Botulinum toxin type B (Myobloc™, NeuroBloc™): a new choice in cervical dystonia

Mark F Lew

Botulinum toxin has dramatically improved the treatment of cervical dystonia. Prior to the use of botulinum toxin for many neurologic disorders, patients had few effective therapeutic options. Botulinum toxin type B (Myobloc™, NeuroBloc™) is a new antigenically distinct botulinum toxin with a unique structure and mechanism of action. Preclinical studies have demonstrated that im. injections of botulinum toxin type B effectively induce a dose-dependent paralysis. Controlled clinical trials have shown that it is safe and effective in alleviating symptoms associated with cervical dystonia. Given its efficacy and safety profile, the clinical use of type B toxin is anticipated to expand into other therapeutic areas.

Contents

Keck School of Medicine, University of Southern California, 1510 San Pablo St, Suite 268, Los Angeles, CA 90033-4606, USA
Tel.: +1 323 442 5728
Fax: +1 323 442 5887
mlew@surgery.usc.edu

KEYWORDS:
acetylcholine blockade, botulinum toxin type B, cervical dystonia, chemical denervation, Myobloc, NeuroBloc, neuromuscular blocking agent, neuromuscular disorder, neurotoxin, spasmodic torticollis

Cervical dystonia is the most common form of focal dystonia [1]. It is characterized by involuntary, patterned contractions of cervical and/or shoulder muscles, causing sustained twisting movements and abnormal postures of the head and neck. Permanent contractures may result from lack of proper treatment. Nearly all patients with cervical dystonia report some degree of disability, ranging from mild-to-severe [2]. Pain is a prominent feature of cervical dystonia and contributes greatly to the disability [3–5]. Although cervical dystonia is not life-threatening, it can dramatically impair the patient's ability to lead a normal life and has been shown to have a negative impact on psychological well-being [6,7].

Cervical dystonia does not respond in a robust fashion to conventional pharmacological or surgical treatments. For many years, oral medications, such as anticholinergics, muscle relaxants and anticonvulsants, were used as first-line therapy. The majority of patients have troublesome side effects from therapeutic doses of virtually all of these medications and the benefits tend to decrease over time [8,9]. Nonpharmacological modalities (physical therapy, hypnotism, biofeedback, acupuncture) have also been employed, but with limited success [10]. Surgical denervation of the involved musculature is invasive, irreversible and frequently unsuccessful over the long-term [11–13].

Botulinum toxin for cervical dystonia

Given the inadequacies of traditional therapies, botulinum toxin therapy has become a welcome addition to the treatment armamentarium for cervical dystonia. The toxin blocks the presynaptic release of acetylcholine at the neuromuscular junction, causing a chemical denervation and subsequent reduction in muscle hypercontractility. The therapeutic value of botulinum toxin is related to its extraordinary specificity, potency, long duration of efficacy and virtual absence of systemic effects [14,15]. Approximately 75% of patients with cervical dystonia improve with botulinum toxin therapy [16]. The initial response to treatment is typically seen in the first 1–2 weeks after im. injection. The maximum response typically occurs within 4 weeks and the effect routinely lasts 3–4 months [10,17]. Multiple studies have illustrated that botulinum toxins are tremendously valuable in treating a variety of neurologic and non-neurologic disorders [18].

Seven antigenically distinct serotypes of botulinum toxin have been identified: A, B, C$_1$, D, E, F and G. The toxin types are identified by their absence of cross-neutralization (for example,

antiA antitoxin does not neutralize the effects of toxin types B–G) [19]. In addition, there are inherent structural, mechanistic and processing differences among serotypes that may translate to differences in clinical efficacy and safety. These differences are only currently evolving, but may become more evident in the clinical setting as more studies are completed and more knowledge is gained. The largest body of clinical experience has been attained with botulinum toxin type A (Botox®, Dysport®; Botox commercially available since 1989). Botulinum toxin type B (marketed as Myobloc™ in the USA and NeuroBloc™ in Europe) is the newest agent to become available (FDA approved for the treatment of cervical dystonia in December, 2000) and is the focus of this article. Clinical experience is currently emerging with botulinum toxin types C and F [20–23].

Limitations of botulinum toxin in cervical dystonia
Secondary resistance
Despite the profound benefit that patients with cervical dystonia experience with botulinum toxin, there are limitations to its use. Experience with the type A toxin has shown that a small percentage of patients fail to respond from the outset (primary nonresponders) and a larger percentage fails after one or more treatment injections (secondary nonresponders) [10]. The latter has been related to the development of neutralizing antibodies that inactivate the clinical effects of the toxin. This is characterized by the absence of denervation and muscle atrophy following an injection [24,25]. High doses, increased frequency of administration and longer duration of treatment are factors that may increase the risk for antibody formation [26–28].

Based on a body of literature derived from retrospective and anecdotal reports, it has been reported that approximately 3–5% of cervical dystonia patients treated with the type A serotype develop secondary resistance [26,29,30]. These reports probably underestimate the actual incidence of secondary resistance, as some patients in the study population had only received a single injection while others were lost to follow-up. No long-term, prospective studies have yet to elucidate the natural history of antibody formation with botulinum toxin type A. However, the improved current formulation of botulinum toxin type A has been shown in rabbit studies to have less immunogenic potential than the original batch (#79-11) [31]. While there is currently no data available addressing the occurrence of secondary resistance to botulinum toxin type B, a large prospective long-term, open-label trial in more than 400 patients with cervical dystonia has been recently completed and may add significant knowledge about resistance to botulinum toxin type B.

Spread effects
Another evolving concern with botulinum toxin therapy is the potential spread of toxin to muscles distant from the site of im. injection [32,33]. Spread of toxin to nearby or adjacent muscles (believed to occur through local diffusion) may be beneficial in some clinical circumstances (such as spasticity). However, spread of toxin to relatively distant sites may pose a safety concern, as it may reflect systemic contact. A recent report documented three patients who developed generalized weakness consistent with mild botulism following treatment with therapeutic doses of botulinum toxin type A [34]. In one of these patients, denervation in distant muscles was confirmed on biopsy. Overall, cases of generalized weakness with botulinum toxin therapy are very rare and in such cases, it is often difficult to ascertain whether the event is truly a drug-related effect or a result of injection technique.

Introduction to botulinum toxin type B
Structural Features
Botulinum neurotoxin type B is synthesized as a single polypeptide chain (1290 amino acid residues long) about 150 kD in weight. In its native state, the neurotoxin exists within a large multiprotein complex that consists of several nontoxic bacterial peptides [35]. The total molecular weight of the type B toxin complex is approximately 700 kD and the complex is most stable in an acidic environment (pH 5–7) [36]. Due to the instability of the neurotoxin moiety, commercial preparations of botulinum toxin consist of purified forms of these multiprotein complexes. The nontoxic proteins function to preserve the stability of the neurotoxin during its manufacture and upon injection into patients [37,38].

The 150 kD neurotoxin is not fully active until it undergoes proteolytic cleavage or 'nicking' by endogenous bacterial proteases [35]. The protein in botulinum toxin type B is approximately 75% nicked, although tissue proteases may produce additional nicking *in vivo* following an im. injection. The cleaved (nicked) protein is transformed into a dichain molecule composed of a light (~ 50 kD) and heavy chain (~ 100 kD), linked by a disulfide bond (FIGURE 1) [39]. Reduction of the disulfide bond separates the dichain and results in a loss of toxicity [40]. The heavy chain can be subdivided into a C-terminal domain (H_C) and N-terminal domain (H_N). Importantly, the H_C domain is the region with the most dissimilarity in amino acid sequence among serotypes. It is
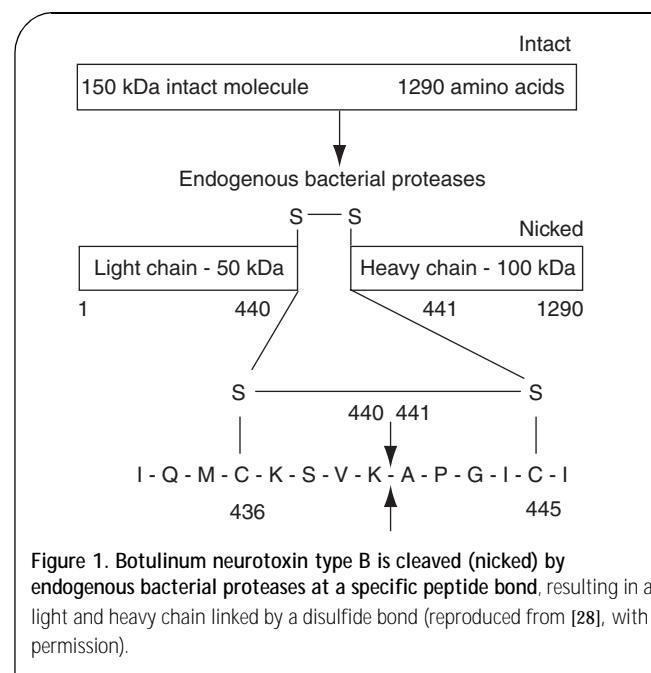

Figure 1. Botulinum neurotoxin type B is cleaved (nicked) by endogenous bacterial proteases at a specific peptide bond, resulting in a light and heavy chain linked by a disulfide bond (reproduced from [28], with permission).

this domain that uniquely characterizes each serotype and contributes to their distinct antigenicities [41,42]. The light chain contains the protein sequence that effects neurotoxicity [43].

Mechanism of action

Botulinum toxins act selectively on peripheral cholinergic nerve endings to inhibit presynaptic acetylcholine release. Toxin-induced neuromuscular blockade is believed to be a three-step process [44,45]:

- H_C binds to serotype-specific acceptors on the presynaptic side of motor nerve terminals. Importantly, each serotype because of its unique H_C domain, has affinity for its own acceptors
- Receptor-mediated endocytosis causes internalization of the toxin/acceptor complexes, followed by release of the vesicle-enclosed light chains into the cytosol
- Light chain cleaves at a specific site on an intracellular target protein responsible for vesicle docking and fusion to the presynaptic membrane

Botulinum toxin type B catalyzes the cleavage of synaptobrevin (also called vesicle-associated membrane protein: VAMP) at the peptide bond between glutamine-197 and phenylalanine-77 [46]. This prevents the release of acetylcholine into the synapse [47,48]. Botulinum toxins type D, F and G all cleave synaptobrevin/VAMP, but at different loci on the protein.

Manufacturing process

Myobloc is produced as a sterile liquid formulation containing purified botulinum toxin type B complexes in slightly acidic medium (pH 5.6). The maintenance of this agent in slightly acidic medium ensures that the toxin complex remains stable and intact during its manufacture and upon injection. In addition, production of Myobloc as a liquid formulation avoids the lyophilization (freeze-drying) process used in the manufacture of botulinum toxin type A preparations. Lyophilization may cause denaturation, which results in a loss of specific activity [37].

To manufacture Myobloc, cultures of *Clostridium botulinum* derived from Type B, Bean strain seed stock are established in an anaerobic fermenter. Toxin is recovered by precipitation and filtration and then further purified by a series of chromatography and filtration steps to yield toxin for commercial use. The robustness and reproducibility of the manufacturing process have been demonstrated under highly stringent conditions of fermentation, recovery and precipitation. In addition, analytical tests on the different batches of the final product show that the type B complexes are highly purified, remain intact throughout the manufacturing process and are consistent from batch-to-batch. Myobloc is stable for at least 36 months in refrigerated conditions and for 9 months at room temperature [49].

Neurotoxic activity

At the present time, there is no sufficiently sensitive biochemical assay that can measure the neurotoxic activity of botulinum toxins. The most commonly used assay is the mouse LD_{50} bioassay.

The LD_{50} is the dose that is lethal in 50% of mice following an ip. injection; this dose correlates with one activity unit (U) of toxin. Difficulties exist with the use of the mouse LD_{50} bioassay. The assay is not standardized (differences in vehicle and dilution scheme between laboratories). In addition, animal species are known to be differentially sensitive to the different botulinum toxin serotypes [28,50]. Consequently, dosing effects cannot be extrapolated from mice to humans. Potency comparisons between serotypes cannot therefore, be made appropriately based on the number of mouse units required to achieve a desired effect.
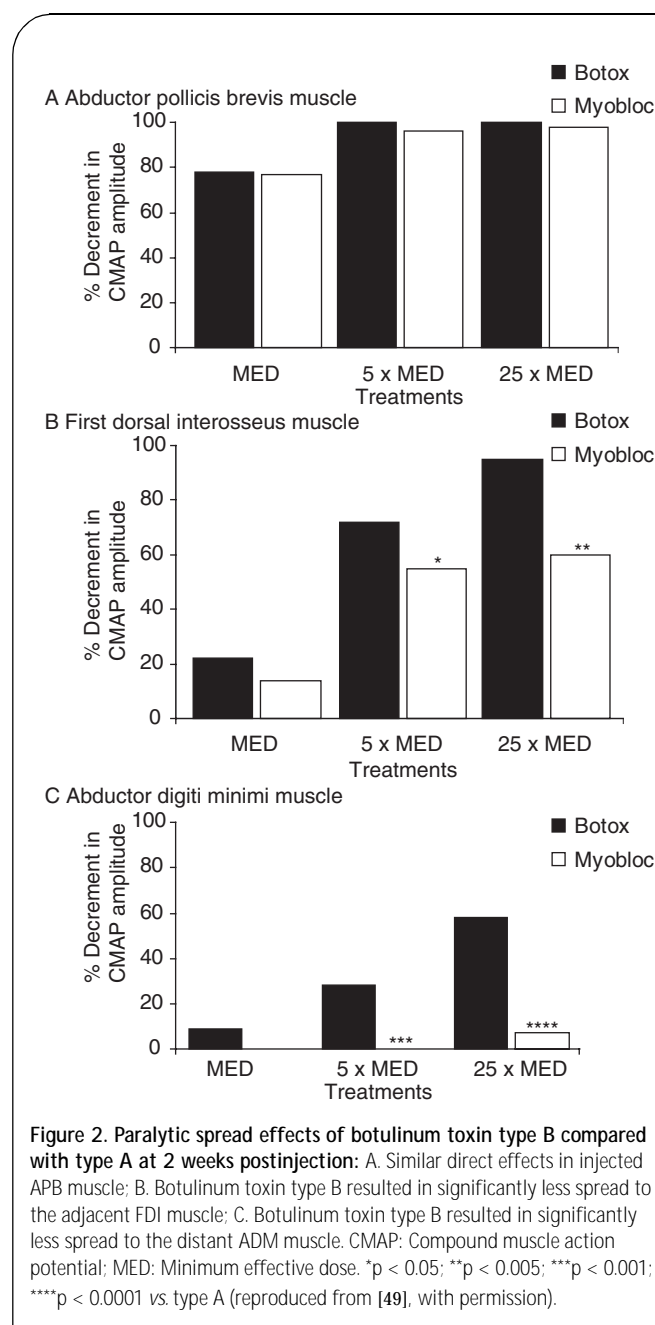
Specific activity can be used as a measure to determine more appropriately the potency of Myobloc. It is calculated as the ratio of mouse LD_{50} potency (U/ml) to concentration of toxin (ng/ml). The specific activity of Myobloc is reported to range between 90 and 107 U/ng [49]. Comparatively, the specific activity of Botox is 20 U/ng [51].

Pharmacological studies

The ability of botulinum toxin type B to induce paralysis following im. administration has been verified using electrophysiological techniques in nonhuman primates [52]. It is well established that a reduction in the peak amplitude of the compound muscle action potential (CMAP) is consistent with a clinical reduction in muscle contraction that is characteristic of botulism [53]. This measurement has been validated as an index of botulinum toxin-induced paralysis in rats and monkeys [52,54]. Thus, comparing the peak amplitude in the CMAP before and after injection allows quantification of the degree of muscle paralysis. Studies in cynomolgus monkeys showed that botulinum toxin type B effectively paralyzed injected muscles (abductor pollicis brevis: APB, muscle of the thumb and the extensor digitorum brevis: EDB, muscle of the foot). At 2 weeks following injection, a greater than 80% reduction in CMAP was observed for all subjects at all doses tested (5–80 U/muscle). Botulinum toxin type B exhibited a dose-related, time-dependent paralysis of skeletal muscle lasting at least 3 months [50].

Spread effects

Electrophysiological techniques also have proved useful in investigating the spread of botulinum toxin to noninjected muscles. In a study consisting of 30 monkeys (10 animals per dose group), the relative spread of botulinum toxin type B was compared with botulinum toxin type A (Botox) [49]. Changes in the amplitude of the evoked CMAP were measured in the injected muscle (APB), in neighboring muscles (first dorsal interosseous: FDI) and in relatively distant muscles (abductor digiti minimi: ADM) of the monkey hand. Values were determined at baseline and 2 weeks postinjection. One APB of each monkey was injected with botulinum toxin type B and the contralateral APB with an equivalent dose of botulinum toxin type A. Doses included the minimum effective dose (MED), 5 times the MED and 25 times the MED. Results confirmed a dose-dependent spread of the effects of toxin. In the injected APB, both toxins induced nearly 100% paralysis of the muscle. However, in nearby (FDI) and distant (ADM) noninjected muscles, botulinum toxin type B exhibited significantly less spread compared with type A (FIGURE 2) [49].

Figure 2. Paralytic spread effects of botulinum toxin type B compared with type A at 2 weeks postinjection: A. Similar direct effects in injected APB muscle; B. Botulinum toxin type B resulted in significantly less spread to the adjacent FDI muscle; C. Botulinum toxin type B resulted in significantly less spread to the distant ADM muscle. CMAP: Compound muscle action potential; MED: Minimum effective dose. *p < 0.05; **p < 0.005; ***p < 0.001; ****p < 0.0001 *vs.* type A (reproduced from [49], with permission).

Toxicity studies

Studies in adult and juvenile cynomolgus monkeys showed that the toxicity of Myobloc is limited to its pharmacological action of reversible local skeletal muscle paralysis [55]. The monkeys in these studies were observed for clinical signs indicative of botulinum toxin poisoning. The maximum tolerated im. dose in the adult monkey was 1990 U/kg. At this dose, the effects were reversible and considered not life-threatening. The approximate lethal dose was 2400 U/kg. On a U/kg basis, this dose is nearly 17-fold higher than the therapeutic dose of Myobloc (10,000 U) administered to humans (70 kg) with cervical dystonia [56,57]. In juvenile monkeys, Myobloc was well-tolerated at all doses tested (up to 1920 U/kg).

Pharmacokinetics & drug interactions

Pharmacokinetic or ADME (absorption, distribution, metabolism, excretion) studies have not been performed. Myobloc is not expected to be present in the peripheral blood at measurable levels following local im. injection of therapeutic doses.

Concurrent administration of Myobloc and aminoglycosides or other agents interfering with neuromuscular transmission (such as curare-like compounds) should be performed with caution as the effect of the toxin may be potentiated. The effect of administering different botulinum toxin serotypes at the same time or within less than 4 months of each other is unknown. Neuromuscular paralysis may be potentiated, however, by coadministration or overlapping administration of different serotypes [58].

Clinical profile of botulinum toxin type B for cervical dystonia

Overview of clinical program

Myobloc has been evaluated as a therapeutic agent for the treatment of cervical dystonia in four placebo-controlled studies and five open-label studies, performed in the USA, Canada and the UK. A total of 568 patients have been exposed to botulinum toxin type B at doses of up to 25,000 U (FIGURE 3). In the three clinical pharmacology studies, 48 patients with cervical dystonia received 88 doses of Myobloc, ranging from 100 U to 12,000 U. Improvements in signs and symptoms of cervical dystonia tended to increase and to last longer with increasing doses [59–61]. Controlled clinical studies consisted of two supportive trials [62,63], which provided the basis for doses used in the two pivotal trials [56,57]. Data from the uncontrolled, open-label studies suggest that doses up to 25,000 U are safe and effective in patients with cervical dystonia [64,65]. In all studies, botulinum toxin type B was found to be safe and well-tolerated. Results of the two pivotal trials that were the basis of approval for Myobloc in the USA and Europe are reviewed herein.

Pivotal studies

Study designs

Both pivotal trials were performed in a multicenter, 16-week, single-treatment, randomized, double-blind, placebo-controlled fashion. The first study (n = 109) included patients with cervical dystonia who were type A toxin responsive and evaluated botulinum toxin type B at doses of 5000 U (n = 36) and 10,000 U (n = 37) [56]. The second study (n = 77) included only patients who were resistant to botulinum toxin type A and examined botulinum toxin type B at a dose of 10,000 U (n = 38) [57]. Resistance was confirmed using a frontalis type A test (F-TAT), which consisted of an injection of 15 U of botulinum toxin type A in the right frontalis muscle. Patients were considered type A-resistant if they were able to wrinkle their right frontalis muscle 2 weeks after the F-TAT injection, indicating no weakness of that muscle. In both studies, patients were randomized to receive im. injections of botulinum toxin type B or placebo into 2–4 affected neck and/or shoulder muscles.
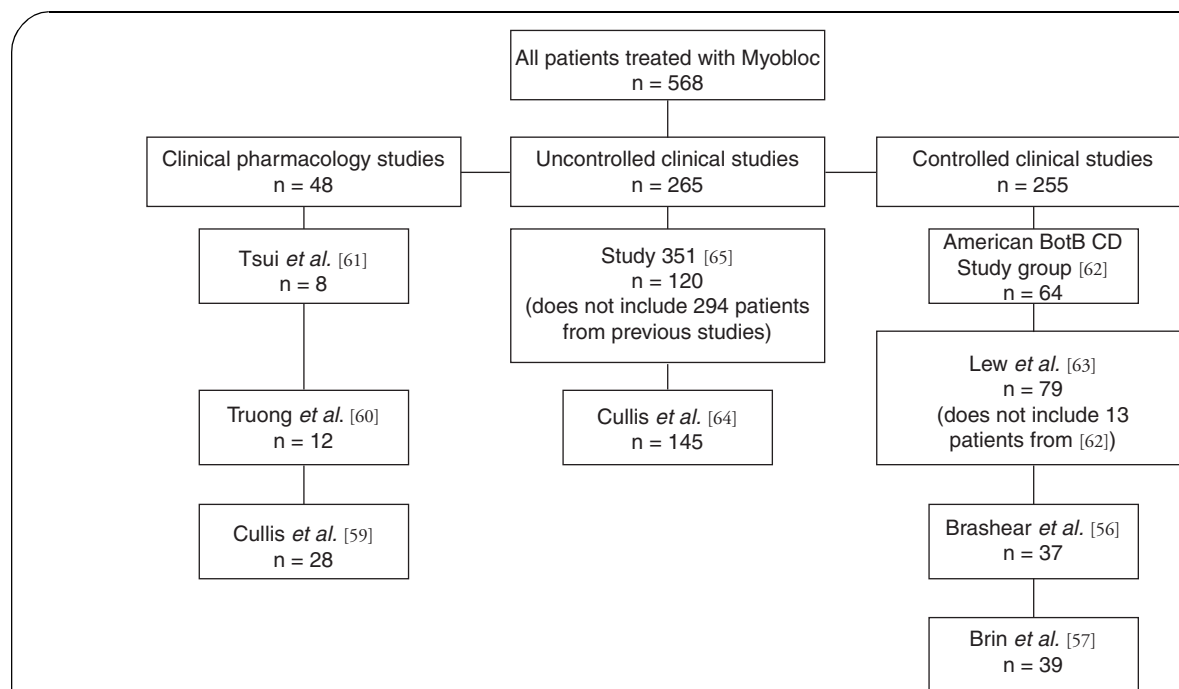
Figure 3. Overview of clinical research program for botulinum toxin type B. Note: number of patients represents only those who received treatment with Myobloc and does not include patients who received placebo. CD: Cervical dystonia.

Efficacy & safety assessments

The primary efficacy assessment was the change in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score (range 0–87) from baseline to week 4. The TWSTRS is a validated outcome measurement for cervical dystonia and consists of three subscale scores, including:

- 'Severity' of abnormal head positioning (range 0–35)
- 'Disability,' the effects of abnormal head positioning and pain on daily activities (range 0–32)
- Severity and duration of 'Pain' (range 0–20)

In either study, patients had a baseline TWSTRS-Total score of at least 20 at entry. Other efficacy assessments included the patient and investigator global assessments of change and patient analog pain assessments. These assessments were completed using a 100 mm visual analog scale. The duration of effectiveness was determined using Kaplan-Meier survival analyses, based on the time to return to baseline TWSTRS-Total score. Safety was assessed by collecting adverse event data at each visit during the studies and obtaining vital signs and clinical laboratory data.
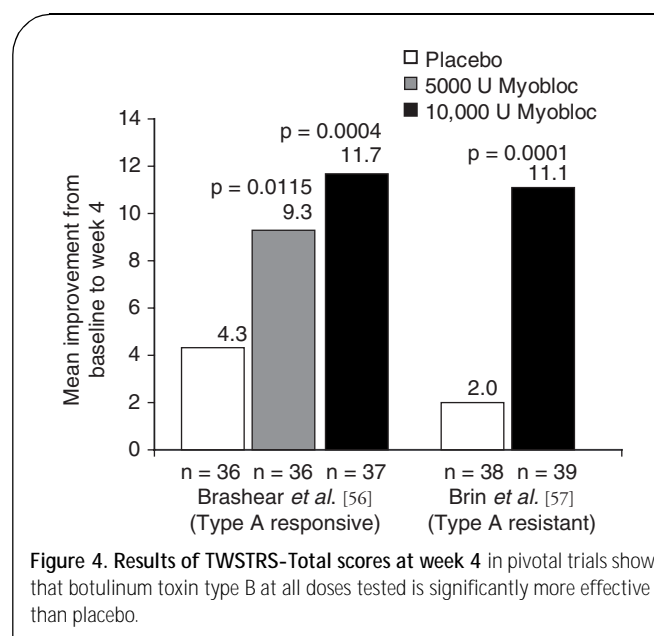
Efficacy results

The treatment groups were well-balanced in terms of demographic and baseline characteristics and there were no statistically significant differences among the studies and across treatment groups. Overall, patients had mean baseline TWSTRS-Total scores ranging from 40 to 55, signifying moderate-to-severe cervical dystonia. In both studies, statistically significant improvements were demonstrated in the botulinum toxin type

B (5000 and 10,000 U) *versus* placebo groups for the TWSTRS-Total scores at week 4 (FIGURE 4). Clinical benefit tended to be greater with the 10,000-U dose. In the study with type A-responsive patients, results of the TWSTRS-subscale scores taken separately were significant for the TWSTRS-pain at both doses and TWSTRS-severity at the higher 10,000-U dose. Improvements in each of the TWSTRS-subscale scores were significant in the other study, which evaluated botulinum toxin type B at the 10,000-U dose only.

Results of other efficacy assessments similarly tended towards a dose-response relationship. Improvements with botulinum toxin type B treatment were significant in the patient and physician global assessments of change. In addition, statistically significant improvements were seen in the patient analog pain assessment (FIGURE 5). Kaplan-Meier analyses showed that the median duration of effect of both doses of botulinum toxin type B was 12–16 weeks in both type A-responsive and type A-resistant group. This correlates well with the clinical pharmacology and earlier supportive studies.

Safety

Botulinum toxin type B was shown to be safe and well-tolerated in the two pivotal trials. The most commonly reported treatment-related adverse effects were dry mouth and dysphagia, which occurred more often in patients who received 10,000 U (TABLE 1). In the study with type A-responsive patients, the incidence of dry mouth was 24% with the 10,000-U dose. Comparatively, in the study with type A-resistant patients, this incidence was 44%. The intensity of dry mouth and dysphagia was generally reported to be mild

Figure 4. Results of TWSTRS-Total scores at week 4 in pivotal trials show that botulinum toxin type B at all doses tested is significantly more effective than placebo.

and the majority of episodes were self-limited. None of the cases required intervention and no patients discontinued from the studies as a result of dry mouth or dysphagia. It should be noted that several studies have illustrated that many patients with cervical dystonia have evidence of pre-existing dysphagia [66,67]. This may be predisposing factor to the dysphagia reported with botulinum toxin treatment. The incidences of other types of adverse effects (such as injection site pain) were similar between placebo and active treatment groups. No systemic toxicity was observed and no clinically significant changes in vital signs or laboratory values occurred in either study.

Expert opinion

Botulinum toxin injections represent the most efficacious treatment for managing the symptoms associated with cervical dystonia. Compared with traditional pharmacological therapy, botulinum toxin effects more profound benefits in a greater percentage of patients, has a specific and predictable dose-response outcome, and has a more tolerable side effect profile. In November, 1990, the National Institutes of Health (NIH) Consensus Development Conference concluded that botulinum toxin therapy is safe and effective and may be the treatment of choice for patients with cervical dystonia [68]. At the time of the NIH Conference, the type A toxin was the only serotype commercially available. Throughout the years of clinical experience with botulinum toxin type A, it has become evident that there are limitations to its use, the most apparent being development of secondary resistance, which prevents further injections from being effective.

Botulinum toxin type B is a valuable and important addition to the therapeutic armamentarium for cervical dystonia. Controlled clinical trials have demonstrated the safety and efficacy of this agent for use in cervical dystonia. Collectively, these studies support the use of botulinum toxin type B as therapy in patients

responsive or resistant to botulinum toxin type A. The clinical profile of botulinum toxin type B is similar to type A in many ways, including: dose-dependent muscle paralysis, relief of symptoms, duration of efficacy and the types and frequencies of adverse effects. Many differences characterize botulinum toxin type B as a unique chemical entity. On the molecular level, it is structurally unique and antigenically distinct and cleaves a different intracellular target protein to prevent acetylcholine release. On a pharmacological level, primate studies have shown that it exhibits significantly less spread to distant noninjected muscles compared with botulinum toxin type A. This may have implications in terms of control and safety in clinical use. In terms of its manufacturing process, botulinum toxin type B is developed as a highly purified and stable liquid formulation that does not undergo lyophilization or require reconstitution prior to use. These factors may decrease the risk of neutralizing antibody formation. Further clinical experience with botulinum toxin type B will reveal whether these differences will truly have an impact on overall clinical response and safety.

Five-year view

In the next 5 years, botulinum toxin type B should prove to be a tremendously useful and powerful therapeutic tool. Clinical trials are currently underway to determine its potential efficacy in numerous other therapeutic areas, including: other dystonias, spasticity, pain, headache and dermatologic conditions.

Information resources

The website for Myobloc can be found at www.myobloc.com. Most cervical dystonia sites are geared towards patients. Several sites including the WE MOVE (World Education and Awareness for Movement Disorders) site and the Dystonia Medical Research Foundation (DMRF) are the most comprehensive and contain information for both healthcare professionals and patients. The website addresses for these associations are www.wemove.org and www.dystonia-foundation.org, respectively.
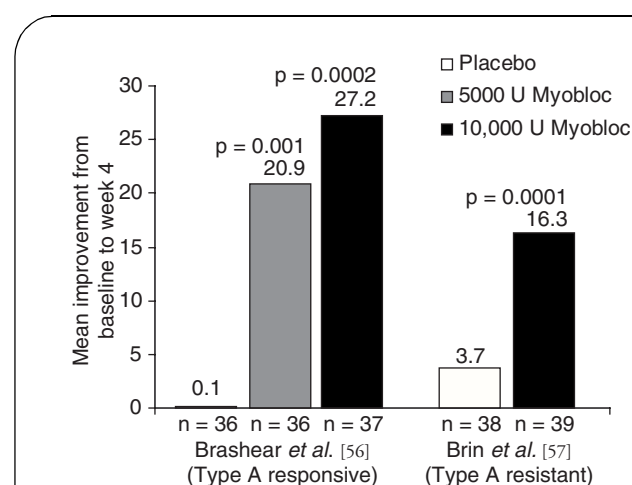

Figure 5. Results of Patient Analog Pain Assessments show that botulinum toxin type B significantly reduces the pain associated with cervical dystonia.

Table 1. Adverse events reported with a frequency ≥10%[§], by study.

| Adverse Event | Patients (%) | | | | |
| | Brashear *et al.* [56] (type A-responsive patients) | | | Brin *et al.* [57] (type A-resistant patients) | |
	Placebo (n = 36)	*5000 U (n = 36)*	*10,000 U (n = 37)*	*Placebo (n = 38)*	*10,000 U (n = 39)*
Dry mouth	3	14	24	3	44
Dysphagia	3	11	22	5	28
Pain secondary to CD	25	31	27	21	21
Infection	28	25	8	16	21
Injection site pain	8	6	11	8	18
Headache	8	25	14	–	–
Flu syndrome	–	–	–	–	–
Nausea	–	–	–	8	15
Pain	14	6	24	–	–
Dyspepsia	8	3	11	–	–

[§]Percentage databased on within-group determinations. CD: Cervical dystonia.

Journal articles related to the use of botulinum toxin type B include:

- Brashear A, Lew MF, Dykstra DD *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A responsive cervical dystonia. *Neurology* 53(2), 1439–1446 (1999).

- Brin MF, Lew MF, Adler CH *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dysplasia. *Neurology* 53(7), 1431–1438 (1999).

- Callaway JE, Arezzo JC, Grethlein AJ. Botulinum toxin type B: an overview of its biochemistry and preclinical pharmacology. *Sem. Cut. Med. Surg.* 20(2), 127–136 (2001).

- Lew MF, Adornato BT, Duane DD *et al.* Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. *Neurology.* 49, 701–707 (1997).

- Setler P. The biochemistry of botulinum toxin type B. *Neurology* 55(Suppl. 5), S23–S28 (2000).

Key issues

- Therapeutic use of botulinum toxin has revolutionized the treatment of cervical dystonia and is the treatment of choice for this disorder.

- Botulinum toxin produces its therapeutic effect of muscle weakness by inhibiting acetylcholine release from the neuromuscular junction.

- Botulinum toxin serotypes are antigenically distinct – antibodies developed against one serotype do not cross-neutralize the effects of another serotype.

- The manufacturing of botulinum toxin type B as a liquid formulation ensures that the toxin complex remains intact and stable before and upon injection, potentially reducing the risk of antibody formation.

- In preclinical studies with nonhuman primates, im. injection of botulinum toxin type B was associated with less spread to distant noninjected muscles than type A toxin.

- Botulinum toxin type B at doses of 5000 or 10,000 U is effective in relieving the pain and excessive muscle contractions associated with cervical dystonia.

- The benefit of botulinum toxin type B is evident in patients with cervical dystonia who respond to botulinum toxin type A and similarly in those who have developed secondary resistance to botulinum toxin type A.

- The duration of efficacy of botulinum toxin type B is 12–16 weeks.

- Botulinum toxin type B is safe and well-tolerated at doses up to 25,000 U.

- Dry mouth and dysphagia are the most common adverse effects and are generally mild and self-limited, requiring no intervention.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1   Nutt JG, Muenter MD, Melton LJ III, Aronson A, Kurland LT. Epidemiology of dystonia in Rochester, Minnesota. *Adv. Neurol.* 50, 361–365 (1988).

2   Rondot P, Marchand MP, Dellatolas G. Spasmodic torticollis – review of 220 patients. *Can. J. Neurol. Sci.* 18, 143–151 (1991).

3   Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov. Disord.* 6, 119–126 (1991).

4   Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. *Pain* 69, 279–286 (1997).

5   Lobbezoo F, Tanguay R, Thu Thon M, Lavigne GJ. Pain perception in idiopathic cervical dystonia (spasmodic torticollis). *Pain* 67, 483–491 (1996).

6   Jahanshahi M, Marsden CD. Psychological functioning before and after treatment of torticollis with botulinum toxin. *J. Neurol. Neurosurg. Psychiatry* 55, 229–231 (1992).

7   Jahanshahi M. Psychosocial factors and depression in torticollis. *J. Psychosom. Res.* 35, 493–507 (1991).

8   Fahn S. Systemic therapy for dystonia. *Can. J. Neurol. Sci.* 14, 528–532 (1987).

9   Greene P, Shale H, Fahn S. Analysis of open-label trials in torsion dystonia using high dosages of anticholinergics and other drugs. *Mov. Disord.* 3, 46–60 (1988).

10 Dauer WT, Burke RE, Greene P, Fahn S. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. *Brain* 121, 547–560 (1998).
•   **This paper provides a good review of the etiology and management of cervical dystonia.**

11 Bertrand CM. Selective peripheral denervation for spasmodic torticollis: surgical technique, results and observations in 260 cases. *Surg. Neurol.* 40, 96–103 (1993).

12 Ford B, Louis ED, Greene P, Fahn S. Outcome of selective ramisectomy for botulinum toxin resistant torticollis. *J. Neurol. Neurosurg. Psychiatry* 65, 472–478 (1998).

13 Krauss JK, Toops EG, Jankovic J, Grossman RG. Symptomatic and functional outcome of surgical treatment of cervical dystonia. *J. Neurol. Neurosurg. Psychiatry* 63, 642–648 (1997).

14 LeWitt AP, Trosch RM. Idiosyncratic adverse reactions to im. botulinum toxin type A injection. *Mov. Disord.* 12(6), 1064–1067 (1997).

15 Tsui JKC, Fross RD, Calne S, Calne DB. Local treatment of spasmodic torticollis with botulinum toxin. *Can. J. Neurol. Sci.* 14(3 Suppl.), 533–535 (1987).

16 Jankovic J, Brin M. Therapeutic uses of botulinum toxin. *N. Engl. J. Med.* 324, 1186–1194 (1991).

17 Jankovic J. Medical therapy and botulinum toxin in dystonia. In: *Dystonia 3: Advances in Neurology.* Fahn S, Marsden CD, DeLong M, (Eds.), Lippincott-Raven publishers, Philadephia, USA 169–183 (1998).

18 Mahant N, Clouston PD, Lorentz IT. The current use of botulinum toxin. *J. Clin. Neuroscience* 7, 389–394 (2000).
•   **A nice simplified review of the many clinical uses of botulinum toxin.**

19 Arnon SS, Schechter R, Inglesby TV *et al.* Botulinum toxin as a biological weapon. *JAMA* 285(8), 1059–1070 (2001).

20 Eleopra R, Tugnoli V, Rossetto O, Montecucco C, De Grandis D. Botulinum neurotoxin serotype C: a novel effect botulinum toxin in human. *Neurosci. Lett.* 24, 91–94 (1997).

21 Greene PE, Fahn S. Use of botulinum toxin type F injections to treat torticollis in patients with immunity to botulinum toxin type A. *Mov. Disord.* 8, 479–483 (1993).

22 Houser MK, Sheean GL, Lees AJ. Further studies using higher doses of botulinum toxin type F for torticollis resistant to botulinum toxin type A. *J. Neurol. Neurosurg. Psychiatry* 64, 577–580 (1998).

23 Mezaki T, Kaji R, Kohara N *et al.* Comparison of therapeutic efficacies of type A and F botulinum toxins for blepharospasm: a double-blind, controlled study. *Neurology* 45, 506–508 (1995).

24 Borodic G, Johnson E, Goodnough M, Schantz E. Botulinum toxin therapy, immunologic resistance and problems with available materials. *Neurology* 46, 26–29 (1996).

25 Sankhla C, Jankovic J, Duane D. Variability of the immunologic and clinical response in dystonic patients immunoresistant to botulinum toxin injections. *Mov. Disord.* 13(1), 150–154 (1998).

26 Greene P, Fahn S, Diamond B. Development of resistance to botulinum toxin type A patients with torticollis. *Mov. Disord.* 9, 213–217 (1994).

27 Jankovic J, Schwartz KS. Response and immunoresistance to botulinum toxin injections. *Neurology* 45, 1743–1746 (1995).

28 Setler P. The biochemistry of botulinum toxin type B. *Neurology* 55(Suppl. 5), S23–S28 (2000).

29 Jankovic J, Schwartz KS. Clinical correlates of response to botulinum toxin injections. *Arch. Neurol.* 48, 1253–1256 (1991).

30 Zuber M, Sebald M, Bathien N, de Recondo J, Rondot P. Botulinum antibodies in dystonic patients treated with type A botulinum toxin: frequency and significance. *Neurology* 43, 1715–1718 (1992).

31 Aoki KR. Preclinical update on Botox® (botulinum toxin type A)-purified neurotoxin complex relative to other botulinum neurotoxin preparations. *Eur. J. Neurol.* 6(Suppl. 4), S3–S10 (1999).

32 Lange DI, Rubin M, Greene PE *et al.* Distant effects of locally injected botulinum toxin: a double-blind study of single fiber EMG changes. *Muscle Nerve* 14, 672–675 (1991).

33 Olney RK, Aminoff MJ, Gelb DJ *et al.* Neuromuscular effects distant from the site of botulinum neurotoxin injection. *Neurology* 38, 1780–1783 (1988).

34 Bhatia KP, Münchau A, Thompson PD *et al.* Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. *J. Neurol. Neurosurg. Psychiatry* 67, 90–93 (1999).

35 Sakaguchi G. *Clostridium botulinum* toxins. *Pharmacol. Ther.* 19, 165–194 (1983).
•   **A good review of the pharmacologic similarities and differences among toxin serotypes.**

36 Sugiyama H. *Clostridium botulinum* neurotoxin. *Microbiol. Rev.* 44, 419–448 (1980).

37 Johnson EA, Goodnough MC. Preparation and properties of botulinum toxin for medical use. In: Handbook of dystonia. Tsui JKC, Calne DB, (Eds.), Marcel Dekker, New York, USA 346–365 (1995).

38 Schantz EJ, Johnson EA. Quality of botulinum toxin for human treatment. In: Botulinum and tetanus neurotoxins. DasGupta BR, (Ed.), Plenum Press, New York, USA 657–659 (1993).

39 Montecucco C, Schiavo G. Structure and function of tetanus and botulinum neurotoxins. *Q. Rev. Biophys.* 28, 423–472 (1995).

40 Sugiyama H, Das Gupta R, Yang KH. Disulfide-toxicity relationship of botulinal toxin types A, E and F. *Proc. Soc. Exp. Biol. Med.* 143, 589–591 (1973).

41 Bavari S, Pless DD, Torres ER *et al.* Identifying the principal protective antigenic determinants of type A botulinum neurotoxin. *Vaccine* 16, 1850–1856 (1998).

42 Dertzbaugh MT, West MW. Mapping of protective and cross-reactive domains of the type A neurotoxin of Clostridium botulinum. *Vaccine* 16, 1538–1544 (1996).

43 Bittner MA, Das Gupta BR, Holz RW. Isolated light chains of botulinum neurotoxins inhibit exocytosis: studies in digitonin-permeabilized chromaffin cells. *J. Biol. Chem.* 264, 10354–10360 (1989).

44 Habermann E, Dreyer F. Clostridial neurotoxins: handling and action at the cellular and molecular level. *Curr. Top. Microbiol. Immunol.* 129, 93–179 (1986).

45 Simpson LL. Kinetic studies on the interaction between botulinum toxin type A and the cholinergic neuromuscular junction. *J. Pharmacol. Exp. Ther.* 212(1), 16–21 (1980).

46 Schiavo G, Benefenati F, Poulain B *et al.* Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. *Nature* 359, 832–835 (1992).

47 Ahnert-Hilger G, Bigalke H. Molecular aspects of tetanus and botulinum neurotoxin poisoning. *Prog. Neurobiol.* 46, 83–96 (1995).

48 Barinaga M. Secrets of secretion revealed. *Science* 260, 487–489 (1993).

49 Callaway JE, Arezzo JC, Grethlein AJ. Botulinum toxin type B: an overview of its biochemistry and preclinical pharmacology. *Sem. Cut. Med. Surg.* 20(2), 127–136 (2001).
•• **This article provides a good review of the pharmacology and biochemistry of botulinum toxin type B.**

50 Moyer E, Setler PE. Botulinum toxin type B: experimental and clinical experience. In: *Therapy with botulinum toxin, neurological disease and therapy series, (Vol 25).* Jankovic J, Hallet M, (Eds.), Marcel Dekkar, New York, USA 71–85 (1994).

51 Botox® Product Monograph. Botox® Botulinum Toxin Type A Purified Neurotoxin Complex. Allergan, Inc, Irvine, California, USA 1998.

52 Moyer ED, Stephens EA, Esch F, Litwak M, Arezzo J. Effects of im. injection of botulinum toxin type B in nonhuman primates. In: *Botulinum and Tetanus Neurotoxins.* DasGupta BR. Plenum Press, New York, USA (1993).

53 Cherington M. Clinical spectrum of botulism. *Muscle Nerve* 21, 701–710 (1998).

54 Cichon JV, Jr., McCaffrey TV, Litchy WJ, Knops JL. The effects of botulinum toxin type A injection on compound muscle action potential in an *in vivo* rat model. *Laryngoscope* 2, 144–148 (1995).

55 Meyer KE. A comparative systemic toxicity study of Neurobloc™ in adult and juvenile cynomolgus monkeys. Presented at the International Conference 1999: basic and

therapeutic aspects of botulinum and tetanus toxin (poster). Orlando, FL. November 16–18 (1999).

56 Brashear A, Lew MF, Dykstra DD *et al.* Safety and efficacy of Neurobloc™ (botulinum toxin type B) in type A-responsive cervical dystonia. *Neurology* 53, 1439–1446 (1999).
•• **This pivotal study evaluates botulinum toxin type B in cervical dystonia patients who are responsive to type A toxin.**

57 Brin M, Lew MF, Adler CH *et al.* Safety and efficacy of Neurobloc™ (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 53, 1431–1438 (1999).
•• **This pivotal study evaluates botulinum toxin type B in cervical dystonia patients who are resistant to type A toxin.**

58 Myobloc Package Insert, Elan Pharmaceuticals, South San Francisco, California, 2001.

59 Cullis PA, O'Brien CF, Truong DD, Koller M, Villegas TP, Wallace JD. Botulinum toxin type B: an open-label, dose-escalation, safety and preliminary efficacy study in cervical dystonia patients. In: *Dystonia 3 - advances in neurology.* Fahn S, Marsden CD, DeLong M, (Eds.), Lippincott-Raven, Philadelphia, USA 78, 227–230 (1998).

60 Truong DD, Cullis PA, O'Brien CF *et al.* Bot B (botulinum toxin type B): evaluation of safety and tolerability in botulinum toxin type A-resistant cervical dystonia patients (preliminary study). *Mov. Disord.* 12, 772–775 (1997).

61 Tsui JKC, Hayward M, Mak EKM, Schulzer M. Botulinum toxin type B in the treatment of cervical dystonia: a pilot study. *Neurology* 45, 2109–2110 (1995).

62 American BotB™ Cervical Dystonia Study Group. BotB (botulinum toxin type B) in the treatment of cervical dystonia (CD) - protocol AN072-008: an interim analysis (abstract). *Mov. Disord.* 10, 2874 (1995).

63 Lew MF, Adornato BT, Duane DD *et al.* Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. *Neurology* 49, 701–707 (1997).

64　Cullis PA. Safety and effectiveness of Neurobloc (botulinum toxin type B solution): an open-label, dose-escalation study. Abstract book of the XVII World Congress of Neurology, London, UK, June 17–22, 2001. *J. Neurol. Sci.* 187(Suppl. 1), S423 (2001).

65　Data on file. Elan Pharmaceuticals, South San Francisco, California.

66　Comella CL, Buchman AS, Tanner CM, Brown-Toms NC, Goetz CG. Botulinum toxin injection for spasmodic torticollis: increased magnitude of benefit with electromyographic assistance. *Neurology* 42, 878–882 (1992).

67　Riski JE, Horner J, Nashold BS, Jr. Swallowing function in patients with torticollis. *Neurology* 40, 1443–1445 (1990).

68　National Institutes of Health Consensus Development Conference Statement, November 12–14, 1990. Clinical use of botulinum toxin. *Arch. Neurol.* 48, 1294–1298 (1991).