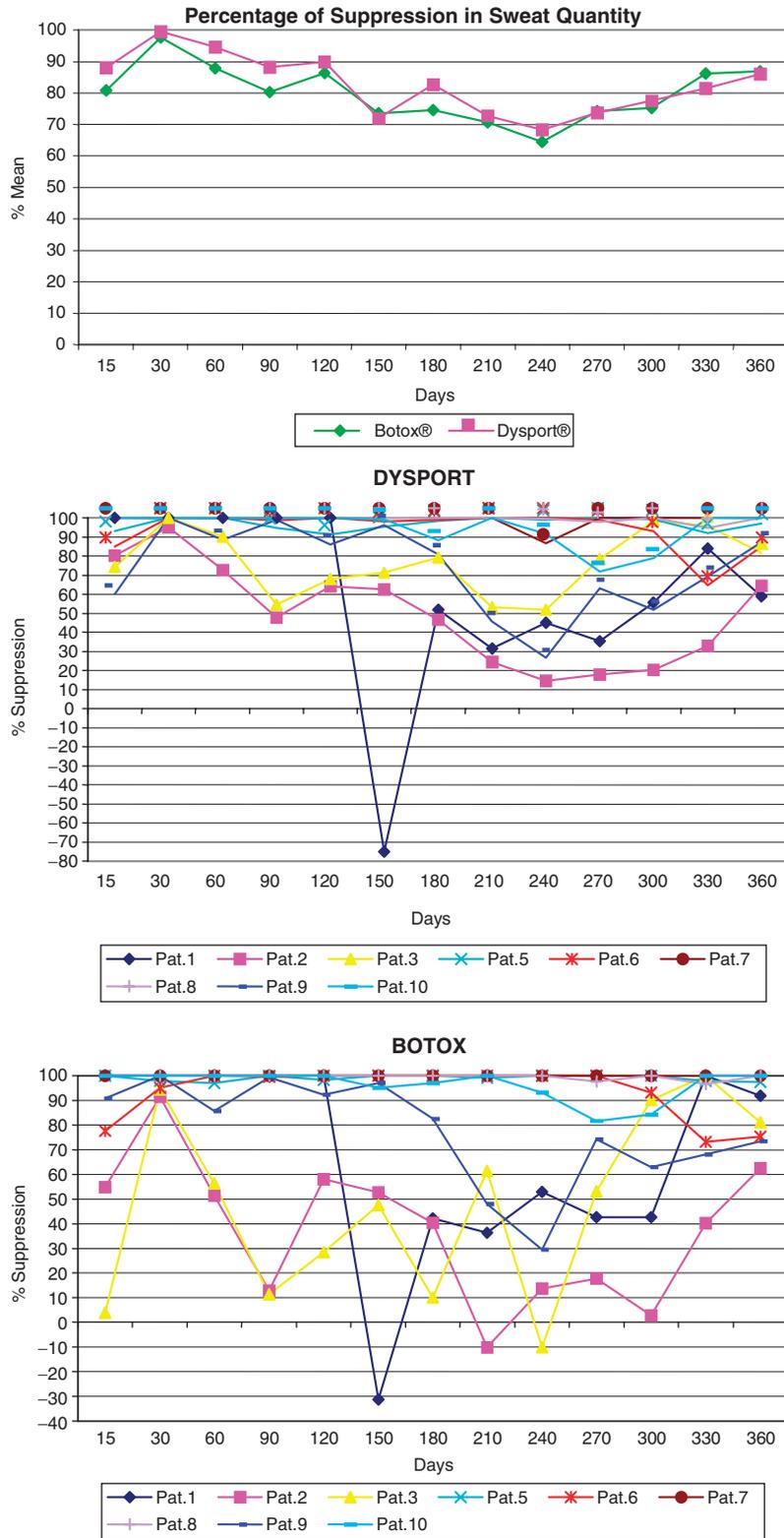
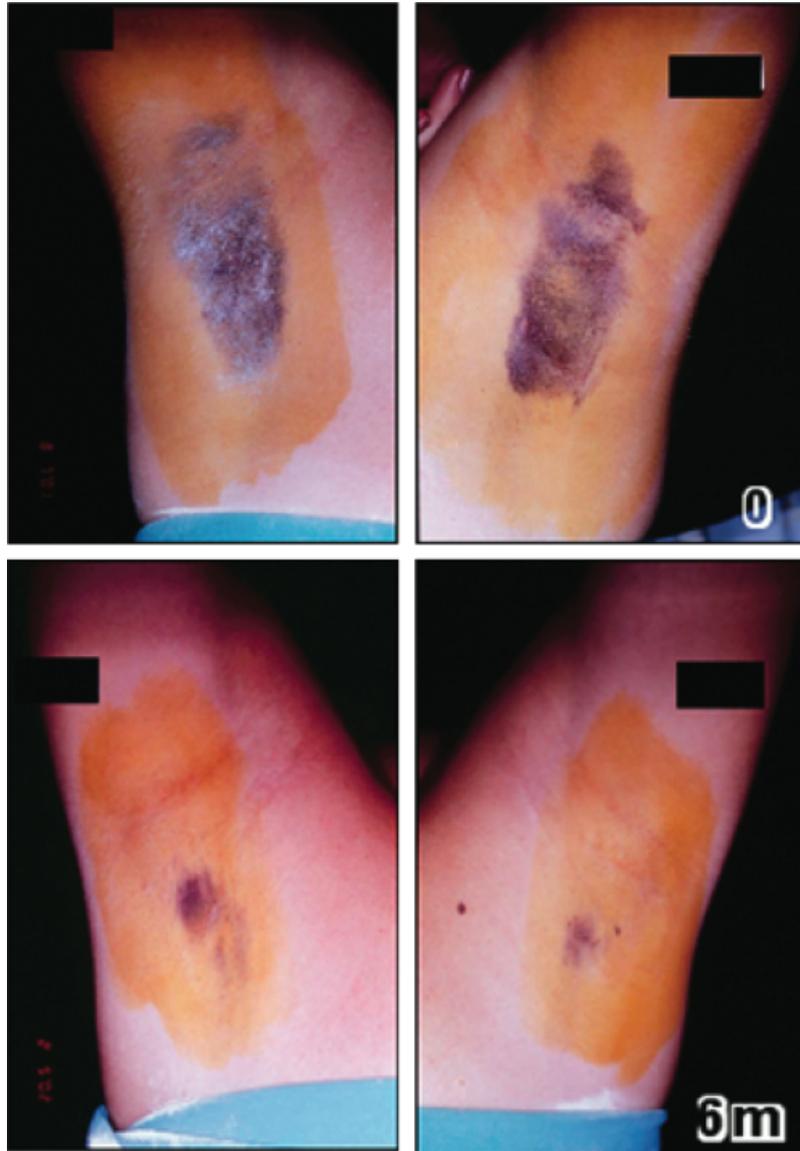


Figure 1. The percentage change in sweat production.



**Figure 2.** Minor's iodine starch test before (D0) and 6 months after comparative injections of BOTOX versus Dysport type A botulinum toxin.

It is interesting to remark that one patient remained with gravimetry at 0 during all 12 months. Another one always maintained some degree of sweating, despite the reduction in quantity.

### **Side Effects**

Two patients reported the occurrence of compensatory sweating, although in minimal quantities, not enough to interfere with the quality of life. No patient developed reduction in muscular force or neu-

rologic deficit. No systemic side effects were observed to any possible absorption of BTX-A originating from the application site.

### **Discussion**

The use of BTX-A in the treatment of primary axillary hyperhidrosis is relatively recent. Previous studies have shown that small doses of BOTOX such as 50 U are capable of inducing anhidrosis in healthy patients, with effect duration of between 6 and 8

months.<sup>4,11</sup> Another two placebo-controlled studies demonstrated the efficacy and safety of BTX-A in the control of primary axillary hyperhidrosis, using 200 and 250 U of Dysport per axilla.<sup>1,9</sup>

Previous studies conducted in neurologic patients proposed conversion factors between BOTOX and Dysport ranging from 3 to 6, and this question still remains debated. Another article discusses the treatment of spasticity with BTX-A using a conversion factor of 5 between BOTOX and Dysport.<sup>14</sup> For facial rejuvenation, Lowe<sup>19</sup> suggests that 1 U of BOTOX is approximately equivalent in potency to 4 U of Dysport. A single-blind, randomized, parallel comparison of two formulations of BTX-A for the treatment of blepharospasm or hemifacial spasm concluded that the 4:1 ratio is a fair estimate of the conversion factor of biologic potency between BOTOX and Dysport.<sup>20</sup> To date only two randomized, controlled studies have tried to answer the question giving conversion factor of 1:3<sup>15</sup> and < 1:3.<sup>18</sup> In a recent study, Simonetta Moreau and colleagues<sup>13</sup> compared the efficacy of BOTOX and Dysport in hyperhidrosis palmar using a conversion factor of 1:4, in which no statistically significant differences were found. The authors suggest that to achieve similar efficacy without differences in incidence of side effects, a lower dose of Dysport should have been used. Therefore, a conversion factor of 1:3.5 or 1:3 may be more appropriate than 1:4 to obtain more precisely the same amount of decrease of sweating with the same duration of beneficial effect for BOTOX in comparison with Dysport.<sup>13</sup> In this study, we compared the efficacy of BOTOX and Dysport in the treatment of primary axillary hyperhidrosis using a conversion factor of 1:3.

The application of two preparations of toxin in the same patient, one in each axilla, was considered appropriate because it eliminated several important factors, such as the difference in the quantity of sweat produced by one individual in comparison to another, possible variations in temperature, and physical and psychological alterations that may lead to variation in the sweat production.<sup>1</sup>

As previously reported, a 50% sweat reduction was selected as a successful study.<sup>8,11,13,21</sup> In the first month, all axillae achieved a 50% reduction of sweating from baseline. The reduction in the sweating quantity at baseline reached levels up to 100% (97.7% BOTOX and 99.4% Dysport) in the first month, indicating that the two BTX formulations have similar levels of efficacy when a conversion factor of 1:3 is adopted. Previous multicenter studies of BOTOX in axillary hyperhidrosis have showed similar level of efficacy, with response rates between 94 and 96.1% at Week 4.<sup>8,11</sup> A similar duration of action was also found between the two groups, with a mean of 260 days for BOTOX and 290 days for Dysport (see Figure 1). The anhydrous response to BTX of more than 5 months is consistent with other reports. In these studies the doses have ranged from 50 U BOTOX and 100 to 250 U Dysport, lasting 4 to 10 months.<sup>1,3,4,8-12,21,22</sup>

In our prospective study no difference was found between BOTOX and Dysport during the 12 months of the follow up. The observed side effects were not related to the preparation of BTX-A, but with the treatment of hyperhidrosis, because compensatory sweating is related to the localized blocking of sweating and occurs in other therapeutic modalities.<sup>5,8</sup> An increase in nonaxillary sweating was also reported by 5% of patients in a multicenter study.<sup>8</sup>

Owing to the excellent result and good tolerability, all patients requested new applications at the end of the study, even one patient that obtained only a partial reduction of the sweating, which, however, led to a significant improvement in quality of life.

## References

1. Heckman M, Breit S, Ceballos-Bauman A, et al. Side-controlled intradermal injection of botulinum toxin A in recalcitrant axillary hyperhidrosis. *J Am Acad Dermatol* 1999;41:987-90.
2. Freeman R, Waldorf HA, Dover JS. Autonomic neurodermatology (Part II): disorders of sweating and flushing. *Semin Neurol* 1992;12:394-407.

3. Maillard H, Briand N, Bara C, Celerier P. Efficacy of botulinum toxin in the treatment of axillary and palmar hyperhidrosis: 10 cases. *Ann Dermatol Venereol* 2003;130:511–3.
4. Buchara KO, Park DM, Jones SC, Schutta HS. Botulinum toxin: a possible new treatment for axillary hyperhidrosis. *Clin Exp Dermatol* 1996;21:276–8.
5. Zacherl J, Huber ER, Imhof M. Long-term results of 630 thorascopic sympathectomies for primary hyperhidrosis: the Vienna experience. *Eur J Surg Suppl* 1988;43–6.
6. Charles PD. Botulinum neurotoxin serotype A: a clinical update on non-cosmetic uses. *Am J Health Syst Pharm* 2004;61:S11–S23.
7. Schnider P, Binder M, Auff E, et al. Double-blind trial of botulinum A toxin for treatment of focal hyperhidrosis of palms. *Br J Dermatol* 1997;135:548–52.
8. 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;15: 596–9.
9. Schnider P, Binder M, Kittler H, et al. A randomized, double-blind, placebo-controlled trial of botulinum A toxin for severe axillary hyperhidrosis. *Br J Dermatol* 1999;140:677–80.
10. Odderson IR. Long-term quantitative benefits of botulinum toxin type A in the treatment of axillary hyperhidrosis. *Dermatol Surg* 2002;28:480–3.
11. Naumann M, Lowe NJ, Kumar CR, et al. Botulinum toxin type A is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. *Arch Dermatol* 2003;139: 731–6.
12. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001;15:488–99.
13. Simonetta Moreau M, Cauhepe C, Magues JP, Senard JM. A double-blind, randomized, comparative study of Dysport vs. Botox in primary palmar hyperhidrosis. *Br J Dermatol* 2003;149:1041–5.
14. Hesse S, Brandi-Hesse B, Bardeleben A, et al. Botulinum toxin A treatment of adult upper and lower limb spasticity. *Drugs Aging* 2001;18:255–62.
15. Odegren T, Hjaltason H, Kaakkola S, et al. A double blind, randomized, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry* 1998;64:6–12.
16. Marion MH, Sheehy M, Sangla S, Soulayrol S. Dose standardization of botulinum toxin. *J Neurol Neurosurg Psychiatry* 1995;59:102–3.
17. Whurr R, Brookes G, Barnes C. Comparison of dosage effects between the American and British botulinum toxin A product in the treatment of spasmodic dysphonia. *Mov Disord* 1995;10:56.
18. Ranoux D, Gury C, Fonadarai J, et al. Respective potencies of Botox and Dysport: a double blind, randomized, crossover study in cervical dystonia. *J Neurol Neurosurg Psychiatry* 2002;72:459–62.
19. Lowe NJ. Botulinum toxin type A for facial rejuvenation: United States and United Kingdom perspectives. *Dermatol Surg* 1998;24:1216–8.
20. Sampaio C, Ferreira JJ, Simões F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. *Mov Disord* 1997;12:1013–8.
21. Lowe PL, Cerdan-Sanz S, Lowe NJ. Botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis: efficacy and duration with repeated treatments. *Dermatol Surg* 2003;29:545–8.
22. Schnider P, Moraru E, Kittler H, et al. Treatment of focal hyperhidrosis with botulinum toxin type A. long-term follow-up in 61 patients. *Br J Dermatol* 2001;145:289–93.

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