Comparisons among Botulinum Toxins: An Evidence-Based Review

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Background: Botulinum neurotoxin treatment is the most common aesthetic procedure in the United States. A number of serotypes and formulations are available worldwide. Similarities and differences among these toxins were evaluated by reviewing the existing literature.
Methods: Reports of botulinum neurotoxin for aesthetic use, published in peer-reviewed literature or presented at recent professional congresses, were reviewed to summarize key features of different toxins. Data from therapeutic uses in comparable anatomical areas were included in the review when aesthetic literature was limited.
Results: Serotypes of neurotoxins share molecular structures and mechanisms of action but exhibit important differences between serotypes and between different formulations within the same serotype, including differences in distribution/diffusion patterns and risk/benefit profiles. The differences attributable to dissimilarities in bacterial strains, manufacturing techniques, and assays are likely to influence clinical performance.
Conclusions: Injection patterns, techniques, dilutions diffusion, and injection volumes established for a specific formulation of botulinum neurotoxin are not likely to be applicable to other formulations, and formulations are not interchangeable by any single conversion ratio. A large proportion of the clinical literature documents the aesthetic uses of the Allergan formulation of botulinum toxin type A. Additional studies are needed to establish optimal procedures for the Ipsen formulation and botulinum neurotoxin, and for diverse aesthetic uses. (*Plast. Reconstr. Surg.* 121: 413e, 2008.)

The cosmetic use of botulinum neurotoxin type A altered aesthetic medicine, providing an effective, safe, and noninvasive method of improving facial appearance. Over time, botulinum neurotoxin type A uses have evolved, both reflecting and spurring changes in aesthetic treatment goals that embrace a broader concept of facial enhancement and creation of a more natural, relaxed look tailored to individual goals.[1–3]

Several commercial preparations of botulinum neurotoxin are available which, unlike generic, nonbiological agents, are unique and therefore not interchangeable in clinical use. This review explores the issues that must be considered when evaluating a botulinum neurotoxin. It provides an in-depth, evidence-based comparison of the two most frequently used formulations of botulinum neurotoxin type A: the 900-kDa formulation (Botox; Allergan, Inc., Irvine, Calif.)[4] and the 500- to 900-kDa formulation (Dysport, expected to be marketed as Reloxin in the United States; Ipsen

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Ltd., Berkshire, United Kingdom),[5] and discusses known and potential clinical consequences of their differences. Another botulinum neurotoxin type A, without complexing proteins (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany), is currently approved for therapeutic applications in Germany.[6]

PROPERTIES AND PREPARATIONS OF BOTULINUM NEUROTOXINS

Botulinum neurotoxins occur in seven known serotypes, two of which are in clinical use, types A and B (Tables 1 and 2).[4,5,7–14] All serotypes share molecular structures and mechanisms of action but differ in specific characteristics that may influence clinical performance.[8,15] Differences also may occur within serotypes because of dissimilarities in manufacturing, bacterial strains used in fermentation, purification methods, and inactive ingredients in the formulation. Disparities in assays also influence the potency and antigenicity of each product.[11,16]

Botulinum neurotoxins are macromolecular protein complexes with molecular weights of 300 to 900 kDa comprising a 150-kDa neurotoxin protein, plus varying amounts of nontoxin proteins.[17] These variations, and pH and physiologic conditions at the injection site, may affect the stability of the toxins, which could influence distribution within target muscles or diffusion to nontargeted muscles.[14,18,19] The development of new toxins without complexing proteins should allow additional examination of this hypothesis.[20,21]

Table 1. Similarities and Differences among Botulinum Neurotoxin Serotypes*

Similarities
Neurotoxin molecule of 150 kDa, synthesized as macromolecular complexes
Basic mechanism of action/inhibition of acetylcholine
Some serum cross-reactivity
Differences
Strain of *Clostridium botulinum*
Neurotoxin complex size
Activation level
Acceptor/receptor sites
Intracellular protein targets and affinity
Muscle weakening efficacy
Duration of action in preclinical and clinical settings
Potential for antigenicity

*Data from Aoki, K. R. A comparison of the safety margins of botulinum neurotoxin serotypes A, B, and F in mice. *Toxicon* 39: 1815, 2001; Aoki, K. R. and Guyer, B. Botulinum toxin type A and other botulinum toxin serotypes: A comparative review of biochemical and pharmacological actions. *Eur. J. Neurol.* 8(Suppl. 5): 21, 2001; and Jankovic, J., Vuong, K. D., and Ahsan, J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. *Neurology* 60: 1186, 2003.

PRECLINICAL STUDIES ON BOTULINUM NEUROTOXINS

Botulinum neurotoxins should act only in the targeted muscle to reduce adverse events from diffusion to nontargeted muscles.[22,23] Relative potency based on muscle weakening, efficacy, safety, and distribution/diffusion properties of botulinum neurotoxins have been examined in preclinical studies.[8,24,25] For example, in the mouse digit abduction scoring assay, groups of mice are given increasing doses of botulinum neurotoxin injected into the targeted gastrocnemius muscle.[24] Muscle weakening is rated by eliciting a startle response, measured by the degree of digit abduction. The resulting data provide the median effective dose, therapeutic margin (an estimate of unwanted diffusion), and safety margin (an esti-

Table 2. Commercial Preparations of Major Botulinum Neurotoxins*

	Botox, Vistabel (Allergan, Inc.)†	Dysport (Ipsen Ltd.)†
FDA approval	Yes	No
Serotype (*Clostridium botulinum* strain)	A (Hall strain)	A (NCTC 2916 strain)
Complex molecular weight (kDa)	900	≈500
Package (units)	100	500
Neurotoxin protein (ng/vial)	≈5	12.5
Other constituents	0.5 mg human albumin, 0.9 mg NaCl	125 μg 20% albumin solution, 2.5 mg lactose
Form	Vacuum-dried	Lyophilized
Diffusion potential	Lower	Higher
pH	≈7	≈7

FDA, U.S. Food and Drug Administration.
*Data from Botox Cosmetic. Package insert. Irvine, Calif.: Allergan, Inc., 2005; Dysport. Package insert. Berkshire, U.K.: Ipsen Ltd., 2001; Myobloc. Package insert. South San Francisco, Calif.: Solstice Neurosciences, Inc., 2004; Aoki, K. R. A comparison of the safety margins of botulinum neurotoxin serotypes A, B, and F in mice. *Toxicon* 39: 1815, 2001; Trindade de Almeida, A. R., Marques, E., de Almeida, J., Cunha, T., and Boraso, R. Pilot study comparing the diffusion of two formulations of botulinum toxin type a in patients with forehead hyperhidrosis. *Dermatol. Surg.* 33: S37, 2007; Aoki, K. R. Botulinum neurotoxin serotypes A and B preparations have different safety margins in preclinical models of muscle weakening efficacy and systemic safety. *Toxicon* 40: 923, 2002; and Hambleton, P., Capel, B., Bailey, N. Production, purification and toxoiding of *Clostridium botulinum* type A toxin. In P. S. Angel and G. E. Lewis (Eds.), *Biomedical Aspects of Botulism.* New York: Academic Press, 1981.
†See prescribing information for each product for indications, reconstitution, and handling.

mate of side effects caused by *distant* actions). This model has consistently demonstrated the 900 kDa botulinum toxin type A (Botox) to be 4- to 5-fold more potent than the 500- to 900-kDa botulinum toxin type A (Dysport), consistent with the clinical literature.[8,24,25] Estimates of the therapeutic margin and safety margin for Botox were larger than for Dysport, suggesting a reduced tendency for Botox to cause undesired local or distant effects through diffusion (Table 3).[8,15,25] These findings clarify clinical results suggesting that similar efficacy at a specific ratio of Dysport to Botox units is attained with a higher incidence of Dysport-associated adverse events.[26] These results also suggest that equivalence in *both* safety and efficacy cannot be achieved with a single dose-conversion ratio; that formulations of botulinum neurotoxins are not interchangeable; and that adjustment in injection volumes, techniques, and patterns would be required to achieve similar clinical results.

CLINICAL STUDIES

Botox has been used to treat hyperfunctional facial lines since the early 1990s.[27,28] Documentation of its safety, predictability, and efficacy for all areas of the face and neck is extensive and unsurpassed by any other formulation or serotype.[2,29,30] Detailed guidelines for aesthetic uses of Botox, based on expert experience and clinical trials, have been published only for the Botox formulation of botulinum toxin type A.[2] Only Botox Cosmetic is approved by the U.S. Food and Drug Administration for glabellar lines at the present time. All other cosmetic uses constitute off-label use.

Table 3. Comparative Effects of Botulinum Neurotoxins in Animal Models of Efficacy and Safety after Intramuscular Administration*

Measure	Rank Order
DAS (highest to lowest)	Botox = BTX-A > Dysport = Myobloc
Safety margin (LD_{50}/DAS ED_50) (greatest to least)	Botox = BTX-A > Dysport = Myobloc
Intermuscular diffusion (most to least)	Myobloc > Dysport = BTX-A > Botox

DAS, digit abduction scoring assay; LD, lethal dose; ED, effective dose; BTX-A, botulinum toxin type A.
*From Aoki, K. R., Satorius, A., Ardila, C., et al. Pharmacology of Botox, Dysport, Myobloc and BTX-A in animal models of efficacy and safety. Abstract presented at the International Conference on Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Denver, Colorado, June 23–25, 2005.

Controlled Noncomparative Trials

Glabellar Lines

Two large, identical, 1-year, multicenter, randomized, controlled trials were conducted with Botox and pooled results reported.[31] A double-blind, placebo-controlled, 4-month phase was followed by an 8-month open-label phase. Subjects first received either placebo injections ($n = 132$) or 20 U of Botox ($n = 405$), divided among five sites (0.1 ml each) in the glabellar area. Subsequently, 373 subjects received injections of Botox at day 120 and 4 months later. Investigator and subject assessments showed Botox to be significantly more effective than placebo at maximum attempted contraction and at rest. Successive treatments progressively improved appearance at rest.[31] Adverse events differing significantly between Botox treatment and placebo were blepharoptosis (Botox, 3.2 percent; placebo, 0 percent) and acne (Botox, 0.5 percent; placebo, 3.1 percent). Blepharoptosis decreased with successive treatments, from 3.0 percent to 2.2 percent to 0.8 percent, suggesting that injection technique contributed to this adverse event.

Dysport was investigated in a randomized controlled trial for the treatment of glabellar lines.[32] Subjects received placebo ($n = 17$) or active treatment (25, 50, or 75 U of Dysport [$n = 34$ per group]) injected into five sites. The injection volume was 0.05 ml to minimize diffusion to nontargeted muscles.[32] At maximum attempted contraction and at rest, each dose of Dysport was significantly more effective than placebo.[32] All groups treated with Dysport reported satisfaction, with the highest percentage of complete satisfaction attained 1 month after injection, by 65.5 percent in the 50-U group. Nine adverse events were considered possibly or probably treatment-related, including one in a placebo-treated subject. No subject experienced blepharoptosis. Headache, migraine, forehead rigidity, vertigo, and rosacea (one each) occurred in the 25-U group. Three adverse events in the 50-U group included forehead muscle spasm, headache, and forehead ecchymosis. No adverse events were reported in the 75-U group. The authors concluded that the 50-U dose was optimal, representing a ratio of 2.5:1 Dysport to Botox. A recent phase II trial, similar in design to the one described above, confirmed that a dose of 50 U was optimal for treating glabellar lines.[33]

The results of these trials cannot be compared directly because of substantial differences in study design, including numbers of subjects, injection patterns, injection volumes, and primary

endpoints.[2,32,34,35] For example, the authors carefully defined the precise anatomical injection points in two of the trials (Fig. 1).[32,35] Additional studies on Dysport are expected to provide more information for evaluating similarities and differences between the formulations and to determine the optimal dose, dilution, and injection patterns for Dysport.

Duration of effect was not a specified outcome in either trial and also cannot be compared. Differences between Botox and placebo were maintained through 4 months, but longer durations were not examined.[31] Dysport effects relative to placebo were sustained through 3 months.[32] In a follow-up Dysport study, most subjects and investigators agreed that a second injection was needed within 3 to 4 months of the first.[36] Additional research is needed on this issue.

Crow's Feet

Botox was investigated in a within-subjects trial in adults with bilaterally symmetrical crow's feet.[37] Subjects received Botox (3, 6, 12, or 18 U) in the orbicularis oculi muscle on one side and placebo contralaterally (three sites per side). Each dose of Botox was safe and more effective than placebo. The most common injection-related adverse event was mild to moderate bruising, occurring equally in all treatment groups. Eighty-nine percent of subjects were satisfied or very satisfied with treatment, and 93 percent indicated they would undergo repeated treatment.

In another study, patients received Botox (12 U) bilaterally in the orbicularis oculi muscle and were assessed at 3, 6, and 9 months after treatment.[38] Trained observers reported significant improvements from baseline at 3, 6, and 9 months after

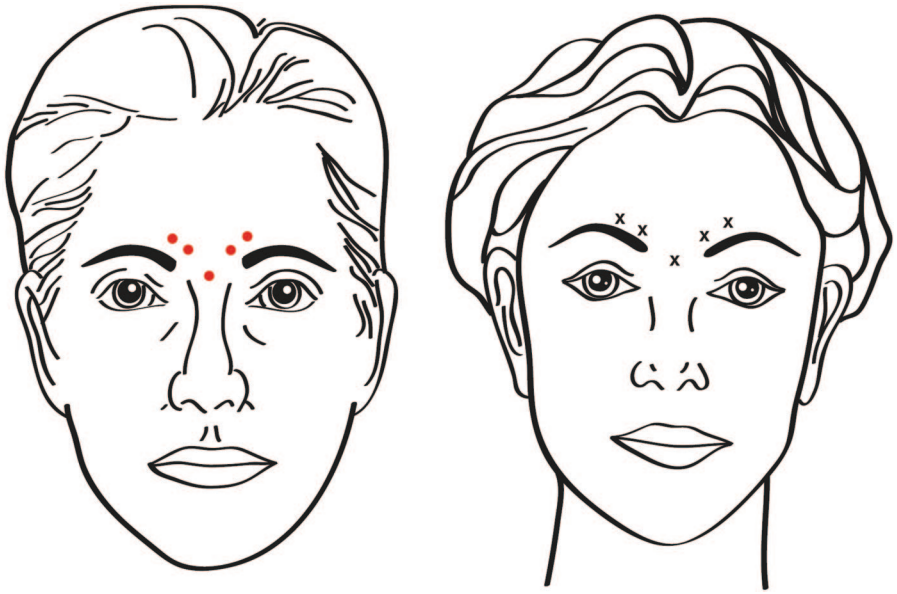

Fig. 1. A comparison of injection sites used to treat glabellar lines with two formulations of botulinum toxin type A. (*Left*) The five injection sites for Dysport (5 U, 10 U, or 15 U in 0.05 ml per injection site). Investigators were instructed to use precisely defined injection sites at the level of the medially located procerus and depressor supercilii and two points in the inner first and second thirds of each corrugator. (Adapted with permission from Ascher, B., Zakine, B., Kestemont, P., et al. A multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety of 3 doses of botulinum toxin A in the treatment of glabellar lines. *J. Am. Acad. Dermatol.* 51: 223, 2004.) (*Right*) The injection sites for Botox (4 U at 0.1 ml per injection site). Investigators were instructed to place a single injection into the procerus muscle at the midline and into each corrugator muscle at its inferomedial aspect, near the origin of the supratrochlear nerve and superolaterally into the superior middle aspect of the muscle at least 1 cm above the bony orbital rim. (Reprinted with permission from Carruthers, J. A., Lowe, N. J., Menter, M. A., et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J. Am. Acad. Dermatol.* 46: 840, 2002.)

treatment, and three-dimensional profilometry showed significant improvements at 3 and 6 months. Both of these measures indicate a long duration of effect when Botox is used to treat crow's feet.

Lower Face

The major aesthetic uses of botulinum neurotoxins are for the upper face, although the safety and effectiveness of Botox for treating moderate chin rhytides have been shown in a controlled study.[30] Experienced practitioners also have found Botox to be useful for treating the perioral area, chin, and platysmal bands.[2,29,30,39] Recommendations for the use of Botox, but not for other botulinum neurotoxin preparations, in the lower face and neck have been published, including experience in more than 1500 patients treated with Botox for platysmal bands.[2,39]

Comparative Trials

Comparative trials of botulinum neurotoxins demonstrate their noninterchangeability, consistent with approved prescribing information for the various products.[4,5,7] The data for Botox and Dysport reveal tradeoffs between efficacy and tolerability at various dosage ratios.

Upper Face

The safety and efficacy of Botox and Dysport were compared in a 20-week, double-blind, randomized, parallel-group study in subjects with glabellar lines of at least moderate severity at maximum contraction.[40] Each subject received five injections of either 20 U of Botox or 50 U of Dysport, based on manufacturer recommendations and published literature.[4,32,40] The incidence of responders (glabellar line severity of none or mild posttreatment) at week 2 was 53 percent for each treatment group (Fig. 2).[40] At week 12, 47 percent of the Botox-treated versus 21 percent of the Dysport-treated subjects were responders. A greater proportion of Botox-treated subjects remained relapse-free throughout the study. Subject satisfaction was significantly greater with Botox treatment at week 12: 64 percent of Botox-treated versus 33 percent of the Dysport-treated subjects reported at least 50 percent improvement. No subject experienced ptosis of the brow or upper eyelid and one Botox-treated subject reported bruising. The investigators concluded that at a ratio of 2.5:1 (Dysport to Botox), the Botox formulation of botulinum neurotoxin type A afforded more prolonged efficacy in diminishing glabellar lines and that both formulations were well tolerated.

Various Facial Rhytides

Dysport and Botox were compared in an open-label study of 20 Korean subjects who received treatments in the lateral canthal area, glabellar area, nasal area, dorsum, or nasolabial fold.[41] Six subjects received Dysport (20 U/0.1 ml) and 14 received Botox (5 U/0.1 ml; a ratio of 4:1). Total doses were based on wrinkle severity, and most subjects received injections in more than one area. Efficacy was similar for each treatment group, but transient adverse events occurred approximately three times more frequently in Dysport-treated subjects (six of six) than in Botox-treated subjects [five of 14 (35 percent)] ($p < 0.05$). No ptosis occurred. Limitations of the study include small

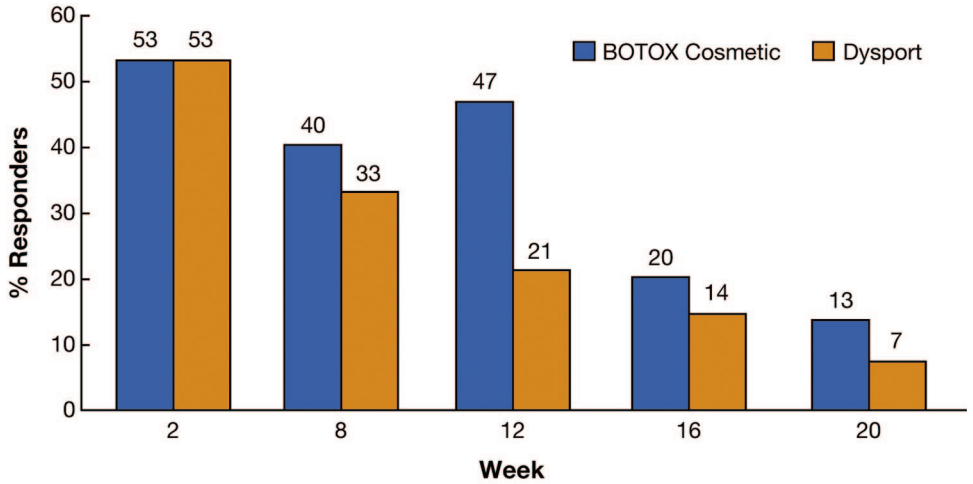

Fig. 2. Percentage of responders as determined by photographic examination at maximum frown. (Reprinted with permission from Lowe, P. L., Patnaik, R., and Lowe, N. J. A comparison of two botulinum type A toxin preparations for the treatment of glabellar lines: Double-blind, randomized, pilot study. *Dermatol. Surg.* 31: 1651, 2005.)

sample size, lack of controls, and variability in treatment areas and doses. Nevertheless, the results suggest that the efficacy of the two formulations of botulinum neurotoxin type A is similar at a 4:1 ratio (Dysport to Botox), but that Botox is associated with significantly fewer complications.

Other Comparative Studies: Therapeutic Indications

Therapeutic trials for blepharospasm and hemifacial spasm, which also involve small facial muscles, furnish additional insight into the relative clinical performance of Botox and Dysport. With other trials on cervical dystonia and palmar hyperhidrosis, these studies provide data on the relative efficacy and safety of Botox and Dysport across a range of dose ratios and indications (Table 4).[26,42–46] These data demonstrate that although both products are efficacious in these indications, the two formulations are not interchangeable at any one fixed dose ratio and that their risk-to-benefit profiles differ, with Dysport tending to result in a greater number of adverse events as shown in four of the six studies summarized. At least some of these adverse events may represent unwanted diffusion from the injection site. In blepharospasm, for example, ptosis occurred in 6.6 percent of patients during Dysport treatment and 1.4 percent of the same patients during Botox treatment ($p < 0.01$).[42] In another study, seven instances of ptosis and four of double vision were reported across all indications in Dysport treatment versus none during Botox treatment.[26] The results of a small study in palmar hyperhidrosis also demonstrated that potentially small, not significant gains in efficacy were offset by a higher incidence of adverse events such as thumb-index finger pinch weakness in four patients on palms treated with Dysport versus two cases when palms were treated with Botox.[45] Another patient reported right upper limb heaviness lasting 8 days on the side injected with Dysport.

A closer look at dose ratios. The retrospective, multinational Real Dose Study examined real-world dosage use of Botox and Dysport in cervical dystonia and blepharospasm.[47] Patients ($n = 114$) who had received either neurotoxin for at least two consecutive treatments and were then switched to the other neurotoxin for at least 1 additional year were eligible. The majority of patients (88 percent) received a ratio of greater than 3:1 (Dysport to Botox), regardless of the direction of the switch (Fig. 3).[47] The overall mean dose ratio was 4.48:1 (Dysport to Botox). Of the 106 total adverse events reported, 71 percent occurred during Dysport treatment. The single most common adverse event in patients treated for cervical dystonia was dysphagia (Dysport, $n = 19$; Botox, $n = 12$). In bleph-

Table 4. Comparative Therapeutic Trials of Dysport and Botox

Study and Design	Therapeutic Area	Mean Dose Ratio (Dysport to Botox)	Key Findings	
			Efficacy	Safety
Bihari, 2005[26]	Blepharospasm ($n = 27$) Cervical dystonia ($n = 12$) Hemifacial spasm ($n = 9$)	4:1; 5:1	Botox → greater duration of effect (blepharospasm, $p = 0.001$; cervical dystonia, $p = 0.014$; hemifacial spasm, $p < 0.014$)	Dysport, 23 in 19 patients; Botox, 0
Nüssgens and Roggenkämper, 1997[42]; crossover study	Blepharospasm ($n = 212$)	4:1	Equivalent (duration)	All adverse events: Dysport, 24%; Botox, 17%; $p < 0.05$ Ptosis: Dysport, 6.6%; Botox, 1.4%; $p < 0.01$
Odergren et al., 1998[43]; parallel group	Cervical dystonia Botox ($n = 35$) Dysport ($n = 38$)	3:1	Equivalent efficacy	Equivalent frequency of adverse events
Ranoux et al., 2002[44]; crossover study	Cervical dystonia ($n = 54$)	3:1; 4:1	Dysport efficacy > Botox ($p \leq 0.02$)	Dysport adverse events > Botox at both dose ratios ($p \leq 0.01$)
Simonetta Moreau et al., 2003; within-subject, double-blind[45]	Palmar hyperhidrosis ($n = 8$)	4:1	Equivalent efficacy in reduction of sweating; similar duration of effect	Dysport adverse events > Botox
Van den Bergh and Lison, 1998[46]	Hemifacial spasm ($n = 10$) Cervical dystonia ($n = 10$)	2.33:1 2.49:1	Equivalent efficacy in both indications	Equivalent, no dysphagia

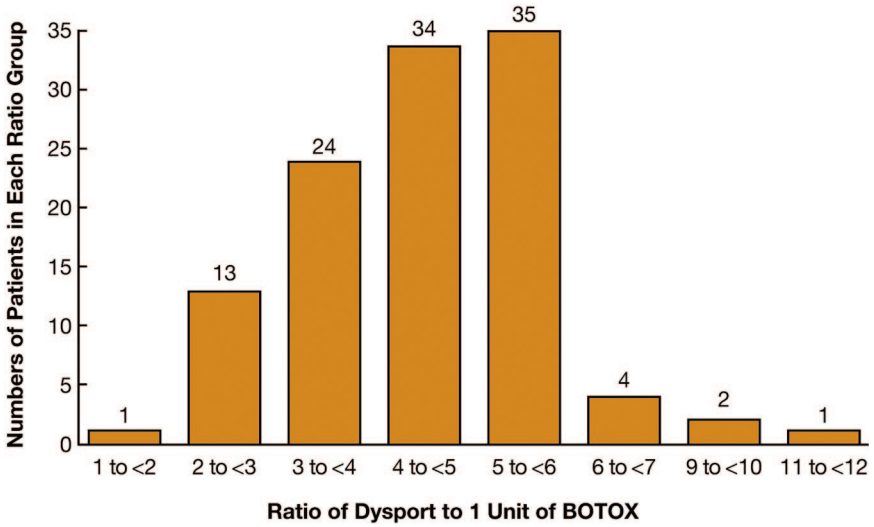

Fig. 3. Dose ratios observed in the Real Dose Study. Eighty-eight percent of patients received a ratio of greater than 3:1 (Dysport to Botox). The mean dose ratio across all patients was 4.48:1 (Dysport to Botox). (Reprinted with permission from Marchetti, A., Magar, R., Findley, L., et al. Retrospective evaluation of the dose of Dysport and Botox in the management of cervical dystonia and blepharospasm: The Real Dose study. *Mov. Disord*. 20: 937, 2005.)

arospasm, ptosis occurred 29 times with Dysport and 12 times with Botox treatment. Five instances of double vision were recorded during Dysport treatment versus none during Botox treatment. These results illustrate the great variability in the dose ratios selected clinically to deliver a given result, substantiate the hypothesis that risk-to-benefit profiles of the two formulations differ in clinical use, and show the difficulties in converting between botulinum neurotoxin type A formulations.

Optimizing Distribution in Target Muscles: Clinical Findings

Clinical data suggest that Botox is less likely to be associated with unwanted diffusion to nontargeted muscles.[12,48–50] Twenty patients with forehead hyperhidrosis each received two injections on each side of the forehead: Botox (3 U/site) was administered on one side; Dysport was administered contralaterally (ratios of 2.5, 3, or 4:1 relative to Botox in identical injection volumes). Anhidrosis halos were significantly larger with Dysport in 93 percent of all comparisons and all dose ratios (Fig. 4).[12,48] Smaller anhidrosis halos produced by Botox did not compromise efficacy in reducing frontalis contraction; muscle inhibition was comparable between the two formulations in 20 of the evaluations, greater for Botox in 11 evaluations, and greater for Dysport in four evaluations. The authors suggest that more widespread diffusion of Dysport could hinder accurate localization of effect in the relatively small muscles of the face.[12,48] These clinical data confirmed results from preclinical studies of diffusion potential for the two formulations.[25] The authors did not comment on the possibility of using lower doses of Dysport or the potential impact of such doses on cost-effectiveness.

Two other, noncomparative studies examined diffusion characteristics in patients with hemifacial spasm or blepharospasm. Thirty-two patients with hemifacial spasm received Botox (15 to 45 U) in the orbicularis oculi.[49] At dosages generally higher than those used to treat crow's feet, Botox treatment reduced muscle spasm of the treated muscle but caused no muscle weakness in untreated muscles as measured by compound muscle action potential.[2,49] In a similar study, 15 patients with blepharospasm or hemifacial spasm received 120 U of Dysport injected into four sites of the orbicularis oculi on one (hemifacial spasm) or both sides (blepharospasm) of the face.[50] At 1 and 2 months after injection, significant decrements in mean amplitudes of compound muscle action potential and motor evoked potentials were recorded from both treated and nearby untreated muscles, which the authors attributed to unwanted diffusion of Dysport to nearby muscles.

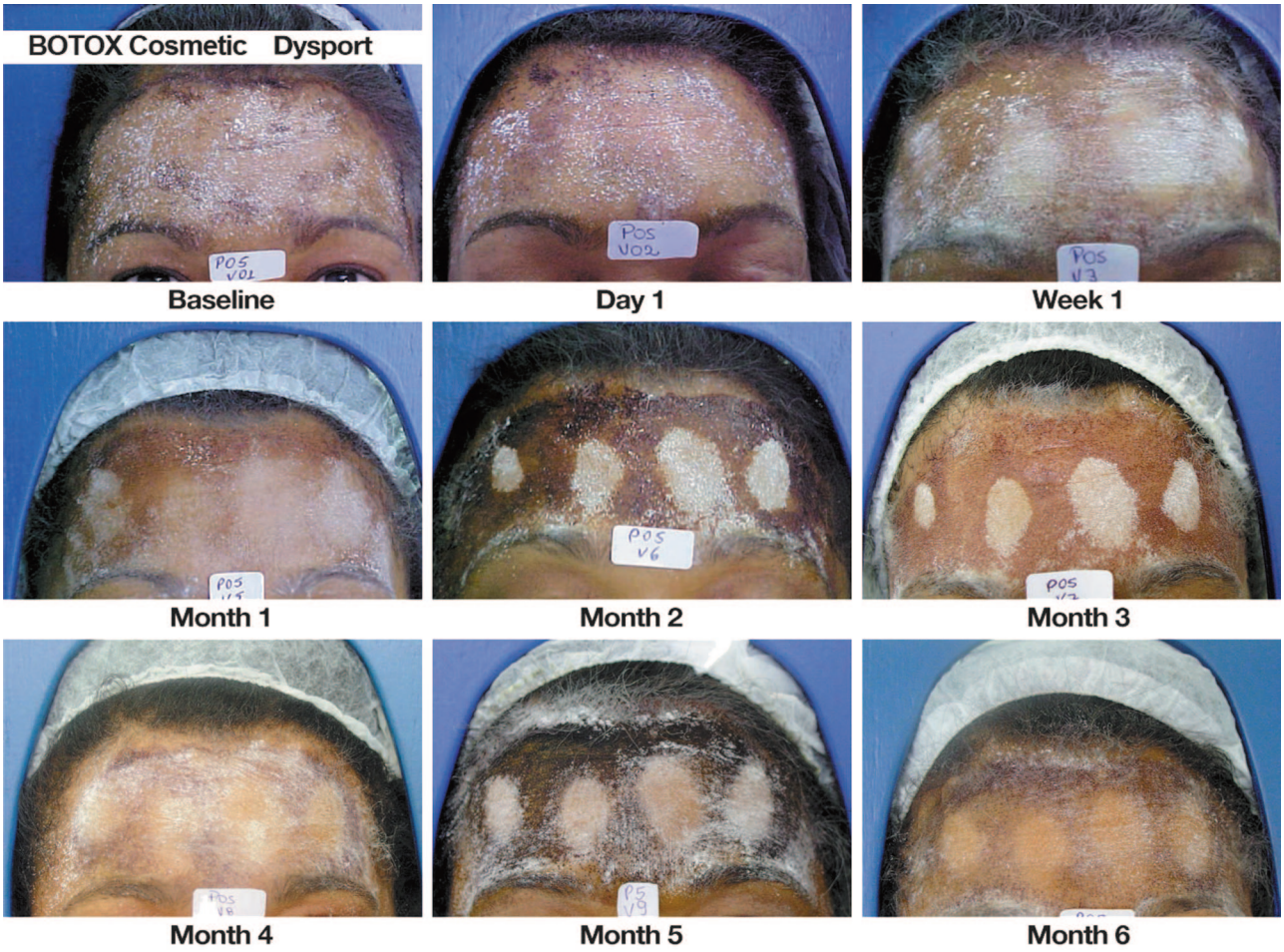

Fig. 4. Comparison of diffusion properties of Dysport and Botox. Pattern of anhidrosis after botulinum neurotoxin type A treatment showing greater area of anhidrosis at the medial injection sites than the lateral injection sites and the greater area of diffusion with Dysport than Botox (injected into patient's left and right forehead, respectively). (Reprinted with permission from de Almeida, A., Marques, E., de Almeida, J., Cunha, T., and Boraso, R. Pilot study comparing the diffusion characteristics of two formulations of botulinum toxin type A with forehead hyperhidrosis. Presented at the European Masters in Aesthetic and Anti-Aging Medicine Meeting, Paris, France, September 30–October 2, 2005.)

LONG-TERM SAFETY IN AESTHETIC INDICATIONS

Long-term safety data in aesthetic indications have been reported for Botox, based on a retrospective analysis of 50 patients who had received at least 10 treatments for hyperfunctional facial lines for up to 9 years.[51] Fewer than 1 percent of 853 sessions resulted in a treatment-related adverse event.[51] Only five adverse events were considered probably or definitely treatment related; four of these were mild and one was of moderate severity.

CONCLUSIONS

A substantial body of published data and clinical experience supports the safe, effective use of Botox in aesthetic indications. Dysport has also been shown to be effective and safe in treating the upper face, but data supporting its use in aesthetic indications are more limited than for Botox. Fewer data substantiate the cosmetic use of Myobloc (botulinum neurotoxin type A), used primarily for cervical dystonia.

This review demonstrates that the two formulations of botulinum neurotoxin type A are not identical and are unlikely to provide equivalence in both safety and efficacy at any single dose-conversion ratio, consistent with their approved prescribing information. Distribution/dilutions diffusion characteristics and risk-to-benefit profiles appear to differ, as suggested by preclinical and clinical data. Thus, injection patterns, injection techniques, dilutions diffusion, and injection volumes that are well established for Botox are un-

likely to be applicable to Dysport. Additional aesthetic studies on Dysport are needed to establish optimal procedures and treatment recommendations. With additional clinical studies and more clinical experience with Dysport, improved techniques may be developed for optimal use of the product. At this time, the wealth of clinical experience with Botox and its well-documented safety and efficacy can help ensure that aesthetic treatments provide physicians with the tools to deliver a natural, relaxed look that satisfies individual needs and goals.

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REFERENCES

1. Fagien, S. Botulinum toxin type A for facial aesthetic enhancement: Role in facial shaping. *Plast. Reconstr. Surg.* 112(Suppl.): 6S, 2003.
2. Carruthers, J., Fagien, S., Matarasso, S. L., et al. Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. *Plast. Reconstr. Surg.* 114(Suppl.): 1S, 2004.
3. Klein, A. W. The clinical use of botulinum toxin. *Dermatol. Clin.* 22: ix, 2004.
4. Botox Cosmetic. Package insert. Irvine, Calif.: Allergan, Inc., 2005.
5. Dysport. Package insert. Berkshire, U.K.: Ipsen Ltd., 2001.
6. Xeomin. Package insert. Frankfurt, Germany: Merz Pharmaceuticals GmbH, 2006.
7. Myobloc. Package insert. South San Francisco, Calif.: Solstice Neurosciences, Inc., 2004.
8. Aoki, K. R. A comparison of the safety margins of botulinum neurotoxin serotypes A, B, and F in mice. *Toxicon* 39: 1815, 2001.
9. Bellew, S. G., Carroll, K. C., Weiss, M. A., and Weiss, R. A. Sterility of stored nonanimal, stabilized hyaluronic acid gel syringes after patient injection. *J. Am. Acad. Dermatol.* 52: 988, 2005.
10. Aoki, K. R., and Guyer, B. Botulinum toxin type A and other botulinum toxin serotypes: A comparative review of biochemical and pharmacological actions. *Eur. J. Neurol.* 8(Suppl. 5): 21, 2001.
11. Jankovic, J., Vuong, K. D., and Ahsan, J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. *Neurology* 60: 1186, 2003.
12. Trindade de Almeida, A. R., Marques, E., de Almeida, J., Cunha, T., and Boraso, R. Pilot study comparing the diffusion of two formulations of botulinum toxin type a in patients with forehead hyperhidrosis. *Dermatol. Surg.* 33: S37, 2007.
13. Aoki, K. R. Botulinum neurotoxin serotypes A and B preparations have different safety margins in preclinical models of muscle weakening efficacy and systemic safety. *Toxicon* 40: 923, 2002.
14. Hambleton, P., Capel, B., Bailey, N., et al. Production, purification and toxoiding of *Clostridium botulinum* type A toxin. In P. S. Angel and G. E. Lewis (Eds.), *Biomedical Aspects of Botulism.* New York: Academic Press, 1981.
15. Aoki, K. R. Pharmacology and immunology of botulinum toxin type A. *Clin. Dermatol.* 21: 476, 2003.
16. Markey, A. C. Dysport. *Dermatol. Clin.* 22: 213, 2004.
17. Inoue, K., Fujinaga, Y., Watanabe, T., et al. Molecular composition of *Clostridium botulinum* type A progenitor toxins. *Infect. Immun.* 64: 1589, 1996.
18. Friday, D., Bigalke, H., and Frevert, J. In vitro stability of botulinum toxin complex preparations at physiological pH and temperature (Abstract). *Naunyn Schmiedebergs Arch. Pharmacol.* 365: R20, 2002.
19. Schantz, E. J., and Johnson, E. A. Properties and use of botulinum toxin and other microbial neurotoxins in medicine. *Microbiol. Rev.* 56: 80, 1992.
20. Benecke, R., Jost, W. H., Kanovsky, P., et al. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. *Neurology* 64: 1949, 2005.
21. Jost, W. H., Kohl, A., Brinkmann, S., and Comes, G. Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (Botox) in healthy volunteers. *J. Neural. Transm.* 112: 905, 2005.
22. Borodic, G. Therapeutic botulinum toxin. *Lancet* 344: 1370, 1994.
23. Borodic, G. E., Ferrante, R. J., Pearce, L. B., and Alderson, K. Pharmacology and histology of the therapeutic application of botulinum toxins. In J. Jankovic and M. Hallett (Eds.), *Therapy with Botulinum Toxin.* New York: Marcel Dekker, 1994.
24. Aoki, R. Preclinical update on Botox (botulinum toxin type A)-purified neurotoxin complex relative to other botulinum neurotoxin preparations. *Eur. J. Neurol.* 6: S3, 1999.
25. Aoki, K. R., Satorius, A., Ardila, C., et al. Pharmacology of Botox, Dysport, Myobloc and BTX-A in animal models of efficacy and safety. Abstract presented at the International Conference on Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Denver, Colorado, June 23–25, 2005.
26. Bihari, K. Safety, effectiveness, and duration of effect of Botox after switching from Dysport for blepharospasm, cervical dystonia, and hemifacial spasm. *Curr. Med. Res. Opin.* 21: 433, 2005.
27. Blitzer, A., Brin, M. F., Keen, M. S., and Aviv, J. E. Botulinum toxin for the treatment of hyperfunctional lines of the face. *Arch. Otolaryngol. Head Neck Surg.* 119: 1018, 1993.
28. Carruthers, A., and Carruthers, J. The treatment of glabellar furrow with botulinum A exotoxin (Abstract). *J. Dermatol. Surg. Oncol.* 16: 83, 1990.
29. Kane, M. A. Nonsurgical treatment of platysmal bands with injection of botulinum toxin A. *Plast. Reconstr. Surg.* 103: 656, 1999.
30. Beer, K., Yohn, M., and Closter, J. A double-blinded, placebo-controlled study of Botox for the treatment of subjects with chin rhytids. *J. Drugs Dermatol.* 4: 417, 2005.
31. Carruthers, A., Carruthers, J., Lowe, N. J., et al. One-year, randomised, multicenter, two-period study of the safety and efficacy of repeated treatments with botulinum toxin type A in patients with glabellar lines. *J. Clin. Res.* 7: 1, 2004.
32. Ascher, B., Zakine, B., Kestemont, P., et al. A multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety of 3 doses of botulinum toxin A in the treatment of glabellar lines. *J. Am. Acad. Dermatol.* 51: 223, 2004.
33. Monheit, G., Carruthers, A., Brandt, F., and Rand, R. A randomized, double-blind, placebo-controlled study of botulinum toxin type a for the treatment of glabellar lines: Determination of optimal dose. *Dermatol. Surg.* 33: S51, 2007.
34. Fagien, S. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. *Plast. Reconstr. Surg.* 112: 31S, 2003.
35. Carruthers, J. A., Lowe, N. J., Menter, M. A., et al. A multicenter, double-blind, randomized, placebo-controlled study

of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J. Am. Acad. Dermatol.* 46: 840, 2002.
36. Ascher, B., Zakine, B., Kestemont, P., et al. Botulinum toxin A in the treatment of glabellar lines: Scheduling the next injection. *Aesthetic Surg. J.* 25: 365, 2005.
37. Lowe, N. J., Lask, G., Yamauchi, P., and Moore, D. Bilateral, double-blind, randomized comparison of 3 doses of botulinum toxin type A and placebo in patients with crow's feet. *J. Am. Acad. Dermatol.* 47: 834, 2002.
38. Levy, J. L., Servant, J. J., and Jouve, E. Botulinum toxin A: A 9-month clinical and 3D in vivo profilometric crow's feet wrinkle formation study. *J. Cosmet. Laser Ther.* 6: 16, 2004.
39. Matarasso, A., Matarasso, S. L., Brandt, F. S., and Bellman, B. Botulinum A exotoxin for the management of platysma bands. *Plast. Reconstr. Surg.* 103: 645, 1999.
40. Lowe, P. L., Patnaik, R., and Lowe, N. J. A comparison of two botulinum type a toxin preparations for the treatment of glabellar lines: Double-blind, randomized, pilot study. *Dermatol. Surg.* 31: 1651, 2005.
41. Lew, H., Yun, Y. S., Lee, S. Y., and Kim, S. J. Effect of botulinum toxin A on facial wrinkle lines in Koreans. *Ophthalmologica* 216: 50, 2002.
42. Nüssgens, Z., and Roggenkämper, P. Comparison of two botulinum-toxin preparations in the treatment of essential blepharospasm. *Graefes Arch. Clin. Exp. Ophthalmol.* 235: 197, 1997.
43. Odergren, T., Hjaltason, H., Kaakkola, S., et al. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J. Neurol. Neurosurg. Psychiatry* 64: 6, 1998.
44. Ranoux, D., Gury, C., Fondarai, J., Mas, J. L., and Zuber, M. Respective potencies of Botox and Dysport: A double blind, randomised, crossover study in cervical dystonia. *J. Neurol. Neurosurg. Psychiatry* 72: 459, 2002.
45. Simonetta Moreau, M., Cauhepe, C., Magues, J. P., and Senard, J. M. A double-blind, randomized, comparative study of Dysport vs. Botox in primary palmar hyperhidrosis. *Br. J. Dermatol.* 149: 1041, 2003.
46. Van den Bergh, P. Y., and Lison, D. F. Dose standardization of botulinum toxin. *Adv. Neurol.* 78: 231, 1998.
47. Marchetti, A., Magar, R., Findley, L., et al. Retrospective evaluation of the dose of Dysport and Botox in the management of cervical dystonia and blepharospasm: The Real Dose study. *Mov. Disord.* 20: 937, 2005.
48. de Almeida, A., Marques, E., de Almeida, J., Cunha, T., and Boraso, R. Pilot study comparing the diffusion characteristics of two formulations of botulinum toxin type A with forehead hyperhidrosis. Presented at the European Masters in Aesthetic and Anti-Aging Medicine Meeting, Paris, France, September 30–October 2, 2005.
49. Cinzia, L., Francesca, G., Sergio, B., and Alfredo, B. Diffusion of botulinum toxin in facial muscles in patients with hemifacial spasm (Abstract). *Mov. Disord.* 20: S175, 2005.
50. Eleopra, R., Tugnoli, V., Caniatti, L., and DeGrandis, D. Botulinum toxin treatment in the facial muscles of humans: Evidence of an action in untreated near muscles by peripheral local diffusion. *Neurology* 46: 1158, 1996.
51. Carruthers, A., and Carruthers, J. Long-term safety review of subjects treated with botulinum toxin type A for cosmetic use. Poster presented at the 13th Congress of the European Academy of Dermatology & Venereology, Florence, Italy, November 17–21, 2004.