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Retrospective Evaluation of the Dose of Dysport and BOTOX in the Management of Cervical Dystonia and Blepharospasm: The REAL DOSE Study

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Abstract: The purpose of this study is to evaluate the real-world dose utilization of Dysport and BOTOX for cervical dystonia and blepharospasm. Six investigational sites (five countries) were identified. Investigators abstracted utilization data for patients who received Dysport before switching to BOTOX or BOTOX before switching to Dysport. Patients were identified during scheduled clinic visits and selected if they met study criteria, which included treatment for at least 2 consecutive years (at least 1 year with Dysport or BOTOX, then switched and maintained on BOTOX or Dysport for at least another year). A total of 114 patients were included in the assessment. Ratios of mean dose for Dysport to BOTOX ranged from a low of 2:1 to a high of 11:1. Thirty-one percent of patients fell into the Dysport-to-BOTOX ratio grouping of 5:1 to less than 6:1; 30% of patients had a mean ratio of Dysport to BOTOX of 4:1 to less than 5:1; and only 21% of all patients evaluated fell into the Dysport-to-BOTOX ratio grouping of 3:1 to less than 4:1. Results are consistent with United Kingdom labeling for botulinum toxins stating that units of different serotype A toxins are not interchangeable and simple dose-conversion factors are not applicable. © 2005 Movement Disorder Society

Key words: cervical dystonia; blepharospasm; botulinum toxin type A; dose ratio; adverse events

Botulinum neurotoxin, produced by *Clostridium botulinum*, is a complex of proteins containing the neurotoxin and one or more nontoxic proteins. The botulinum neurotoxin, which consists of a heavy chain of 100 kDa and a light chain of 50 kDa linked by a single disulfide bond, is synthesized as a relatively inactive single-chain polypeptide with a molecular mass of approximately 150 kDa but is the active part of the complex. The nontoxic proteins help maintain the structure of the neurotoxin, which is similar for all serotypes; however, the overall size of the protein complex depends on the nontoxic proteins present. Activation of the neurotoxin occurs upon proteolytic cleavage into the heavy and light chains.

There are seven botulinum toxin serotypes (A, B, C, D, E, F, and G), all of which inhibit acetylcholine release, although their intracellular target proteins, the characteristics of their actions, and their potencies vary substantially. Botulinum neurotoxin type A has been the most widely studied serotype for therapeutic purposes. Two botulinum toxin type A serotypes are commercially available in Europe, BOTOX (Allergan, Inc., Irvine, CA) and Dysport (Ipsen Limited, Slough, Berkshire, UK), for

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patients with movement disorders such as cervical dystonia, blepharospasm, and hemifacial spasm.

The availability of multiple botulinum toxin products to treat dystonias has led to debate concerning the comparative effectiveness and safety as well as the dose-equivalency ratio that should be used in clinical practice. There is growing debate as to whether a true dose-equivalency ratio exists.

The two commercially available botulinum toxin type A serotypes have distinct numbers of units and amounts of botulinum neurotoxin protein. BOTOX contains less than 5 ng of botulinum toxin type A in a 900-kDa complex, whereas Dysport contains 12.5 ng of botulinum toxin type A in a 900-kDa preparation. This difference is due to the different production methods of the two products. Because they are typical biologics, their properties in many respects (pharmacodynamics/ pharmacokinetics) may be the reason for any differences observed. Therefore, the protein load of Dysport is greater (12.5 ng), which may impact the risk of antibody formation compared to a less than 5-ng protein load for BOTOX. The BOTOX formulation contains sodium chloride, whereas Dysport contains lactose. The products also contain different amounts of serum albumin. Each product's distinct formulation results in a unique interaction with biologic systems after injection. The system is exposed to different ingredients and different numbers of molecules that likely influence local osmotic gradients and diffusion. Mclellan and colleagues concluded that different preparations, because of their unique formulation and stability, are differentially affected by some of these factors and that these differences might well contribute to the differences observed in their clinical use.[1]

It is clear from the literature and from clinical experience that neither the formulations nor the units used to quantify the toxin activity of the two products are equivalent. The potential effects of such differences have not been adequately studied. Consequently, several attempts have been made to evaluate currently available formulations. Elston and Russell,[2] followed by Foran and associates[3] and Aoki,[4,5] demonstrated differences in the potency and biologic activity of botulinum toxin serotypes, but the paucity of clinical data and ongoing unfounded claims related to benefits and limitations of currently marketed brands have led to confusion. In addition, attempts to relate product potency to a single arbitrary dose-conversion factor or ratio add to the confusion. Single-treatment cycle studies have shown equivalence in therapeutic effect or duration at a dose ratio ranging from 3:1 (Dysport-to-BOTOX units) to as high as 6:1 but suggest differences in the incidence of adverse events.[6–13]

In a prospective, open-label pharmacoeconomic study of 835 patients with dystonia who were treated at four different movement disorder clinics in Germany, Dodel and coworkers found that the percentage response to BOTOX was rated significantly higher than that to Dysport ($P < 0.001$).[14] The overall adverse event rate was significantly higher after treatment with Dysport than with BOTOX ($P < 0.001$). These results suggest that the clinical effects of the two formulations are distinct and argue against applying a simple dose conversion.

Dose ratios of Dysport to BOTOX, predetermined by study design, do not necessarily reflect real-world conditions and actual clinical utilization. Moreover, most of the research evaluated therapeutic effectiveness and treatment response on the basis of a single delivered dose, which does not reflect actual clinical practice in which multiple treatments are often administered. Unquestionably, additional research is needed.

To enhance understanding of current botulinum toxin use in real-world clinical practice settings and to contribute evidence to the debate surrounding product equivalence, a multinational observational study (Retrospective Evaluation of the Dose of Dysport and BOTOX in the Clinical Management of Cervical Dystonia and Blepharospasm [REAL DOSE]) was conducted in Europe, specifically to evaluate long-term continuous drug utilization in terms of the actual per-patient, per-visit delivered doses of the available type A toxins, Dysport and BOTOX, for the treatment of patients with cervical dystonia and/or blepharospasm. The REAL DOSE Study was a multicenter, retrospective, observational review of randomly selected medical records of patients in actual clinical practices who had received Dysport and BOTOX consistent with a double-arm crossover design.

MATERIALS AND METHODS

A prestudy assessment was undertaken by questionnaire at eight potential investigational sites in Europe: (1) to estimate the size of the population of patients who received Dysport and BOTOX for cervical dystonia and/or blepharospasm in compliance with the study design, (2) to determine the accessibility of charts as well as the quality of medical records, and (3) to gauge interest and ability to contribute de-identified data to the study. Six centers in five countries (United Kingdom, Czech Republic, Norway, Poland, and Slovenia) passed site-screening criteria and were eligible for participation; two centers failed site screening because they could not provide information on the patient population of interest or cited constraints that would compromise the timely submission of data.

Investigators from eligible centers participated in a prestudy orientation session in which study objectives, methods, data elements, and endpoints were discussed and the protocol and case report form (CRF) was reviewed. All investigators agreed to maintain the confidentiality of their patients, to provide only de-identified data, and to obtain the appropriate reviews and consents required by their respective institutions.

Patients with a confirmed diagnosis of cervical dystonia or blepharospasm were eligible to be included in the study if they were at least 18 years of age and had received Dysport or BOTOX for at least 1 year before and after the drug crossover. Patients were ineligible for study inclusion if they had received any medication for neuromuscular disorders (e.g., pyridostigmine, neostigmine, dantrolene, tubocurarine, streptomycin, aminoglycosides), were involved in other investigational pharmaceutical research, had an unstable medical condition (e.g., diabetes, hypertension, heart surgery), or were unresponsive to either Dysport or BOTOX during the assessed clinical period. By virtue of the study design, patients were their own controls.

Potential study patients at each investigational site were identified from medical records obtained during their scheduled clinic visit, at which time each patient was screened for eligibility based on the pre-established inclusion/exclusion criteria. If a patient was found to be ineligible by the study investigator, the investigator disqualified the patient and recorded the reason(s) for exclusion. If the patient was found to be eligible by the investigator, then that patient's medical records were reviewed and data were abstracted as per protocol and CRF requirements. As soon as 20 patients passed investigator screening or the pool of potential patients was exhausted at a study site, the patient qualification process was closed at that site.

Primary data elements for the study were the total doses of Dysport or BOTOX administered during previously recorded patient treatment visits that had occurred during the relevant clinical assessment period (i.e., at least 1 year before and after drug crossover). Secondary data elements were the incidence of adverse drug reactions (ADRs) previously recorded during the relevant clinical assessment period (e.g., dysphagia after treatment for cervical dystonia or ptosis, diplopia, or ecchymosis after treatment for blepharospasm). Other abstracted data elements included age, gender, onset of condition, and investigator-estimated disease severity. Although data were not requested for patients who failed initial eligibility screening, the reason for disqualification was required.

TABLE 1. *Inclusion/exclusion criteria*

Inclusion criteria
The following requirements must all be met for entry into the study:
1. Patient has a confirmed diagnosis of idiopathic cervical dystonia or blepharospasm
2. Patient was started on Dysport and was switched to BOTOX or started on BOTOX and switched to Dysport
3. Patient was on study drugs for ≥1 year prior to switch and ≥1 year after switch
4. Patient was ≥18 years of age at first recorded injection
Exclusion criteria
The following are grounds for exclusion from participating in the study:
1. Patient had a neuromuscular junction transmission disorder or was taking any medications (e.g., pyridostigmine, neostigmine, dantrolene, tubocurarine, streptomycin, aminoglycosides) that could affect neuromuscular junction transmission
2. Patient was involved in another investigational drug study or participating in a clinical trial during the relevant chart review period
3. Patient had an unstable medical condition (e.g., diabetes, hypertension, heart surgery)
4. Patient was nonresponsive to either Dysport or BOTOX or both

After data abstraction and transcription from patient records to CRFs were complete for screen-qualified patients, a written copy of the CRFs was provided to the study coordinator. Each CRF was then reviewed for legibility and completeness by the coordinator. Thereafter, the correctness of recorded information was confirmed, and coordinator queries were answered. On completion of the review process, all submitted data were entered into a relational database, using a double-key entry method that helped ensure the accuracy of the transfer. A final assessment of the accuracy of the data entry was undertaken, and identified discrepancies were corrected.

On completion of the data-entry process, the populated database was imported into *SPSS v. 10.0* software (SPSS, Inc., Chicago, IL) and analyzed for patient demographics, per-patient, per-visit mean doses of Dysport and BOTOX before and after the crossover, per-patient mean ratio of Dysport to BOTOX, mean dose for all patients on each drug, and overall incidences of adverse events. Further analyses stratified patients based on condition (cervical dystonia and/or blepharospasm) and the initially delivered toxin (Dysport or BOTOX).

RESULTS

A total of 422 patient records were reviewed for study entry criteria (Table 1) at the six participating investigative sites. Of the 422 patient records that were screened, 121 were screen qualified for study inclusion. The most common reason for screen disqualification was failure to

TABLE 2. *Reasons for screen disqualification*

Reason	Patients disqualified (N = 301)
Patient did not have a confirmed diagnosis of idiopathic cervical dystonia or blepharospasm (other conditions)	54
Patient had not started on Dysport and was switched to BOTOX or had not started on BOTOX and was switched to Dysport (noncompliant drug utilization per protocol)	152
Patient was not on study drugs for ≥1 year prior to switch and ≥1 year after switch	257
Patient was <18 years of age at first recorded injection	9
Patient was involved in another investigational drug study or clinical trial during the relevant treatment period	16
Patient had an unstable medical condition (e.g., diabetes, hypertension, heart surgery)	7
Patient was nonresponsive to either Dysport or BOTOX or both	21

Same patient may have been disqualified for more than one reason.

meet the criterion for time on study drug before and after the crossover (i.e., at least 1 year before and after the drug switch; Table 2). Of the 121 patients who met study entry criteria, 7 were excluded from analyses because of multiple switches between toxins during the clinical period of assessment, leaving 114 patients for evaluation. Of these, 35 were men and 78 were women (one patient record did not indicate gender), with a mean age of 58 years; 70 patients had cervical dystonia, and 44 patients had blepharospasm (Table 3). Most patients (86%) had had their disorder for more than 5 years, and, based on investigator impression, the majority of cases (67%) were described as moderate in severity.

TABLE 3. *Patient demographics and condition*

	Cervical dystonia	Blepharospasm
Gender, n[a]		
Male	21	14
Female	47	31
Mean age, yr (±SD)	53.61 (12.99)	63.46 (10.88)
Condition	70	44
Onset of condition, n[a]		
<1 year	1	0
1 to 5 years	9	6
>5 years	58	37
Degree of severity, n[a,b]		
Mild	8	1
Moderate	42	32
Severe	16	12
Number of injections		
BOTOX	487	242
Dysport	452	218

[a]May not total 114 because information was not recorded by investigator.
[b]Based on investigators' impression. No formal severity-assessment instrument was used.

TABLE 4. *Mean dose by drug start and condition*

	Dysport units (±SD)	BOTOX units (±SD)
Dysport starts (n = 94)		
Cervical dystonia (n = 63)	601 (±234)	130 (±44)
Blepharospasm (n = 31)	125 (±49)	31 (±10)
Overall mean ratio	4.44	1
BOTOX starts (n = 20)		
Cervical dystonia (n = 7)	468 (±139)	112 (±30)
Blepharospasm (n = 13)	147 (±58)	33 (±12)
Overall mean ratio	4.6	1

Overall mean ratio computed based on mean per-patient ratio.

Ninety-four patients had received Dysport before receiving BOTOX as the crossover drug (Table 4). Among all patients in this Dysport-to-BOTOX crossover subgroup, the mean ratio of doses (i.e., mean per-patient, per-visit delivered dose of Dysport compared to mean per-patient, per-visit delivered dose of BOTOX) was 4.44:1 (i.e., Dysport-to-BOTOX units).

Twenty patients had received BOTOX before Dysport in the drug crossover (Table 4). Among all patients in this BOTOX-to-Dysport crossover subgroup, the mean ratio of doses (i.e., mean per-patient, per-visit delivered dose of BOTOX compared to mean per-patient, per-visit delivered dose of Dysport) was 1:4.6 (i.e., BOTOX to Dysport units).

When mean dose of delivered drug was assessed by the type of disorder being treated (Fig. 1), with the exception of one site per indication, all investigational centers used similar doses of Dysport and similar doses of BOTOX (Figs. 2 and 3) regardless of indication or the

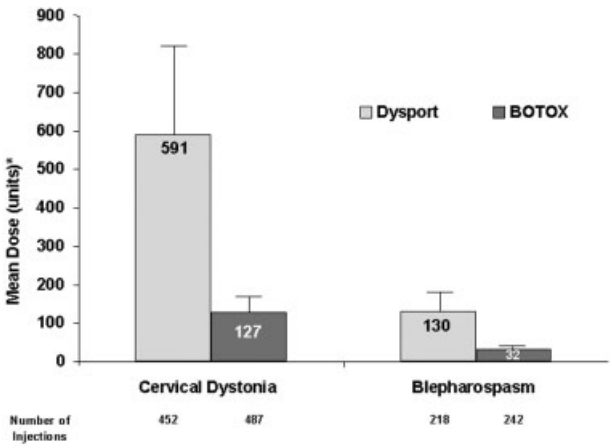

FIG. 1. Mean dose by drug and condition. Mean dose was computed by dividing the total dose by the total number of injections. T-bars indicate standard deviation.

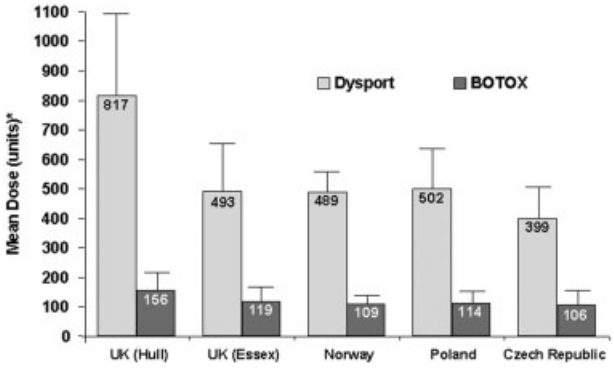

FIG. 2. Mean dose across centers for cervical dystonia. Five centers (excluding Slovenia) provided data on patients with cervical dystonia.

direction of drug crossover. Indeed, mean ratios were highly consistent regardless of location of treatment, direction of the drug switch (i.e., Dysport to BOTOX or BOTOX to Dysport), or the treated condition (i.e., cervical dystonia or blepharospasm; Fig. 4).

A wide distribution of ratios was observed among the 114 patients who were evaluated. The overall mean ratio for the group was 4.48 (n = 114) with a range of computed mean ratios from 2:1 to 11:1 (delivered dose of Dysport compared to delivered dose of BOTOX on a unit-to-unit basis; Fig. 5). The largest number of patients, comprising 31% of the total evaluated population, had a mean ratio of Dysport to BOTOX that fell in a range of 5:1 to less than 6:1 (Table 5). The second largest group, comprising 30% of patients, had a mean ratio of Dysport to BOTOX that fell in a range of 4:1 to less than 5:1, and only 21% of patients fell into the Dysport-to-BOTOX ratio group of 3:1 to less than 4:1. Closer examination of the remaining 21 patients who had ratios of less than 3:1 or greater than 6:1 indicated that the dosing profile was stable for all of these patients except for 4 patients who exhibited dramatic titration from visit to visit.

The majority of reported ADRs were noted while patients were receiving Dysport (11.0% of all side effects reported) compared to BOTOX (4.25% of all side effects reported). While on Dysport, 37 patients had reported at least one ADR. While on BOTOX, 22 patients reported at least one ADR. The most commonly reported ADR in the subgroup of patients with cervical dystonia was dysphagia, whereas ptosis was the most commonly reported ADR in the blepharospasm subgroup (Table 6). Among patients who reported an ADR, the total mean toxin dose was lower than that observed for patients not reporting an ADR, regardless of toxin or condition.

DISCUSSION

The objective of this medical records review was to evaluate drug utilization in the form of actual delivered doses of Dysport and BOTOX used in real clinical practice in the treatment of patients with cervical dystonia and/or blepharospasm. Previously reported toxin doses and dose ratios (Dysport to BOTOX) generally were arbitrarily chosen on the basis of a predetermined conversion factor used in a clinical study or single-dose response evaluation. Consequently, the dosing information and techniques that arise from single-dose studies may not accurately reflect actual clinical practice in which dose titration for maximum effect and minimum adverse event occurrence is used. The observational research reported here (The REAL DOSE Study) captured drug utilization usage based on the actual practice of respected physicians who have recognized expertise in the management of patients with movement disorders.

The relative doses and wide distribution of dosing ratios observed in this study indicate that no simple conversion factor exists for botulinum toxins, regardless of drug start and that each patient is managed according to his or her individual need and therapeutic response. A conversion factor (3 units of Dysport to 1 unit of BOTOX) suggested by some[12,13] was not widely observed in this evaluation and calls into question the appropriateness of using a set ratio when trying to establish the optimum dose for patients with varying conditions. In the population of patients evaluated in this study, only 21% were treated with doses of Dysport and BOTOX that converted into a ratio ranging from 3:1 to less than 4:1 (Dysport to BOTOX) after a therapeutic switch was performed, and more than 66% of patients had received the toxins in a dose ratio that was 4:1 or greater (Dysport to BOTOX). It should be noted that the mean ratio was similar regardless of drug start (4.4 for Dysport start [n =

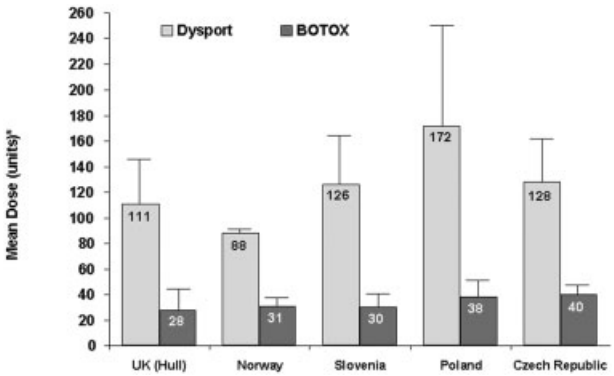

FIG. 3. Mean dose across centers for blepharospasm. Five centers (excluding UK [Essex]) provided data on patients with blepharospasm. T-bars indicate standard deviation.

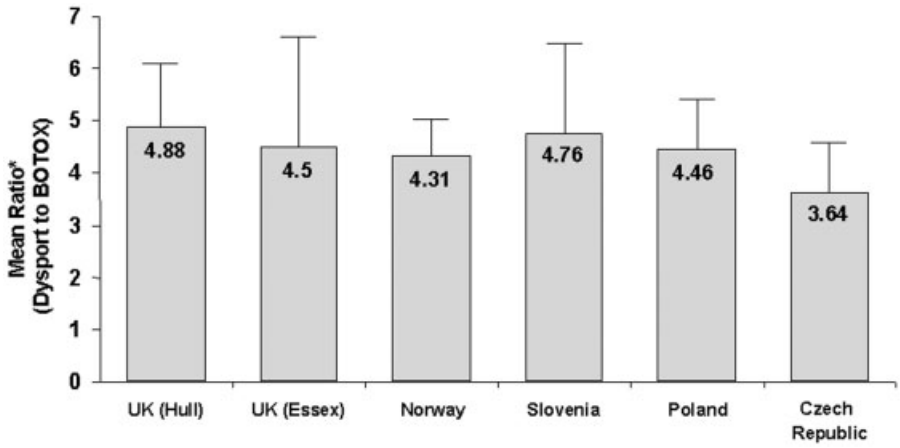

FIG. 4. Mean ratio by center. Grand mean of per-patient ratios across all patients was 4.48. T-bars indicate standard deviation.

94] vs. 4.6 for BOTOX starts [n = 20]), suggesting that the mean conversion ratio reported is stable, although fewer cases of BOTOX starts were included in the evaluation compared to Dysport starts. Further work currently is under way to evaluate this finding with a larger sample size.

Seven patients had a dose–conversion ratio equal to or greater than 6:1. The overall impact on the mean dose ratio of Dysport to BOTOX by removing these patients from the analysis did not significantly change mean ratio (4.48 to 4.23, $P = 0.09$). It should be noted that these patients represent real findings, and, as such, what may be perceived as outliers should nevertheless be considered as part of the evaluation. Ignoring them may simply overstate or understate the real-world utilization of both products. Although the Hull center had higher dose utilization than that of other centers, its overall dose-conversation ratio was not statistically different from that of other sites. The mean ratios with and without the Hull data are 4.48 and 4.32, respectively ($P > 0.05$). Furthermore, the incidence of ADRs reported at Hull were similar at two centers (Czech Republic and Slovenia), with the remaining three centers reporting fewer side effects. The relationship between dose and incidence of ADRs should be addressed prospectively.

Effectiveness measures, such as the Toronto Western Spasmodic Torticollis Rating scale and the Jankovic scale, are not routinely used in clinical practice. Consequently, these data were not collected and reported in the findings of this observational research. However, the standard practice of dose titration to achieve maximum clinical benefit and minimal incidence of adverse events was used by the physicians who served as study investigators, and no diminution of therapeutic response was noted among patients who had received both toxins in the crossover design. Moreover, according to the physician investigators involved in the study, therapeutic effectiveness was maintained during the clinical assess-

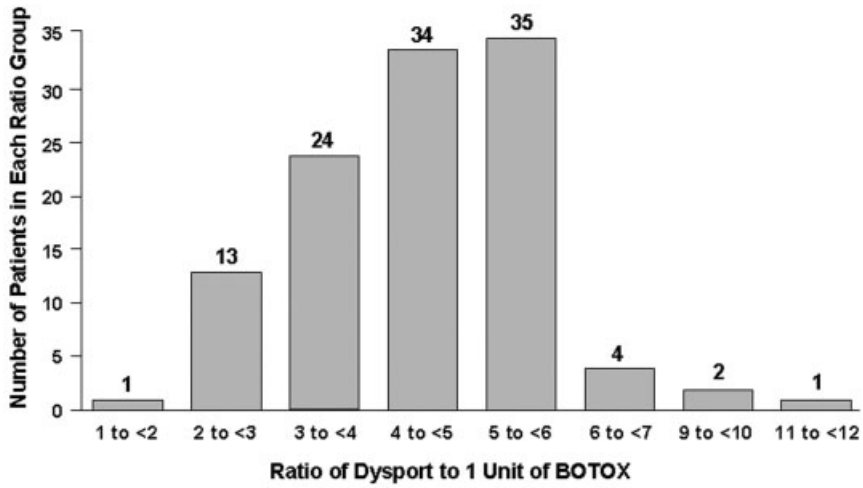

FIG. 5. Number of patients within each ratio group. Total injections = 1,399; n = 114.

ment period of at least 2 years (1 year or more on drug before and after the crossover), based on the implicit assumption that patients choosing to remain on drug were being controlled satisfactorily. Patients who were not responsive to either toxin during the clinical assessment period would have been excluded from the study based on screening criteria. Duration of effect was not reported, because injection visits were scheduled and not determined by the need for injection. Prospective evaluations are necessary to better understand both the duration and the magnitude of drug effect.

Identifying centers to provide patients who were treated with both products was very challenging. The centers identified for this study switched patients from one product to the other because of payor pressure or the unavailability of either product. Because the study objective was to assess utilization of both products, these patients comprised a valid cohort for evaluation.

Data and information related to ADRs experienced in actual clinical practice are generally reported during subsequent visits and interviews, not by formal diary or other types of reporting systems common in clinical trials. Although these data may lack the rigor of more formally captured information, they can highlight obvious problems that persist in the minds of patients. These types of data were collected as part of the observational research herein reported. Differences in reported rates of ADRs may be meaningful, because each patient had received both toxins by virtue of the drug crossover design that had occurred during their treatment.

Botulinum neurotoxin preparations cannot be accurately compared by using a dose-conversion ratio. The most that can be gleaned from the doses used in trials and in clinical settings is that such doses represent the distinct effective unit range of each product, not an empirically derived conversion ratio that will predictably yield a comparable safety and efficacy profile of the alternate formulation of botulinum neurotoxin. Clinical decisions regarding the use of neurotoxins, therefore, should be made independently of dose-conversion factors that have not been established or accepted by a consensus of practitioners. Such decisions should be made on the basis of established safety and effectiveness of each product for various disorders, commonly used doses used in clinical practice, and individual patient profiles.

TABLE 5. *Percentage of patients in each ratio group*

Proportion of total patients, % (N = 114)	Patients (n)	Ratio (Dysport to BOTOX), units
30.7	35	5 to <6
29.8	34	4 to <5
21.1	24	3 to <4
11.4	13	2 to <3
3.5	4	6 to <7
1.8	2	9 to <10
0.9	1	1 to <2
0.9	1	11 to <12
0	0	7 to <8
0	0	8 to <9
0	0	10 to <11

TABLE 6. *Reported adverse drug reactions by drug and condition*

	Dysport	BOTOX
Cervical dystonia		
Dysphagia	19	12
Other - total	13	4
Flu-like symptoms	4	0
Paresthesia of the tongue and lips	1	0
Neck weakness	1	1
Dysarthria	1	0
Dysphonia/swelling of the neck	1	0
Paresthesia of right arm	2	0
Early wearing off	1	0
Twitching	1	0
Pain	2	2
Throat pain	0	1
Blepharospasm		
Ptosis	29	12
Double vision	5	0
Other - total	8	3
Numb mouth	4	0
Droopy mouth	4	0
Unclear vision	0	1
Flu-like symptoms	0	1
Increased hanging of left side of mouth	0	1

Total reported ADRs. Same patient may have reported more than one ADR. ADR, adverse drug reaction.

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