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Botulinum Neurotoxin Therapy: Overview of Serotypes A and B

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ABSTRACT

Botulinum toxin, a naturally occurring protein with high therapeutic value in a purified form, effectively treats a variety of disorders characterized by abnormal muscle tone. This review explores the differences that exist between the two approved serotypes—A and B—in structure, mechanism of action, amount of neurotoxin protein activated, duration of activity, and protein load per dosing unit. Although not confirmed clinically, these pharmacologic differences suggest that serotype A may display a longer duration of action and a reduced risk for the development of neutralizing antibodies. Further, this review examines the growing body of investigational clinical data supporting the use of botulinum neurotoxin in the management of idiopathic dystonias, spasticity, sweating, vocal and gastrointestinal tract disorders, and pain associated with migraine and simple headaches. The clinical evidence suggests that botulinum neurotoxin can be effective and well tolerated in the treatment of numerous spastic disorders, although virtually all of the investigational studies have focused on botulinum neurotoxin serotype A.

Supplement Objectives

- Identify the pharmacologic differences between botulinum toxin types A and B.
- Discuss the potential for immunogenicity associated with botulinum toxin types A and B.
- List the approved indications for botulinum toxin types A and B.
- Describe the clinical uses of the botulinum toxins.
- Address the tolerability of botulinum toxins type A and B.
- Describe the dosing issues associated with botulinum toxins type A and B.

Introduction

Botulinum toxin displays remarkable clinical value. When appropriately injected by a highly trained specialist into specific muscles in low doses, it can offer clinical benefits in a variety of nerve and muscle disorders. Indeed, since gaining approval by the Food and Drug Administration (FDA) in 1989, botulinum toxin has transformed the management of focal dystonias, providing the first effective, long-acting treatment for these conditions.

Currently two forms of botulinum neurotoxin have been approved for use in the U.S.: botulinum toxin type A (Botox™) and botulinum toxin type B (Myobloc™). Another botulinum neurotoxin type A, Dysport™, is available outside the U.S. The first commercial botulinum toxin therapy, Botox, was approved in 1989 for the treatment of strabismus and blepharospasm and in 2000 for the treatment of cervical dystonia. Myobloc was approved in 2000 for the treatment of cervical dystonia.

It is noteworthy that these botulinum toxin preparations display pharmacologic differences that may have impor-

Key Words: *Botox, Myobloc, botulinum neurotoxin, pharmacology, efficacy.*

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tant clinical implications for achieving optimal patient care. In this article, we compare the pharmacology of botulinum toxin types A and B—highlighting the potential clinical implications of differences in structure and mechanism of action—and examine the data supporting their current indications and potential off-label uses.

Pharmacology

Structure

The principal source of botulinum toxin, *Clostridium botulinum*, an anaerobic bacillus, synthesizes neurotoxin in seven immunologically distinct serotypes, designated A through G.[1,2] Pharmacologically, each serotype differs in its potency, duration of action, or cellular target; thus, no two are precisely alike. Thus far, only formulations of botulinum serotypes A and B have been approved for clinical use.

All botulinum neurotoxins are synthesized as a complex that contains a 150-kilodalton (kD) neurotoxin protein and several neurotoxin-associated proteins, such as hemagglutinin and nontoxic nonhemagglutinin. The nonhemagglutinin proteins stabilize and protect the neurotoxin protein component. [3] The composition and molecular weight of a specific neurotoxin complex vary according to serotype and the synthesizing clostridial strain. [4] For instance, only serotype A is capable of forming a 900-kD complex, the largest. Serotype B, in contrast, forms a 300-kd and a 500-kD complex. Yet all seven botulin toxins contain a 150- kD neurotoxin protein, which, in the initial single-chain form, displays minimal toxic or therapeutic activity.[5,6] Full activity is achieved when the single-chain molecules are exposed to proteases and cleaved, or nicked, to form a 100-kD heavy chain and a 50-kD light chain.[6,7] The dichain form of the molecule accounts for both the toxic and the therapeutic action of botulinum toxin (Figure 1). Of potential clinical relevance, the serotypes differ in the amount of neurotoxin nicked to their active forms. Whereas serotype A is recovered from culture 95% nicked,[8] a smaller portion of the serotype B neurotoxin molecules is nicked.[9] In vivo, nicking of the serotype B single-chain molecule by bacteria-associated proteases may be limited by its genetic structure.[10] Increased levels of unnicked neurotoxin may eventually increase the risk for neutralizing antibody formation, compromising efficacy.

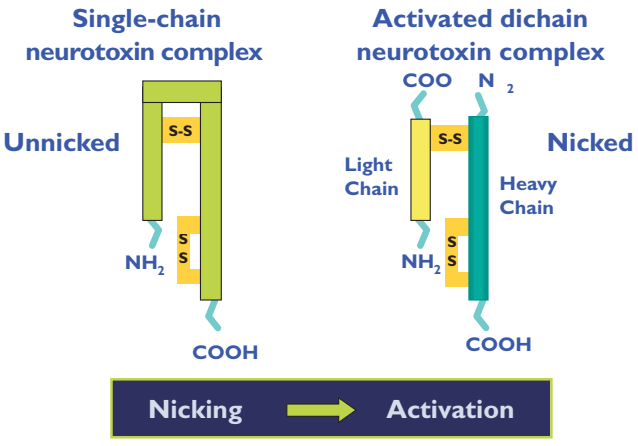

Figure 1 Diagram of botulinum neurotoxin single-chain protein and activated dichain protein.

Mechanism of Action

When injected directly into hyperactive muscles, botulinum toxin induces reversible cholinergic blockade at the neuromuscular junction, thus reducing muscle contractions. The blockade of acetylcholine release involves three steps: binding, internalization, and inhibition of exocytosis. Botulinum toxins, like other toxins such as cholera and tetanus, contain specific components responsible for cell binding and enzymatic activity.[11] For instance, the botulinum toxin heavy chain, selective for cholinergic nerve terminals, is responsible for receptor binding and internalization, whereas the light chain is responsible for inhibition of exocytosis.[12] Botulinum toxin serotypes A and B bind to distinct membrane receptors on cholinergic neurons that trigger endocytosis.[13] During this process, the plasma membrane invaginates or folds around the entire toxin-receptor complex, forming a toxin-containing vesicle within the nerve terminal. [14] Once internalized, the vesicles release the neurotoxin light chain, a zinc-dependent endopeptidase that cleaves intracellular proteins essential

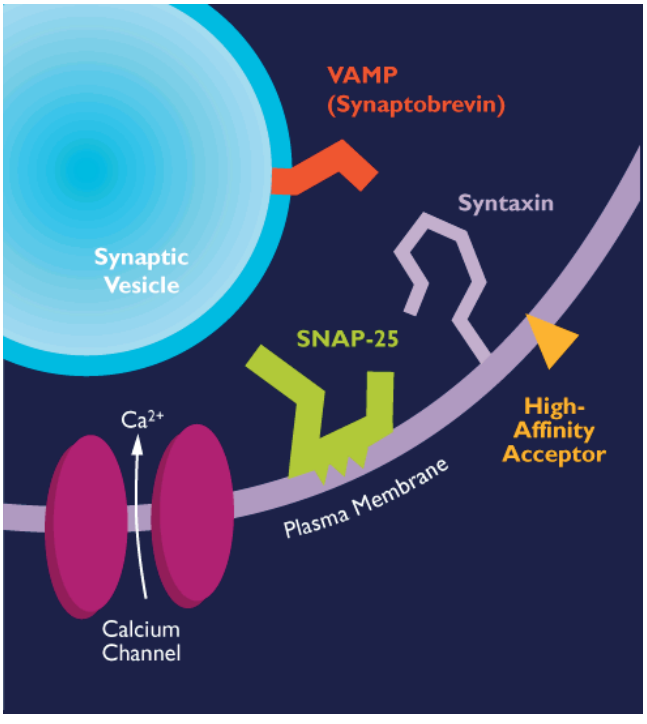

Figure 2 Intracellular botulinum neurotoxin proteins.

for exocytosis and acetylcholine release (Figure 2). Botulinum neurotoxin serotypes A, C, and E cleave SNAP-25, a 25-kD synaptosomal-associated protein located on the inner surface of the neuronal cell membrane. Botulinum serotypes B, D, F, and G target a separate protein, synaptobrevin or vesicle-associated membrane protein (VAMP), located on the outside surface of the synaptic vesicle. Although both of these actions inhibit the docking of synaptic vesicles with the cell membrane and, in turn, exocytosis and release of acetylcholine into the synaptic cleft, this difference in protein binding among the serotypes may contribute in some yet-to-be defined way to differences in their pharmacologic profiles.

Once chemical denervation has been accomplished with botulinum neurotoxin, the cholinergic neurons begin to adapt over time. The presynaptic end-plate region expands and collateral axonal sprouts develop, eventually reinnervating the neuromuscular junction. [15] The new axon sprout may eventually retract once the original junction regains functionality.[16] Although chemical denervation with botulinum neurotoxin is reversible, the effect is long-lasting. Periodic dosing, however, is required to maintain efficacy.

Pharmacologic Actions

The duration of action of botulinum neurotoxin serotypes A and B has been directly compared in vitro and in healthy human subjects. To examine the molecular basis for the prolonged neuromuscular denervation seen with botulinum neurotoxin serotypes A and B, investigators exposed adrenal chromaffin cells—a model system for the study of exocytosis—to 6.6 nM botulinum toxin type A or 66.0 nM botulinum toxin type B and, in turn, monitored cellular functioning for two months.[17] For the serotype B exposed cells, exocytosis and neurotransmitter release resumed after 56 days (10% inhibition), presumably because of the reappearance of intact synaptobrevin. However, at the 56-day evaluation point, neurotransmitter release was still inhibited by 64% for the cells exposed to serotype A, secondary to prolonged protease activity of the serotype A light chain. These results suggest a molecular basis for a potentially longer clinical action for botulinum serotype A than for serotype B.

In a study that included 17 healthy subjects, electromyographic measurements were used to assess the action of botulinum serotypes A (Botox) and B (Myobloc) when injected into the extensor digitorum brevis, a muscle in the foot that helps extend the toes.[18] The M-wave amplitude was measured four times before and six times after injection with 17 different doses of serotype B (1.25 to 480 U). This process established a dose–response curve for serotype B that was compared with a previously established dose–response curve for serotype A. Volunteers were then randomly assigned by dose and were injected with botulinum toxin serotype A and B into opposite digitorum brevis extensor muscles. Changes in M-wave amplitude, the primary outcome, were measured 13 times over 57 weeks after injection. At two weeks after injection, a maximal paralysis of 50% to 75% was seen with 320 to 480 U doses of serotype B, whereas a maximal paralysis of 70% to 80% was achieved with 7.5 to 10 U doses of serotype A. Further, the paralytic effect of serotype B returned to baseline values by week 11. In contrast, serotype A displayed 65% of its maximal paralytic effect by week 11 and 22% by week 57 after injection. The results of this study suggest that in humans the paralytic actions of botulinum serotype B are not as complete or as long-lasting as those associated with serotype A. Although these data support the proposition that botulinum neurotoxin serotype A displays a longer duration of action than serotype B, this issue will not be completely resolved until both serotypes are compared head-to-head in clinical studies that measure the length of symptom remission in actual patient populations.

The duration of clinical action of botulinum serotype B (Myobloc) in cervical dystonia was evaluated in two double-blind, placebo-controlled studies that used changes in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTERS) as the main outcome measure. One study included 109 patients responsive to serotype A,[19] and the other study included 77 patients resistant to serotype A.[20] In these 16-week studies, significant improvements were detected with serotype B (10,000 U) compared to placebo in the main outcome measure at 12 weeks after injection in one study[20] and at four weeks in the other study.[19] A subsequent poststudy Kaplan-Meier survival analysis extended the duration of action to 16 weeks.

The mean duration of effect for botulinum toxin serotype A (Botox) was evaluated in a retrospective study that included 60 patients with cervical dystonia treated at an academic center and at a private neurology practice between January 1, 1998 and March 31, 1998. [21] In this study, 102 patients treated with serotype A for cervical dystonia were identified and randomized for chart review, and the charts for the first 60 patients who met the eligibility criteria (at least 18 years of age and a diagnosis of idiopathic cervical dystonia) were analyzed. With the time between the first four injections used as a measure of duration of effect, the mean per-patient Botox duration of action was 15.5 weeks, with a range of 12.2 to 24.3 weeks.

Antigenicity

Immunogenicity

Exposure to a foreign protein complex, such as botulinum toxin, might elicit an immune response. The resulting antibody production may neutralize botulinum toxin, thus reducing efficacy. Because the effective management of focal dystonias and other spastic disorders requires long-term treatment with repeated dosing, neutralizing antibody formation becomes an important

clinical issue. Although the factors that influence the formation of neutralizing antibodies secondary to botulinum neurotoxin treatment are not completely understood, overall exposure to the botulinum neurotoxin protein may play an important but modifiable role. Overall, neurotoxin exposure is influenced by the amount of neurotoxin protein per effective dose, frequency of injections, and the experience of the administering clinician in identifying and efficiently using the lowest effective dose.

In a retrospective study, 86 patients treated for cervical or oromandibular dystonia with an older formulation of botulinum toxin serotype A were tested for the presence of botulinum neurotoxin antibodies.[22] All 20 patients who tested positive were unresponsive to treatment. When these 20 patients were compared with 22 randomly selected antibody-negative patients, the antibody-positive patients were found to have had higher mean doses per visit (249 U verus 189 U) and higher mean total cumulative doses (1,709 U versus 1,066 U). Other than a younger age at disease onset among the antibody-positive patients, no factors other than neurotoxin protein exposure and subsequent neutralizing antibody formation could account for the development of treatment resistance.

Another retrospective study examined the relationship between annual botulinum toxin exposure and neutralizing antibody formation.[23] Between October 1988 and May 1998, serum samples were tested from 195 patients who were treated for dystonia with botulinum serotype A (Botox). Serum samples for neutralizing antibodies were analyzed for the 88 patients with complete data on the amount of botulinum serotype A injected during the previous year. These patients were divided into four groups, according to their annual exposure to neurotoxin protein. A clear relationship was discerned between the amount of botulinum neurotoxin protein exposure and the percentage of patients with neutralizing antibodies (Table 1). It should be pointed out that this study used an older formulation of Botox that contained a higher neurotoxin protein load per unit (25 ng/100 U) than the purer, current formulation (5 ng/100 U).

Table 1 **Relationship Between Annual Serotype A Neurotoxin Complex Exposure and Formation of Neutralizing Antibodies**

Dosage	N	% Positive
< 500 U	45	4
500–1000 U	24	45
1000–2000 U	18	83
> 2000 U	1	100
Total	88	33

From: Hatheway & Dang, 1994. In Jankovic & Hallet, eds. *Therapy with Botulinum Toxin*, 1994.

Botox, at 5 ng of neurotoxin protein per 100 U, contains about 12 ng of neurotoxin per 236 U, the mean total Botox dose for the treatment of cervical dystonia in Phase III clinical trials.[24] In contrast, Myobloc, at 1 ng of neurotoxin protein per 100 U, contains 50 ng of neurotoxin per 5,000 U, a recommended dose for cervical dystonia.[25] In clinical trials, however, Myobloc was most effective at a total dose of 10,000 U, or 100 ng of neurotoxin.[19,20] The low risk for neutralizing antibody formation with Botox, predicted from the low neurotoxin protein load, was indirectly supported in a study that included 83 patients with cervical dystonia. [26] In this uncontrolled study, all of the patients who initially responded to Botox treatment continued to respond at the 19-month follow-up evaluation, suggesting an absence of clinically meaningful neutralizing antibody formation.

Together, these findings imply that although neutralizing antibodies actually have been identified in a minority of patients treated with botulinum toxin, minimizing the annual amount of neurotoxin protein administered might lower the risk for neutralizing antibody formation over time for all patients treated and, in turn, the development of treatment resistance. Prospective, controlled clinical studies are still needed, however, to clarify the link between botulinum neurotoxin protein load and neutralizing antibody formation.

Cross-reactivity

Cross-reactivity — the ability of an antibody to react with an antigen other than the one that initially induced the antibody — has been shown to occur among the different botulinum serotypes. In mice, certain fragments of botulinum serotype A stimulate the production of antibodies that react to epitopes on the heavy-chain proteins on serotypes B, C, D, E, and F.[27] Further, in mice, an 11-protein fragment, which was similar or identical across serotypes, apparently provided a common antibody target among the different botulinum neurotoxin serotypes.[28] In addition, a study that examined 13 botulinum serotype A heavy-chain murine peptide sequences containing antibody or T-cell epitopes found that the sequence of a number of these epitopes was similar to those detected in serotypes B and F.[29] Of the 13 botulinum serotype A epitopes examined, seven had five or more contiguous residues that were similar or identical to corresponding regions on serotype B, and eight epitopes had five or more contiguous residues that were similar to regions on serotype F. These preclinical data provided evidence of a biochemical basis for cross-reactivity among the different serotypes and suggested that cross-reactivity, and thus cross-neutralization, might be present in the clinical setting as well.

Cross-reactivity between botulinum serotypes A and B was explored in a study that extracted serum samples from 47 patients with cervical dystonia who had become nonresponsive and had antibodies to serotype A

(Botox).[30] Serum samples for 33% of these patients showed neurotoxin neutralizing antibody binding to serotype B as well. In this study, the two putative epitope regions of serotypes A and B displayed a 54% and 44% homology, respectively. These data suggest that botulinum serotypes A and B may manifest potential clinically relevant cross-reactivity. Moreover, if a patient is exposed to a high neurotoxin protein load initially, the resulting neutralizing antibodies may more readily compromise the response to subsequent therapy using an alternative serotype with a lower botulinum protein load. Therefore, the best therapeutic course might be to start therapy with a botulinum toxin with the lowest protein load.

Clinical Uses

Botulinum neurotoxin injections have become an indispensable tool in the management of a variety of focal dystonias. Botulinum neurotoxin serotype A (Botox) was first approved in 1989 for the treatment of strabismus, a condition characterized by misalignment of the eyes, and blepharospasm, a muscle spasm that manifests itself as an uncontrollable, forcible closure of the eyelids, often rendering the patient functionally blind. In 2000, Botox received approval for the treatment of cervical dystonia, a typically idiopathic condition characterized by abnormal postures and twisting movements of the neck. In 2002, Botox™ Cosmetic was approved for the temporary improvement of moderate to severe glabellar or frown lines. Botulinum serotype B (Myobloc) was approved in 2000 for the treatment of cervical dystonia. Because of the relatively long clinical history of serotype A, virtually all of the studies examining the potential therapeutic uses of botulinum neurotoxin have focused on this serotype.

Approved Indications

Cervical Dystonia

The efficacy of botulinum serotype A in intractable cervical dystonia has been explored and confirmed in several studies.[31–34] In these studies, clinically significant improvements were seen in 60% to 86% of patients. In a study that followed 232 patients with cervical dystonia for up to four years, Botox injections were found to provide complete pain relief in 76% of the 89 patients who reported pain before treatment.[31] Further, in a double-blind, placebo-controlled, parallel-group study that included 55 patients treated for cervical dystonia with Botox, patients manifested clear and significant subjective and objective improvements in symptomatology, functionality, and pain relief, when compared with placebo treatment.[34]

In these studies, mean Botox doses generally ranged from 25 U to approximately 200 U, depending on the muscle site chosen. In addition, 86% of patients treated for cervical dystonia with the most current formulation of Botox (5 ng of neurotoxin/100 U) sustained a response after 9.2 months (mean) of therapy with an average cumulative dose of 562 U (± 418 U), suggesting long-term responsiveness in the management of cervical dystonia with the use of a low-protein serotype A.[26] Typically, side effects, including dysphagia, fatigue, and injection site pain, were transient. Other studies have shown that Dysport (500 U) is effective in ameliorating the symptoms and pain associated with the major types of cervical dystonia[35] and, when given at three or four times the recommended dose of Botox, may be more effective than Botox in reducing impairment and pain in these patients.[36] However, injecting Dysport at these dosing ratios did result in an increased incidence of adverse events, particularly dysphagia. Overall, these studies indicate that botulinum serotype A is effective and safe in the management of rotational cervical dystonia and pain secondary to cervical dystonia.

Two double-blind, placebo-controlled studies examined the efficacy of botulinum serotype B (Myobloc) in the treatment of resistant cervical dystonia. In these studies, change in the TWSTERS total score was the main outcome measure. One study included 109 patients responsive to serotype A,[19] and the other study included 77 patients resistant to serotype A.[20] In these 16-week studies, significant improvements in the main outcome measure, versus placebo, were seen after Myobloc injections at a dose of 10,000 U at week 12 in one study[20] and at week four in the other.[19]

Strabismus

For the treatment of congenital or acquired strabismus, botulinum toxin type A has been reported to be an effective alternative to surgery, with the greatest effect in esotropia (in-turning of the eyes) of small to moderate angles.[37] A 65% reduction in strabismus angle can be expected after two or three injections into the eyelids or extraocular muscles.[38] This procedure is generally well tolerated.

Blepharospasm

For most patients, botulinum serotype A provided the first effective nonsurgical treatment for blepharospasm.[39] Pharmacotherapies, such as anticholinergics and muscle relaxants, provide sustained relief for only 20% of patients. In contrast, Botox therapy provides significant relief in 69% to 100% of patients, a response rate that equals, and sometimes exceeds, that seen with surgery.[39] In a study that included 39 patients with essential blepharospasm intractable to conventional pharmacotherapy, single-dose Botox therapy provided rapid, long-lasting, and well-tolerated symptomatic relief for most patients.[40] In other studies,[41,42] symptomatic improvements with Botox treatment ranged from 61% to 90%, with a mean duration of action of 12.5 weeks.[41] The results of these studies clearly support a role of bot-

ulinum serotype A as primary therapy in the management of essential blepharospasm.

Glabellar Lines

In April 2002, the FDA approved botulinum toxin type A (Botox Cosmetic) as an approach for providing temporary improvement in the appearance of moderate to severe glabellar lines ("frown lines") between the brows caused by contraction of the corrugator and/or procerus muscles. In a double-blind, randomized, placebo-controlled study, 264 patients with moderate-to-severe glabellar lines received either intramuscular Botox injections (20 U) or placebo and were followed for 120 days after injection.[43] At all follow-up visits, the 203 patients who received Botox experienced significant reductions in glabellar severity. In addition, side effects, mostly mild blepharoptosis, were infrequent.

Off-Label Clinical Uses

Botulinum toxin has been studied in a variety of spastic and neurologic conditions secondary to excessive cholinergic activity (Table 2). Virtually all the studies have examined the actions of botulinum neurotoxin type A.

Table 2 **Neurotoxin Type A* Investigational Uses**

Idiopathic dystonia
- Laryngeal dystonias
- Temporomandibular disorders
- Hemifacial spasm
- Myoclonus
- Tics
- Writer's cramp

Sweating disorders
- Hyperhidrosis
- Frey syndrome

Spastic disorders related to
- Stroke
- Cerebral palsy
- Parkinson's disease

Vocal Disorders
- Essential vocal tremor
- Spasmodic dysphonia

Pain
- Migraine
- Simple headache
- Low back pain

Gastrointestinal tract disorders
- Achalasia
- Anal fissure

*Based on published data and reflects use of neurotoxin botulinum type A only.

Other Idiopathic Dystonias

Botulinum toxin type A has demonstrated well-tolerated efficacy in a variety of idiopathic dystonias, including laryngeal dystonia, temporomandibular disorders, hemifacial spasm, myoclonus, tics, and writer's cramp.

Laryngeal or spastic dystonias are characterized by involuntary contractions of the laryngeal muscle, resulting in choked or strained vocalizations. Botulinum toxin injections have produced marked improvements in speech in 75% to 100% of patients, with the effects lasting about four months after injections without notable side effects.[39,44] As would be expected with a significant improvement in symptomatology in these patients, treatment with Botox also significantly improved the patients' social functioning and overall mental health.[45] Although injections can be performed on an outpatient basis, the clinician should have the equipment available to treat reflex laryngeal stridor, a condition linked to this procedure. [39] In the appropriate setting, Botox is generally an effective and well-tolerated alternative for the treatment of laryngeal dystonia.

Temporomandibular disorders typically result from asynchronous muscle spasms of the face and jaws and can cause significant chronic pain. Although modest improvements can be achieved with muscle-relaxing agents, such as baclofen and benzodiazepines, treatment with botulinum toxin injection can provide substantial, long-lasting relief in many patients. In an uncontrolled, eight-week study that included 46 patients with temporomandibular disorders, Botox at a dose of 150 U (50 U into each masseter muscle and 25 U into each temporalis muscle) produced a significant reduction in symptomatology, increasing mouth opening and decreasing tenderness and pain.[46] Although this study was uncontrolled, it suggests an important role for botulinum toxin serotype A in temporomandibular disorders.

Patients afflicted with hemifacial spasm, characterized by embarrassing unilateral facial twitching, resulting from the synchronous contractions of the muscles innervated by the facial nerve, can gain partial relief with the use of anticonvulsant agents such as phenytoin and carbamazepine.[39] Although they are more effective, surgical procedures, including facial nerve blocks, can be painful and may result in side effects, such as facial weakening, that are often more disabling than the original disorder. Botox has a long history of efficacy and tolerability in the treatment of hemifacial spasm. [39] Indeed, 90% of the patients treated with Botox typically have achieved substantial symptomatic improvement that lasted about four months after injection, with minimal side effects.[39,42] In fact, side effects were typically infrequent and transient, with facial weakness, ptosis, and eyelid swelling affecting 5% or fewer patients.[42]

Patients with myoclonus, a chronic involuntary contraction of any muscle group, typically do not respond satisfactorily to standard oral therapy, such as benzodiazepines. A small study that included nine patients with

generalized or focal myoclonus demonstrated that injections of botulinum toxin type A at four- to eight-month intervals can provide dramatic symptomatic relief and improved ambulation.[47] Botulinum toxin type A has also been shown to reduce tic frequency in patients with Tourette syndrome[48] and simple tics.[49] In these patients, targeting the muscle group responsible for the most disruptive tics is important for reducing disability and enhancing quality of life. Writer's cramp, an activity-specific focal dystonia, has also been shown to respond well to botulinum toxin type A therapy, with significant improvement in posture, pain, and ease and speed of writing noted within 10 days (mean) and lasting about 9.5 weeks (mean).[50]

Spasticity

Spastic disorders, including those linked to stroke, cerebral palsy, and Parkinson's disease, have been shown to respond well to botulinum toxin type A treatment. In a study that included 202 patients with acute and chronic spasticity secondary to a variety of conditions, including stroke and brain and spinal injury, single-dose botulinum toxin type A treatment at a mean dose of 181 U produced significant reductions in spasticity severity and increases in functioning in 94% (191) of the patients.[51] These effects lasted for an average of almost eight weeks. Adverse effects, which affected 6% of the patients, were mild or moderate and transient.

In a 12-week, placebo-controlled study, 40 patients with spasticity in an arm functionally compromised secondary to stroke were randomized to receive botulinum toxin type A (1000 U divided between elbow, wrist, and finger flexor muscles) or placebo.[52] Significant reductions in forearm flexor spasticity were seen through week 12 after injection and in elbow flexor spasticity through week two, compared with placebo. Significant reductions in overall disability, present at week two after botulinum toxin injection, disappeared by week 12. No reductions were observed in the pain associated with arm spasticity at any point during the study, and grip strength declined in the affected arm after botulinum toxin injection. In this study, botulinum toxin reduced stroke-related muscle spasticity but treatment-associated muscle weakness could further reduce the functional capacity of the affected muscles. No serious adverse events were linked to botulinum toxin treatment. Other studies have shown that the reductions in upper and lower limb spasticity, secondary to stroke, that are seen with botulinum toxin type A can be sustained for at least four to six months.[53,54]

Botulinum toxin type A has been used increasingly to reduce spasticity in certain muscle groups in children affected with cerebral palsy.[55] Placebo-controlled trials have shown that botulinum toxin type A can ameliorate spastic equinus and improve walking for three months or longer.[56] In addition, freezing of gait (FOG), a disturbing and poorly understood symptom of Parkinson's disease, has been shown to respond to botulinum toxin type A therapy. In an open study that included 10 Parkinsonian patients with prominent FOG, botulinum toxin type A injected into the calf muscle produced improvement in 80% of the patients, with the therapeutic effect lasting an average of six weeks.[57]

Pain

Botulinum toxin has been shown to be useful in reducing the pain associated with migraine and simple headache, low back pain, and other spastic disorders discussed earlier. In migraine headache, the pain-relieving actions of botulinum toxin type A are thought to be related not only to its anticholinergic properties but also to its inhibition of the parasympathetic nervous system. In an open-label study that included 77 patients with migraine headache, botulinum toxin type A injected prophylactically into the glabellar, temporal, frontal, and/or suboccipital regions of the head and neck was associated with a 50% reduction in symptomatology for 89% of the patients.[58]

Further, the pain relief lasted three to four months. Similar findings were observed in a double-blind study that included 123 patients with a history of moderate-to-severe migraine headaches.[59] In this three-month, placebo (saline)-controlled study, single botulinum toxin type A injections (25 U) into multiple pericranial muscle sites significantly reduced the number and severity of migraine headaches as well as acute migraine medication usage. In this study, the incidence of treatment-related side effects with botulinum toxin treatment was typically comparable to that with placebo.

In the treatment of tension headache, the effects of botulinum toxin type A were compared with those of methylprednisolone when injected into the tender points of the cranial muscles.[60] At 60 days after injection, a significant decease in pain scores, based on changes in the Visual Analogue Scale, were seen with botulinum toxin type A compared to methylprednisolone. All patients treated with botulinum toxin experienced a progressive decrease in pain scores at 30 and 60 days after injection, with the beneficial effects continuing to improve at 60 days after injections. In contrast, the effects of steroid therapy declined at the 60-day time point.

The role of botulinum toxin type A has also been investigated in the treatment of chronic low back pain. In a placebo-controlled, randomized, double-blind study that included 31 patients with low back pain, 15 patients received 200 U botulinum toxin type A (40 U/site at five lumbar paraventricular levels) and 16 patients received saline injections.[61] After three weeks of treatment, pain relief was reported by 73.3% (11/15) of the patients treated with botulinum toxin compared to 25% (4/16) of those treated with saline ($P = .012$). Further, pain relief persisted at eight weeks for 60% of those in the botulinum toxin group versus 12.5% of those in the saline group ($P = .009$). No side effects were detected in either

group. This study suggests that botulinum toxin type A can provide long-lasting (at least eight weeks) and well-tolerated pain relief in patients with chronic low back pain.

In cerebral palsy, postoperative pain has been attributed to muscle spasm, a condition that is difficult to manage effectively. In a study of 16 children with cerebral palsy about to undergo an operation, preoperative botulinum toxin type A injected into the targeted surgical muscle significantly reduced pain scores by 74% postoperatively, and mean postoperative analgesic requirements by 50%, when compared with placebo injections.[62] In this study, the mean hospital stay was significantly reduced—by 33%—with botulinum toxin treatment.

In a prospective, multicenter study, 60 patients with pain associated with a variety of acute and chronic spasticity disorders received 166 U (mean) of botulinum toxin serotype A (Botox) in the muscles exhibiting increased muscle tone associated with pain during passive joint movement.[3] Pain reductions were reported by 90% (54/60) of patients; side effects, primarily local injection pain, hematoma, edema, and weakness, were mild and transient. These studies suggest that botulinum toxin type A is a promising therapeutic alternative in difficult-to-treat spasticity-related pain.

In the treatment of chronic neck pain, however, botulinum toxin type A was found to be no more effective than saline injections.[64] In a four-month study that compared the effects of single botulinum toxin type A injections with saline injections into the affected neck muscle, both treatment groups displayed significant, and similar, declines in impairment and pain over time.

Sweating Disorders

Hyperhidrosis, an often neglected and potentially troublesome sweating disorder, is typically confined to the axillae, palms, and soles of the feet. It is commonly treated with topical aluminum chloride and, in severe cases, surgery, which is expensive and often poorly tolerated.[65,66] Botulinum toxin type A has been shown to be an effective and well-tolerated treatment alternative for severe hyperhidrosis, especially of the axillae and palms.

In an open study in which botulinum toxin type A (Dysport) was injected intradermally to patients with severe axillary hyperhidrosis, sweat production, measured by gravimetry, was reduced by more than 90%, with no notable side effects, such as skin irritation and muscle weakness.[65] In another study that included 10 patients with frontal (forehead) hyperhidrosis, botulinum toxin type A (Botox) injected at multiple sites over the forehead at a mean dose of 86 U produced significant reductions in the amount of sweat four weeks after injection, with the effect lasting at least five months in 90% of patients.[66] Side effects, such as injection site pain and forehead muscle weakness, were transient. Similar long-term effects have been reported with the use of Dysport.[67] In a study that included 61 patients with axillary or palmar hyperhidrosis, single injections of Dysport, at total doses of 460 U, induced improvements that lasted 25 and 34 weeks, respectively, for palmar and axillary hyperhidrosis.[67] In this study, side effects were limited to transient and mild weakness of the small hand muscles in patients with palmar hyperhidrosis.

The tolerability of high-dose (200 U per axilla) botulinum toxin type A was examined in 24 patients with axillary hyperhidrosis.[68] Cessation of sweating was noted within six days for all patients, and lasted for at least seven months for most patients. During the five- to 15-month (mean 10 months) follow-up, Botox was remarkably well tolerated with no evidence of muscle weakness or systemic reactions. Another study evaluated the long-term efficacy of high-dose (200 U per axilla) botulinum toxin type A in 47 patients with axillary hyperhidrosis.[69] Again, all patients reported cessation of sweating within six days of injection, and in most patients antihidrotic effects were sustained for 19 months. The relapse rate within the first 12 months after injection was 12%, with the longest relapse-free interval 29 months.

Another difficult-to-treat sweating disorder, Frey syndrome, a common complication of parotid surgery, is characterized by unilateral flushing and sweating in the cheek and behind the ears after eating. This disorder has been shown to respond for up to three years to intracutaneous botulinum type A therapy with minimal side effects.[70]

Voice Disorders

Botulinum toxin type A has been examined as a treatment for essential voice tremor. When injected bilaterally into the thyroarytenoid muscle, a reduction in tremor frequency and to a lesser extent, tremor amplitude, was seen for up to 10 weeks after injection.[71] In another study in patients with essential voice tremor, bilateral or unilateral Botox injections produced objective reductions in tremor severity for no more than 30% of patients, although a majority (80%) experienced subjective improvements that correlated with a reduction in laryngeal airway resistance.[72] Botulinum toxin type A also has been shown to produce subjective, acoustic, and perceptual improvement in patients with adductor spasmodic dysphonia, although the voice quality and function did not return to normal in all patients.[3,74]

Gastrointestinal Tract Disorders

Botulinum toxin has proved useful in the treatment of a variety of spastic disorders involving the gastrointestinal tract, including achalasia and anal fissure.

An uncommon but insidious and difficult-to treat disorder, achalasia is characterized primarily by failure of the lower esophageal sphincter (LES) to relax during swallowing. The resulting defective esophageal emptying causes progressive dilation of the esophagus, leading to

dysphagia and regurgitation. In addition, inability to swallow can lead to malnutrition. The LES abnormalities in achalasia have been linked to loss of inhibitory neurons in the myenteric plexus secondary to unbridled cholinergic excitation of the smooth muscles.[75]

In a study of 78 patients with achalasia, intrasphincteric injections of botulinum toxin serotype A (Botox 100 U or Dysport 250 U) have been shown to produce reductions in esophageal sphincter pressure and symptomatology for up to six months after treatment.[76] In a placebo-controlled study that included 21 patients with achalasia, injections of botulinum toxin type A (80 U) into the LES produced significant reductions in symptom scores and LES pressure measurements and increases in the width of the LES opening, one week after treatment.[77] At six months after treatment, 67% of patients treated with botulinum toxin were still in remission. In addition, no serious adverse events were detected during the study. These studies suggest that, for patients with achalasia, botulinum toxin therapy can provide an effective and safe treatment alternative to traditional treatments such as balloon dilation and surgery.

Chronic anal fissure, a tear in the anal canal lining, involves spasm of the internal anal sphincter, resulting in inflammation and pain. Traditional treatments, such as lateral internal sphincterotomy and the topical application of nitroglycerine ointment, aim to reduce hypertonia and promote healing. Surgery, however, is associated with serious and permanent side effects, among them rectal incontinence. Recently, clinical studies have pointed to a potentially important role for botulinum toxin in the treatment of this disorder. In one study, 76 patients with uncomplicated anal fissure received injections of botulinum toxin (40 U on each side of fissure).[78] Complete and partial recovery was experienced by 67% and 25% of the patients, respectively. In this study, botulinum toxin permitted chemical denervation of the internal sphincter, promoting healing of the anal fissure.

In another study, botulinum toxin type A, as a single 20 U injection into the anal sphincter, was compared with glyceryl nitrate, 0.2% ointment, in a randomized study of 50 patients with symptomatic anal fissure.[79] After two months, healing occurred in significantly more patients treated with botulinum toxin (96%) than with glycerine nitrate (60%). This finding suggests that botulinum toxin type A may provide effective therapy for patients with anal fissure not responsive to nitroglycerine therapy, and, with the proper dosing expertise, might be suitable first-line therapy for this condition. Further, in this study there were no reports of relapse, side effects, or complications after a 16-month (mean) follow-up period.

Botulinum toxin treatment is also being explored in other sphincter and nonsphincter gastrointestinal syndromes, including diabetic gastroparesis, noncardiac chest pain, postoperative pylorospasm, and sphincter of Oddi dysfunction.[80,81]

Cosmetic Uses

Because it prevents the release of acetylcholine at the neuromuscular junctions, producing reversible paralysis of striated muscles, botulinum toxin has been found to be effective in the treatment of facial lines and wrinkles and in improving outcomes during laser facial resurfacing.[82-84] Botulinum toxin type A (Botox Cosmetic) has received FDA approval as an approach for providing temporary improvement in the appearance of moderate to severe glabellar lines. In addition, botulinum toxin type B may show similar benefits. In a small 12-week study that included 24 patients with hyperkinetic facial lines, botulinum serotype B (400 to 800 U) injected into the corrugator, orbicularis oculi, or frontalis muscles brought about significant reductions in the Wrinkle Improvement Score and Rated Numeric Kinetic Line Scale, with an onset of action within 72 hours after injection.[85] Although no complications were reported, patients noted that the pain associated with the botulinum serotype B injections was greater than that experienced with serotype A injections.

Tolerability

Generally, both botulinum toxin type A (Botox) and B (Myobloc) are safe and share a similar tolerability profile. Side effects are typically mild to moderate in severity and transient. According to their respective product labels,[24,25] however, these agents differ somewhat in the types and incidence of adverse reactions reported in trials of patients with cervical dystonia, a condition for which they share a common approved indication. For Myobloc, the most commonly reported adverse events were dry mouth (34%), dysphagia, (25%), dyspepsia (10%), and injection-site pain (15%). The incidences listed reflect the occurrence of these events at a dose of 10,000 U. Typically, fewer patients were affected at lower doses. For Botox, the most commonly reported adverse events were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Dysphagia, associated with the use of both Botox and Myobloc, may result from the diffusion of toxin away from the injection site and toward the larynx and, in rare cases, may be of sufficient severity to require the use of a gastric feeding tube. Dry mouth is another reaction that may result from toxin dispersion away from the injection site. This reaction was reported by about a third of the patients from Myobloc trials but by 10% or less of the patients treated with Botox. Whether the elevated occurrence of transient dry mouth associated with Myobloc will interfere with treatment remains to be determined. Myobloc is associated with a relatively high incidence of injection-site pain that might limit its usefulness when injections are needed into highly sen-

Table 3 **Botox™ and Myobloc™ Dosing Recommendations for Approved Indications**

Indication	Botox™	Myobloc™
Cervical dystonia	• Mean dose in Phase III studies is 236 U intramuscularly (range 198–300 U) divided among the affected muscles. • Dosing is tailored to the individual patient. Patients without prior use of botulinum toxin should be started with a lower initial dose. • Limiting the total dose injected into the sternocleidomastoid muscles to 100 U or less may decrease the occurrence of dysphagia.	• Initial dose in patients with a history of tolerating botulinum toxin injections: 2500–5000 U divided among affected muscles • Lower initial dose in patients without a history of tolerating botulinum toxin
Blepharospasm	• The initial recommended dose is 1.25–2.5 U (0.05–0.1 mL per site) injected at each site. • With repeated treatment, the dose may be increased up to twofold if the response from the initial treatment is considered insufficient. • Cumulative dose in a 30-day period should not exceed 200 U.	
Strabismus	• Injection should be carried out only with electromyographic guidance. • 1.25–2.5 U in any one muscle (for horizontal strabismus of 20 prism diopters to 50 prism diopters) • 2.5–5 U in any one muscle (for persistent VI nerve palsy of one month or longer duration) • 1.25–2.5 U in the medial rectus muscle (for subsequent dosing for residual or recurrent strabismus) • For patients experiencing incomplete response, subsequent doses may be increased up to twofold. • Maximum recommended dose as a single injection: 25 U	

sitive areas, such as the face and anal areas. The side effects of botulinum neurotoxins will likely vary, depending on the conditions treated, because of variations in injection sites and the doses needed to achieve a satisfactory clinical effect.

Dosing Issues

The product labels for botulinum toxin type A (Botox) and type B (Myobloc) both indicate that their units of biological activity—measured as median LD_{50} mouse units—are not interchangeable and cannot be directly compared or converted. This noninterchangeability reflects differences between humans and mice in botulinum neurotoxin sensitivity and differences in the various mouse LD_{50} assays used to determine activity. Clinically, the noninterchangeability means that doses of botulinum toxin types A and B cannot be directly compared and that the clinical actions of each product should be evaluated through product-specific clinical research studies.

In the treatment of cervical dystonia, the recommended initial dose of Myobloc ranges from 2,500 to 5,000 U, divided among the affected muscle groups (Table 3). In clinical studies, however, the greatest benefit with Myobloc was achieved with higher doses (e.g., 10,000 U).[19] Because of the lack of clinical data, effective dosing levels in conditions other than cervical dystonia are uncertain. The recommended Botox dose varies widely, depending on the condition treated, ranging from 1.25 U per site in blepharospasm and strabismus to as high as 100 U per site in cervical dystonia (Table 3). Across the cervical dystonia trials, the mean dose of Botox was 236 U, divided among the affected sites. Because of its 10-year history as a standard of care for cervical dystonia, the dosing with Botox is comparatively

well established. In contrast, because of the limited experience with Myobloc thus far, dosing in patients with cervical dystonia and other conditions is far less clear.

Because botulinum neurotoxin is an antigen, it can trigger an immune response, rendering treatment ineffective. Neutralizing antibody formation has been linked to high cumulative doses of botulinum toxin protein.[23,86] Thus, to reduce the potential for immunogenicity, the lowest possible effective dose should be used along with the longest interval between injections.[86]

Because appropriate drug preparation and administration are important, only a physician trained in the use of botulinum neurotoxins should administer these agents. Botulinum neurotoxin therapy cannot be oversimplified. This form of treatment often requires multiple, titrated doses precisely administered into the affected site to achieve optimal efficacy and to avoid unnecessary side effects.

Conclusions

The biological basis for the therapeutic value of botulinum toxin in an array of neuromuscular disorders can be attributed to local cholinergic cell selectivity, which reduces the chances for systemic side effects. In addition, these agents display a long duration of action. However, to achieve optimal therapeutic outcomes, botulinum toxin should be administered by specialists trained in neuromuscular chemodenervation injection techniques and diagnostic procedures, such as electromyography.

Moreover, clinically important differences might exist between the approved botulinum toxin types. In addition to the noninterchangeability of doses, which requires the clinical actions of each product to be evaluated on its own merits, potentially significant differences might exist in the pharmacology and side-effect profiles of these agents as well. Botulinum neurotoxin type A, for instance, displays greater activation or "nicking," and a lower neurotoxin protein load than serotype B, theoretically reducing the potential for immunogenicity. In addition, botulinum toxin type B is associated with a greater incidence of injection-site pain and dry mouth, events that might limit its usefulness in some patients. Nonetheless, head-to-head studies between botulinum toxin types A and B will be required to identify clinically meaningful differences in actual patient populations.

In addition to its FDA-approved indications, botulinum toxin type A has demonstrated therapeutic efficacy and safety in an array of neurologic and spastic disorders, as well as gastrointestinal conditions involving abnormalities in smooth muscle and sphincter control. At present, the clinical data are insufficient to determine whether other botulinum neurotoxin types, especially type B, will share the same clinical profile as serotype A. It is reasonable to assume that, over time, the approved indications for botulinum serotype A will expand to encompass some of the investigational uses for which it has provided benefits comparable to or superior to currently available treatment alternatives. A clear example would be the treatment of achalasia and anal fissure, where botulinum toxin type A has proved to be a simple and effective treatment alternative, when compared with some traditional treatments, such as surgery. It is also reasonable to assume that future clinical studies will not only elucidate but also expand the potential therapeutic role of other botulinum neurotoxin serotypes in the management of diverse neuromuscular disorders.

In a broader sense, the future of botulinum toxin therapy will be determined not only by the clinical evidence supporting its use in a variety of settings but also by its acceptance or rejection by managed care decision-makers. Given the growing evidence for the off-label uses of botulinum toxins, payers will need to monitor and compare the therapeutic and cost-effectiveness of these agents with each other and with traditional treatments. Over time, this comparison should help to identify which botulinum toxin type is best suited for a given spastic condition. Thus far, the clinical data suggest that botulinum toxin type A can be a cost-effective treatment alternative in several difficult-to-treat spastic conditions. As the clinical evidence builds, there might be increasing demands for botulinum toxin coverage that managed care organizations should be prepared to meet.

In sum, the clinician should realize that important differences in pharmacology exist between botulinum serotypes A and B, although the clinical relevance of these differences will not be fully understood until the completion of head-to-head clinical studies. Accumulating evidence supports the use of botulinum neurotoxin in myriad disorders associated with abnormal muscle.

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Evaluation Form

Botulinum Neurotoxin Therapy: Overview of Serotypes A and B

Participant Name: _____ Date: _____
Program Expiration Date: April 4, 2004

ACPE Universal Program Number: 067-999-02-037-H04.
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To keep your supplement intact, please photocopy this form. Your assistance in the evaluation process is greatly appreciated. To provide anonymity, your name is not required. Please return this form to the address on page 17.

Using the scale below for Objectives 1 through 6, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program:

SCALE FOR OBJECTIVES 1–6

1 = Not at all	4 = Well
2 = Not very well	5 = Very well
3 = Somewhat well	

Objectives

1. Identify the pharmacologic differences between botulinum toxin types A and B. _____
2. Discuss the potential for immunogenicity associated with botulinum toxin types A and B. _____
3. List the approved indications for botulinum toxin types A and B. _____
4. Describe the clinical uses of botulinum toxin types A and B. _____
5. Address the tolerability of botulinum toxin types A and B. _____
6. Describe the dosing issues associated with botulinum toxin types A and B. _____

Using the scale below for Questions 1 through 3, please indicate the number which best expresses your opinion:

SCALE FOR QUESTIONS 1–3

1 = Poor	4 = Very good
2 = Fair	5 = Excellent
3 = Good	

Questions

1. What is your overall rating for this program? _____
2. How would you rate the pertinence of the program materials to your practice? _____
3. Please rate each of the folowing program aspects:
   a. Content _____
   b. Clarity _____
   c. Knowledge gained _____
4. To what degree do you anticipate changes in patient care as a result of the material presented? *(Circle one)*

   1 2 3 4 5
   No change *Significant change*
5. Please indicate the length of time it took to complete this program: *(Circle selection)*

   Hours: 1 2 3
   Minutes: 0 15 30 45
6. Please rate the difficulty factor for completing this continuing education program: *(Circle selection)*

   Easy Moderate Difficult
7. Please rate your willingness to recommend this program to colleagues: *(Circle selection)*

   Very Willing Willing Not Willing
8. Please indicate which venue you prefer for obtaining continuing education: *(Circle selection)*

   Written monograph Slides Videos
   Internet-based Live sessions

Post-Test Form

Please circle the correct answer

1. Each of the seven botulinum neurotoxins differs in potency, duration of action, or cellular target.

True or False

2. When injected into hyperactive muscles, botulinum toxin induces

a) irreversible cholinergic blockade at the neuromuscular junction.
b) reversible cholinergic blockade at the neuromuscular junction.
c) irreversible dopaminergic blockade at the neuronal junction.
d) reversible dopaminergic blockade at the synaptic junction.

3. Cross-reactivity does not occur among the different botulinum serotypes.

True or False

4. Dysphagia has been associated with the use of both botulinum toxin type A and type B.

True or False

5. Cervical dystonia is

a) a muscle spasm that manifests itself as an uncontrollable, forcible closure of the eyelids.
b) a condition characterized by misalignment of the eyes.
c) an idiopathic condition characterized by abnormal postures and twisted movements of the neck.
d) characterized by unilateral flushing and seating in the cheek and behind the ears after eating.

6. In the U.S., botulinum toxin type A (Botox) is indicated for the treatment of

a) blepharospasm and strabismus only.
b) blepharospasm, strabismus and cervical dystonia in adults.
c) cervical dystonia only.
d) hyperhidrosis only.

7. In the United States, botulinum toxin type B (Myobloc) is indicated in the treatment of

a) cervical dystonia.
b) blepharospasm.
c) strabismus.
d) cervical dystonia, blepharospasm and strabismus.

8. Botulinum toxin has proved useful in the treatment of

a) achalasia.
b) anal fissure.
c) both of the above.
d) none of the above.

9. The units of biological activity of botulinum toxin type A can be readily converted into those of botulinum toxin type B.

True or False

10. The potential for immunogenicity associated with botulinum toxin can be reduced by

a) administering the lowest possible effective dose.
b) allowing for the interval between injections.
c) none of the above.
d) both A and B.

Record of Attendance

Botulinum Neurotoxin Therapy: Overview of Serotypes A and B

Date: _____ Program Expiration Date: April 1, 2004

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