

Botulinum Toxin

in Movement Disorders

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INTRODUCTION

Clostridial neurotoxins encompass tetanus and botulinum neurotoxins (BoNTs), which have 7 different serotypes. Clinical observations of cases of botulism (systemic intoxication with BoNTs) have shown that the effects are widespread with paralysis of the neuromuscular junctions and blockade of neurosecretion and the autonomic nervous system (1). The availability of highly purified toxins raised the possibility of using BoNTs as therapeutic tools.

Type A BoNT (BoNT-A) has been introduced in clinical practice in 1980. Since then, it has proven to be the most flexible tool for medical treatment, with more than 50 indications that apply to many medical conditions (Fig. 44.1). With the notable exception of anal fissure, BoNTs do not provide a cure but constitute a symptomatic remedy producing topical chemodenervation. Following a reduction in the release of neurotransmitters in the injected area, BoNTs reduce the activity of striated or smooth muscles and the secretory function of glands. Thus, the general indication for their use is to reduce muscle overactivity, release sphincter spasm, and inhibit gland secretion (2). Since the injections are topical and the indications are so diverse, there are different modalities to deliver the toxin at its targets. BoNT injections can be intramuscular, subcutaneous, intradermic, or intraglandular and can be performed by direct inspection or with instrumental guidance (electromyography [EMG], endoscopy, ultrasonography, or computed tomography [CT] scan). Other factors affecting the clinical outcome are dilution and reconstitution, needle gauge, anatomical approach, muscle location and size. In addition, recently proposed alternative delivery techniques are iontophoresis or cream application. BoNT clinics are places

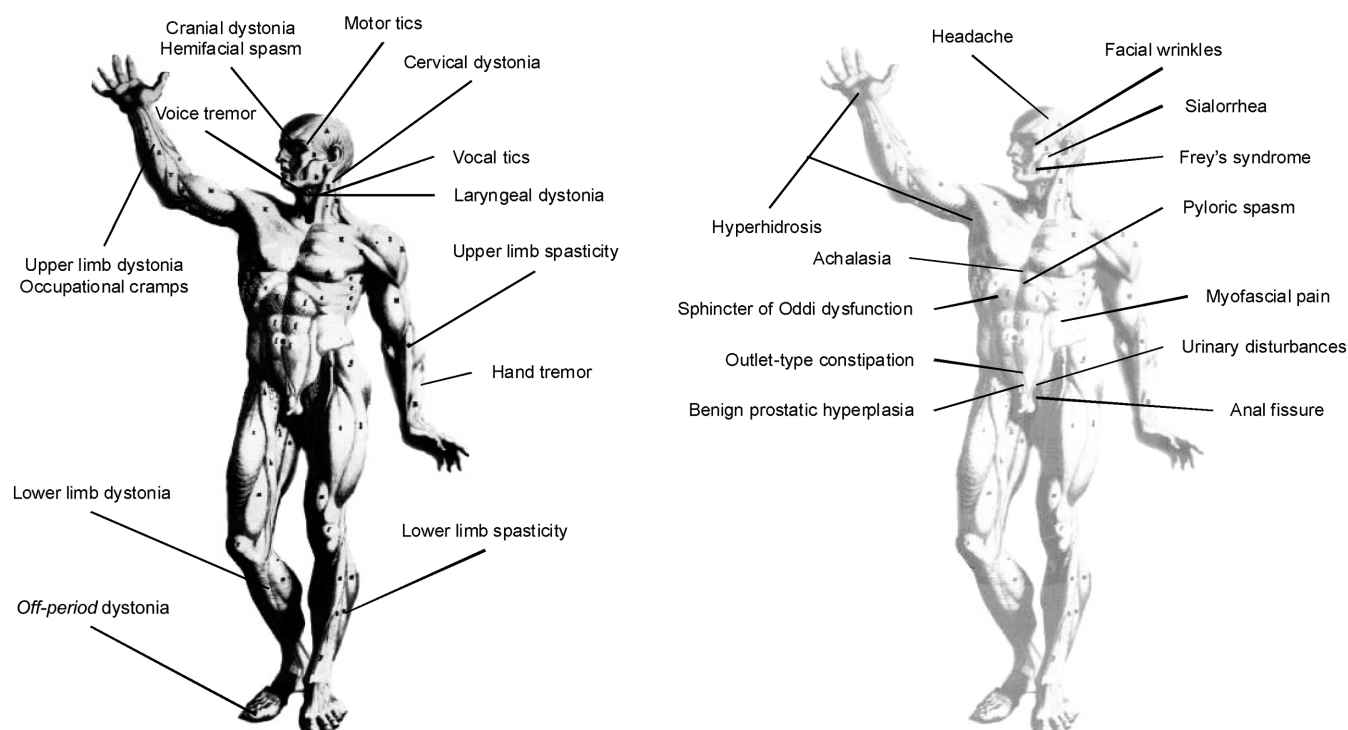
where highly skilled artisans apply theoretical knowledge with hands-on expertise.

BOTULINUM NEUROTOXINS: MECHANISM OF ACTION

BoNTs produce a chemical denervation that is topical, reversible, and dose-dependent. They inhibit the docking and subsequent opening of synaptic vesicles containing acetylcholine in the presynaptic musculoskeletal terminal, thereby impeding neuromuscular transmission. In addition, BoNTs exert a similar action on neuroglandular and autonomic terminals. The limiting factor for the action of BoNTs is receptor-mediated endocytosis. At least three different groups of presynaptic BoNT receptors, with different serotype specificity, are present at nerve terminals. Their molecular identity is not known, nor is known their exact distribution on the different presynaptic terminals (Fig. 44.2).

Although the 7 BoNT serotypes (named from A to G) are antigenically distinct, they have a similar structure and molecular weight, consisting of a heavy chain and a light chain joined by a disulfide bond. BoNTs are zinc (Zn^{2+}) endopeptidases composed of 3 functional domains where the catalytic function is confined to the light chain, with proteolytic activity located at the N-terminal end; translocation activity is concentrated at the N-terminal half of the heavy chain, and receptor binding at the C-terminal half. Three steps are involved in BoNT-mediated paralysis: internalization, disulfide reduction and translocation, and inhibition of neurotransmitter release. BoNTs bind to the presynaptic nerve ending and enter by receptor-mediated selective and saturable

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Other Indications

Figure 44.1 Synopsis of the main indications for clinical use of BoNT in movement disorders and other medical conditions.

endocytosis. The Zn-dependent catalytic domain of the toxin specifically cleaves different proteins essential for the fusion of synaptic vesicles containing the neurotransmitter. Table 44.1 lists the substrates cleaved by each BoNT serotype. Cleavage of any of these proteins interferes with the proper binding and fusion of a vesicle to the plasma membrane, and therefore impedes exocytosis-mediated neurotransmitter release.

Nerve terminals containing active BoNT do not degenerate; neurotransmitter release takes place again when the effect of BoNT wanes following degradation by proteolysis. Muscle denervation promotes a compensatory sprouting of nerve terminals and the formation of new synaptic contacts. This usually takes from 2 to 3 months and becomes a relevant phenomenon when repeated BoNT injections are performed in the same site. Following injection into a muscle or in the surroundings of nerve terminals, the main effect of BoNT is to produce a chemical denervation of neuromuscular junctions, resulting in weakness and atrophy of the striated muscle. BoNT diffuses from the injection site, depending on some physical variables; toxin spread is directly related to the total toxin dose injected and indirectly related to its concentration in the injection volume (3). Following injection into a muscle, BoNT diffuses locally and also may reach adjacent muscles and even

may trespass the muscle fascia. It also has been observed that BoNT can spread from the site of injection via the lymphatic system or bloodstream to reach distant sites, commonly producing subclinical effects (4). Clinical or subclinical BoNT-induced denervation can be detected by EMG, showing a reduction in the amplitude of compound motor action potentials (CMAP) following single or repetitive supramaximal nerve stimulation.

Although BoNT exerts its main action on the neuromuscular junction, some of the therapeutic responses observed in movement disorders appear not to be due only to peripheral effects. In most patients who receive treatment for dystonia or spasticity, the clinical benefit generally parallels muscle weakness; but other cases have been documented in whom the benefit is disproportionate, either because a significant improvement occurs without muscle weakness or, conversely, because there is little improvement notwithstanding marked weakness. In addition, BoNT-A also has been shown to inhibit release of mediators involved in nociception, such as substance P, calcitonin gene-related peptide (CGRP), and glutamate (5).

Some of the therapeutic responses observed in movement disorders are due to effects on the central nervous system (CNS). BoNTs do not cross the blood-brain barrier, and there is no in vivo convincing evidence that,

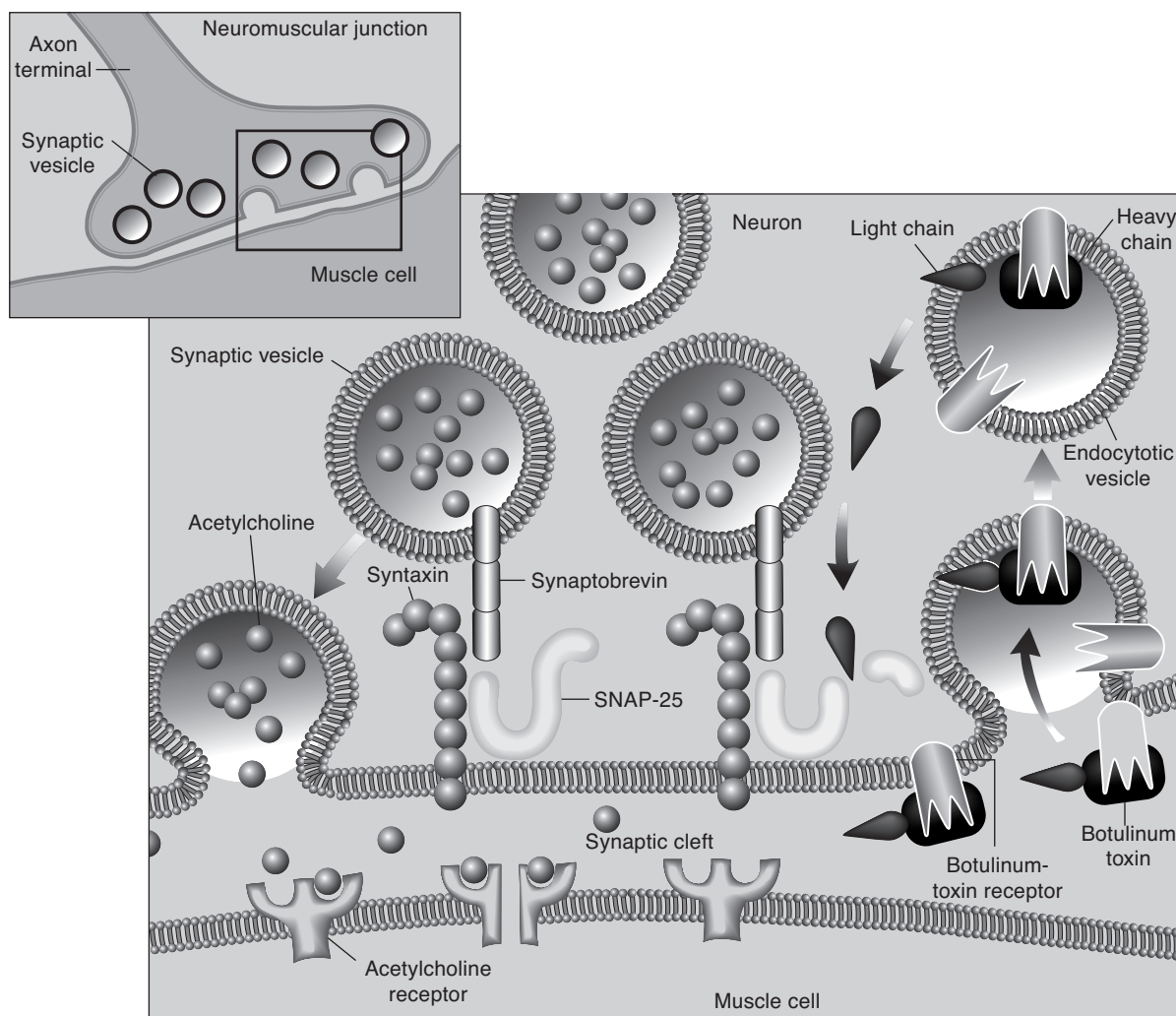


Figure 44.2 Sequence of action (from right to left) of botulinum neurotoxin type A (BoNT-A) at the neuromuscular junction: binding to the presynaptic terminal, entrance into the cell by endocytosis, and cleavage of SNAP-25 (25-kd synaptosomal-associated protein). The substrates of other BoNT serotypes are listed in Table 44.1. (From Hallett M. One man's poison: clinical applications of botulinum toxin. *N Engl J Med* 1999;341:118–120. With permission.)

TABLE 44.1
CLEAVAGE SITES OF BOTULINUM TOXINS

Serotype	Target
A	SNAP-25
B	Synaptobrevin
C	SNAP-25
	Syntaxin
D	Cellubrevin
	Synaptobrevin
E	SNAP-25
F	Cellubrevin
	Synaptobrevin
G	Synaptobrevin

SNAP-25, 25-kd synaptosomal-associated protein.

following injection in the periphery, they can reach the CNS and directly influence central sensory-motor integration. Notwithstanding, human and animal studies suggest that BoNT-A may indirectly influence the functional organization of the CNS by affecting the intrafusal terminals. Following BoNT denervation of gamma motor neurons, muscle spindle activity is decreased and inflow directed to the spinal alpha motor neurons is reduced (6). Since muscle activity is supported by afferent feedback, there may be a reduced alpha motor neuron drive. Furthermore, it has been postulated, but not demonstrated, that in humans BoNT may enter the CNS via retrograde axonal transport and may directly affect Renshaw cell activity by influencing the cholinergic recurrent motor neuron collateral (7). Many researchers have tried to elucidate the central effects

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of BoNT in patients with dystonia. In addition to the considerations mentioned, there is evidence to support that BoNT injections reverse a lack of inhibition that plays a pathogenetic role in dystonia, as demonstrated by the normalization of reciprocal inhibition and of intracortical inhibition. There is evidence of changes in the cortical organization, because cortical maps, which are distorted and extended in patients with dystonia, are normalized following peripheral injection of BoNT. Positron emission tomography (PET) studies on upper limb dystonia have demonstrated increased activation in the parietal cortex and in the caudal supplementary motor area, leaving unchanged the reduced activity of the primary motor cortex (8). The ultimate consequence of the reorganization of the human motor system induced by BoNT treatment may be long-term plastic changes in motor output.

COMMERCIALLY AVAILABLE NEUROTOXINS

Three BoNTs are available for clinical practice: 2 are serotype A and 1 is serotype B. These toxin brands differ for specific activity, packaging, constituents, excipients, and storage. Their main features are summarized in Table 44.2. Another BoNT-A, Xeomin produced by Merz Pharma (Germany), has been marketed in Germany. Furthermore, 3 additional BoNT-A products are to be released in the future: Linurase (Prolenium, Inc., Canada), CBTX-A (Lanzhou Biological Products Institute, China), and Neuronox (Medy-Tox Inc., South Korea). In addition to branded products, locally available BoNT-C and BoNT-F have been tested in blepharospasm, hemifacial spasm (9), and upper limb dystonia (10).

The 3 branded BoNTs are all marketed worldwide for cervical dystonia, which currently is the only approved

indication for Myobloc/Neurobloc. In addition, Botox and Dysport have a number of approved indications, including other focal dystonias, spasticity, hyperhidrosis, hemifacial spasm, and facial wrinkles. Official approval has been granted with remarkable differences in different countries within these broad categories. For example, in Italy and in Spain, Botox is currently licensed only for upper limb spasticity, whereas Dysport is licensed for both upper and lower limb spasticity. Remarkably, there are a number of randomized controlled trials showing efficacy of BoNT brands for other indications (e.g., anal fissure, benign prostatic hyperplasia) for which approval has not been sought.

The potency of branded BoNTs is measured by using a mouse protection assay, as LD₅₀ mouse units (U) that cannot be directly compared. Therefore, there is no formula to predict reliably which dose of a different toxin brand is to be used in a patient who already has received a standard treatment with another brand. A rough estimate is that 1 Botox U corresponds to 3–5 Dysport U and to 50 Myobloc/Neurobloc U. However, the equivalence varies based on the indication, the injected site, and the dilution. A gross equivalence ratio is required for practical reasons, particularly when it is necessary to shift a patient from one preparation to another. A critical revision of the available evidence on the comparability of Botox and Dysport has concluded that there are relevant intrinsic differences not allowing identification of a consistent bioequivalence (11). The two BoNT-A products differ in potency and tendency to diffuse, and their equivalence presumably varies according to the body part injected. Botox and Dysport must be reconstituted first; all the toxins are diluted before being loaded into a syringe for injection. The dilution ratio, the syringe size, and the needle gauge affect the immediate diffusion of the toxin into the injected tissue. Later diffusion depends on lymphatic drainage, blood supply, and local barriers (e.g., muscle fascia, connective tissue).

TABLE 44.2
MANUFACTURED BRANDS OF BOTULINUM TOXIN

Brand Names	Botox	Dysport	Myobloc/Neurobloc ^a	Xeomin
Manufacturer	Allergan Inc (USA)	IPSEN (France)	Solstice (United States)	Merz (Germany)
Serotype	A	A	B	A
Specific activity	20 U/ng	40 U/ng	70–130 U/ng	167 U/ng
Packaging	100 U/vial	500 U/vial	2500; 5000; 10,000 U/vial	100 U/vial
Constituents and excipients	Human albumin; sodium chloride	Hemagglutinin; human albumin 20% solution; lactose	Hemagglutinin and non-hemagglutinin proteins; human albumin solution 0.05%; sodium chloride; sodium succinate (pH 5.6)	Human albumin; sucrose
Preparation	Lyophilized	Lyophilized	Solution (5000 U/ml)	Lyophilized
Storage of packaged product	–5°C	Room temperature	Room temperature	Room temperature
Storage once reconstituted	2°C–8°C for several hours	2°C–8°C for several hours	2°C–8°C for several hours (if diluted)	2°C–8°C for several hours

^a Myobloc is the brand name in the United States, Neurobloc is the brand name in Europe.

Based on the available evidence, BoNT-A provides the first choice treatment for all approved indications, because of the best combination of efficacy, duration of action, and tolerability. BoNT-B has a shorter duration of action and more side effects than BoNT-A (12,13).

PRIMARY AND SECONDARY FAILURE

The success rate of BoNT treatments depends on a number of variables, such as the affected body site and the usage of instrumental guidance. Failures may occur at the beginning of a treatment sequence or after a number of successful treatments.

Primary failure is defined as a lack of clinical response (less than 25%) following the first and, at least, the second consecutive treatments. Secondary failure is defined as a lack of clinical response following further treatment in a patient who previously had adequate clinical improvement. A rate of 9.1% primary nonresponders and of 7.5% secondary nonresponders was observed in a series of 235 patients (14); these data are in keeping with those reported by other investigators (15). The main causes for primary failure are an incorrect diagnosis, inappropriate choice of injection sites, insufficient dose, and decreased potency due to mishandling of toxin during storage and transport. The main causes of secondary failures are changes in the treated condition (worsening or changes of pattern of muscle involvement in dystonia); technical reasons (wrong or suboptimal target choice, muscle identification, or BoNT delivery); and development of antibodies against BoNT.

There is agreement that the development of neutralizing antibodies can cause secondary failure; this possibility is now considered much rarer than originally estimated. Toxin-neutralizing antibodies have been detected mostly in subjects who underwent repeated treatments with high doses of BoNT-A for long periods (16,17). Practical issues that are thought to increase the probability to develop neutralizing antibodies are injection of high BoNT doses, frequent and repeated treatments (less than 2 to 3 months since previous injections), and high total amount of BoNT injected. Studies have shown that the heavy-chain fragment of the BoNT protein contains epitopes that are recognized by anti-heavy chain antibodies and by heavy-chain-primed T lymphocytes. The antibodies directed against the 150 kDa neurotoxin complex are the only ones that block the toxic function, whereas those directed against the light-chain or the nontoxin protein components of the complex are ineffective (2). The occurrence of nonneutralizing antibodies explains why enzyme-linked immunosorbent assay (ELISA), which has been long used to detect antibodies, is no longer applied. The finding of antibodies does not allow the assertion that they are neutralizing or directly responsible for secondary failure. Several methods are currently used to detect BoNT antibodies; however, the mouse protection assay is considered the most useful in the clinic, as it detects blocking antibodies (18). An alternative

to the biologic assays is to test immunoresistance simply by performing a standard injection of BoNT, which is known to produce a focal paralysis, into a superficial muscle that is easy to inject and to test in terms of strength and EMG activity, such as the extensor digitorum brevis (19), the frontalis, or the sternocleidomastoid (20). The presence of blocking antibodies, as determined by the mouse protection assay or clinical test, means that the patient will no longer respond to the serotype that induced the antibodies but may respond to another serotype. However, because of epitope homology among the various serotypes, the cross-reactivity also may result in immunoresistance to other serotypes. In a single case, it has been shown that plasma exchange can deplete antibodies against BoNT and restore efficacy to subsequent treatments.

BOTULINUM NEUROTOXINS IN MOVEMENT DISORDERS

Dystonia

Dystonia has been the first movement disorder treated with BoNT (21); it is dominated by repetitive and patterned muscle contractions producing abnormal movements and postures. Localized injections of BoNT provide a symptomatic remedy for primary and nonprimary forms of dystonia, as demonstrated by some randomized controlled studies and by a much larger cohort of uncontrolled studies.

Local treatment with BoNT is considered the first choice for cranial, cervical, and laryngeal dystonia. The overactive muscles can be identified by direct inspection or by EMG-guided targeting. As mentioned, direct inspection is usually sufficient to target a superficial muscle, such as most facial and some cervical muscles. EMG is necessary to target the sublingual, laryngeal, and most limb muscles; EMG-guided targeting also provides a second-line approach whenever improvement of muscle selection is needed (e.g., in cervical dystonia).

Blepharospasm and Cervical Dystonia

Although there are no high-quality, randomized, controlled efficacy data to support the use of BoNT in blepharospasm (22), several open-label studies on large series indicate that it is efficacious and safe and support its use (23). In keeping with this, the recently set guidelines of the European Federation of Neurological Societies provide a class-A recommendation that BoNT-A (or BoNT-B if there is immunoresistance to serotype A) is a first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia (24). The efficacy in blepharospasm has been confirmed by more than 50 open-label studies (that have recruited more than 2500 patients), and by few controlled studies. Typically, a total dose of 20–40 Botox U, of 75–175 Dysport U, or of 2500 Myobloc/Neurobloc U is injected. The average latency from the time of injection to the onset

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of improvement varies from 3 to 5 days; a benefit lasting for 2 to 3 months was observed in almost all patients. Side effects occur in less than 10% of treated patients and include ptosis, blurring of vision, diplopia, tearing, and local hematoma. The side effects normally resolve in fewer than 2 weeks. Blepharospasm may differentially affect the 3 concentric parts of the orbicularis oculi muscle; inadequate results are obtained if the toxin is injected in the orbital portion of a patient suffering from a predominant involvement of the pretarsal portion of the muscle (25). Furthermore, some patients with a predominant pretarsal involvement may have prevalent tonic eye closure and difficulty in voluntarily opening the eyelids (so-called *eyelid opening apraxia*) (26). EMG shows loss of the normal reciprocal inhibition between the levator palpebrae and the pretarsal portion of the orbicularis oculi, with co-contraction. BoNT-A is helpful in these cases if injected in the pretarsal portion and at doses lower than those used in the orbital part of the muscle (27). Secondary resistance to BoNT is exceedingly rare in patients who receive long-term treatment for blepharospasm (14); this is probably because the doses are lower and they are injected less often than in cervical dystonia or spasticity.

Cervical dystonia is the most common focal primary dystonia. BoNT is the first-choice treatment for this condition. As a result of early intervention with BoNT in patients with cervical dystonia, permanent neck contractures are now rare and surgical treatment, such as selective peripheral denervation, is seldom necessary (28). In a 12-week controlled trial, Dysport was found to be more efficacious than trihexyphenidyl, providing an obvious clinical advantage with fewer adverse events (29). Seven randomized controlled trials on cervical dystonia, encompassing a total of 233 patients, demonstrated beneficial effects (between 66% and 80% of subjective improvement) of repeated BoNT-A injections (30). The average total dose injected is 100–300 Botox U, 400–800 Dysport U, or 10,000–20,000 Myobloc/Neurobloc U; however, the doses can vary considerably based on individual variability. Most studies report that the average latency of clinical action is approximately 1 week; the average duration of efficacy is approximately 12 weeks or 3 months for BoNT-A and 12 to 16 weeks for BoNT-B. There is agreement that BoNT is more efficacious (and for longer) for pain reduction than it is for the control of involuntary movements. The most severe side effect and dose-limiting factor is dysphagia, which occurred in up to 36% of patients in a study. Open-label studies allow for greater flexibility than do randomized controlled trials in choosing BoNT doses and selecting the muscles to inject. These studies report efficacy of BoNT in cervical dystonia and point to a better outcome than randomized controlled trials. In keeping with this, it has been demonstrated that fixed BoNT doses and rigid muscle selection criteria provide less than optimal results (31). Two studies compared the efficacy of Botox and Dysport in cervical dystonia. In one study, Dysport proved to be more efficacious than

Botox in controlling pain and dystonic movements; however, there was a higher incidence of transient side effects (dysphagia, dysphonia, asthenia, neck weakness), probably because Dysport diffuses more than Botox (32). Dysphagia and dysphonia are thought to be caused by diffusion of BoNT injected in the sternocleidomastoid muscle to the underlying pharyngeal and laryngeal muscles. Particular care should be taken to avoid diffusion outside the sternocleidomastoid toward deeper structures.

The occurrence of primary or secondary failure is substantial in cervical dystonia. In a long-term study on 106 patients with cervical dystonia, 20 discontinued treatment for primary or secondary resistance and 13 were lost at follow-up (possibly due to inadequate improvement) (14). Controlled trials also have shown the efficacy of BoNT-B in cervical dystonia either in drug-naïve patients or in patients resistant to BoNT-A. Transient dysphagia and neck weakness are the most frequent complications. Compared to BoNT-A, BoNT-B is more likely to produce dryness of the mouth, presumably because it is more potent in blocking cholinergic release in postganglionic parasympathetic fibers to the salivary glands. BoNT-F also has been tested in cervical dystonia; the duration of efficacy, however, is much shorter and lasts for approximately 8 weeks (10).

Other Focal Dystonias

Several open studies, including more than 900 patients, have established the efficacy and safety of BoNT-A in the treatment of adductor and abductor laryngeal dystonia (also known as *spasmodic dysphonia*) (33). BoNT is considered the treatment of choice for this disorder despite the fact that no controlled studies have been performed. Most investigators report a 75% to 95% improvement in voice symptoms and a significant improvement in the quality of life. Adverse events include transient breathy hypophonia, hoarseness, and occasionally dysphagia with aspiration.

Other focal forms of dystonia (specifically oromandibular and upper limb dystonia) are improved by BoNT treatment, but the outcome is less satisfactory than that observed in cranial, cervical, or laryngeal dystonia. The main reason is that these forms usually have a complex combination of muscle involvement, making it difficult to find a therapeutic scheme with an acceptable side-effect profile. EMG-guided muscle selection and targeting are necessary in these cases. In addition, upper limb dystonia often occurs as an occupational cramp in people performing skilled fine movements with the hand or arm (e.g., musician's cramp, writer's cramp); in such cases, it remains difficult to ensure the requested quality of voluntary movement, without weakness, following BoNT treatment. A controlled trial on the efficacy of BoNT-A in oromandibular dystonia reported improvement in less than 40% of patients. The efficacy of BoNT-A treatment in writer's cramp has been the object of 2 placebo-controlled studies. In the first study, 5 patients (59%) had a

nonsignificant improvement; in the second study, speed and accuracy of pen control improved in 7 patients (35%). Overall, BoNT-A treatment has provided variable efficacy in upper limb dystonia, with an average improvement of 60% to 70% observed in some, but not all, patients (estimated from 35% to 85%). Pain is the symptom that most frequently improves after treatment, often independently of motor function.

In addition, BoNT-A has been injected successfully into the masseter and temporalis muscles of patients with jaw closure dystonia or into the submental muscles and the lateral pterygoid muscles of patients with jaw opening dystonia. This treatment may markedly improve the symptoms of temporomandibular joint syndrome and other oral and dental problems, as well as dysarthria and chewing difficulties. Transient swallowing difficulties have been reported to occur after fewer than 20% of treatment sessions.

Hemifacial Spasm

Hemifacial spasm (HFS) is a unilateral, involuntary, intermittent, and irregular clonic (rarely tonic) contraction of the muscles supplied by the facial nerve. Usually the disorder starts with involvement of the orbicularis oculi muscle, which is eventually followed by a gradual ipsilateral spread to other muscles, such as the frontalis, procerus, zygomaticus, risorius, levator labii superioris, depressor labii inferioris, depressor anguli oris, and platysma. This movement disorder has been attributed most frequently to the occurrence of a direct contact between the facial nerve and an ectopic anatomical structure (e.g., the basilar artery) or a pathological process (e.g., neurinoma of the acoustic nerve). Familial HFS also has been described. The spasm is thought to be generated by an axono-axonal ephaptic transmission and a hyperexcitable facial motor nucleus. Peripheral facial nerve injury or prior Bell's palsy also can result in HFS, sometimes combined with mild ipsilateral facial weakness. Although not a life-threatening condition, HFS may cause unremitting social disability, sometimes making the patients unable to sleep. HFS rarely subsides spontaneously, and most patients must pursue treatment for many years, if not throughout life. Several symptomatic drugs have been tried. Carbamazepine is the most common oral medication that has been reported to alleviate HFS in approximately 50% of patients. Surgical vascular decompression of the facial nerve (Janetta's technique) is a potentially curative approach successfully performed in a high percentage of patients (from 80% to 97%). Surgery has a recurrence rate of up to 25% during 2 years of follow-up; these patients are candidates for a second surgical treatment or can be treated with BoNT. In addition, a significant proportion of the patients may have permanent complications such as unilateral deafness or facial palsy.

Local infiltrations of BoNT-A are currently recognized as the symptomatic treatment of choice for HFS. At variance

with surgery, this treatment must be repeated to provide continued benefit. It has been suggested that BoNT also acts at the level of the nucleus of the facial nerve, following retrograde axonal transport to the cell body. This possibility has been confirmed by radionuclide studies in animals, but has not been further substantiated in humans. The efficacy and safety of BoNT-A in HFS are rated class A (34). In most cases it is sufficient to inject the periocular region to obtain improvement either in the upper or in the lower facial nerve territories. Therefore, a stepped approach is warranted with a progressive adjustment of the treatment scheme. A prudent dose choice is particularly advisable in cases of postparalytic HFS. In most studies, the average total dose injected is between 12.5 and 60 Botox U or between 10 and 120 Dysport U. It is considered that a minimum threshold BoNT dose is necessary to obtain benefit, particularly for the first treatment, and that the following doses must be titrated up or down according to the patient's response.

The average latency of clinical efficacy varies from 2 to 6 days, and the overall response to treatment is satisfactory with a successful outcome in 66% to 100% of patients. The mean duration of efficacy is reckoned to vary between 10 and 28 weeks. The duration of efficacy has been reported to increase with repeated treatments, more rarely to decrease or to remain unchanged. It also has been observed that the duration of benefit is shorter in severe cases than in those of moderate severity. The treatment is well tolerated. Facial weakness is the most commonly reported side effect, occurring in 75% to 95% of cases, particularly when injections are placed in the mid or lower face. In most patients who receive BoNT injections only in the orbicularis oculi region, marked benefit is also observed in mouth spasm, probably due to local diffusion of the toxin. Ptosis may occur following injections into the orbicularis oculi, with an incidence variably reported from 0% to 53% of cases. Primary or secondary failures are uncommon in patients with HFS. It has been reckoned that the incidence of primary failure varies from 0.02% to 1.4% of patients per year, and that secondary failure is as low as 0.9% of patients per year.

Spasticity

Spasticity is defined as a velocity-dependent increase in tonic stretch reflexes that arises from abnormal processing of sensory afferent inputs to the spinal cord. It is a central disorder of muscle tone characterized by increased resistance of an initially passive limb to externally imposed joint motion. Increase in tone is a reflection of the loss of descending inhibitory (reticulospinal) influences, resulting in increased excitability of dynamic gamma (fusimotor) and alpha neurons. In addition to the increase in tone, other frequently present features are increased muscle stretch reflexes, occurrence of muscle spasms and clonus, weakness (spastic paralysis), and

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impairment of voluntary movements. The goal of treatment is to reduce spasticity and the associated positive phenomena without worsening weakness (paresis). In addition, reducing antagonist muscle overactivity may uncover functional residual power. The therapeutic approach to spasticity requires a comprehensive and multidisciplinary judgment of functional goals. BoNT therapy is just one tool in a complex treatment plan (including physical therapy, orthosis, medication, etc.) that has to be progressively adjusted based on changing priorities. The simplest treatment paradigm is adult-onset focal spasticity, which customarily can be treated just with BoNT; at the other end of the spectrum, childhood-onset spasticity requires complex and gradually tuned medical decisions.

BoNT has been used to treat spasticity associated with juvenile cerebral palsy, stroke, brain trauma, amyotrophic lateral sclerosis, and multiple sclerosis, in which functional impairment includes difficulty in coping with activities of daily living and in obtaining adequate nursing care (dressing, hygiene). Often there are associated disabling limb and trunk postures, decreased range of motion of the joints, and excoriation of the palm caused by incoercible digit flexion. Severe or longstanding spasticity may lead to contractures and joint ankylosis. As a result, early treatment with BoNT may prevent musculoskeletal deformities and other orthopedic problems later in life, thus avoiding surgical interventions.

BoNT is injected into spastic muscles to balance muscle forces across joints. The approved indications in most countries are upper or lower limb spasticity, regardless of the etiology, and lower limb spasticity due to cerebral palsy. The amount of toxin injected into individual muscles depends on the toxin brand, the muscle size, the number of nerve terminals located in the muscle, and the patient's weight (Tables 44.3 and 44.4). As a rule, the doses of BoNT used in spasticity are higher than those used to treat other movement disorders. The dose limits for the use of BoNT in the treatment of spasticity, particularly in children, have been the object of evaluation. It is believed that a maximum of 6 Botox U/kg (body weight) in each muscle with a maximum total dose of 19 Botox U/kg should be injected (35); a safe upper limit for Dysport is 30 U/kg, with a maximum total dose of 1000 U in a child (36); a safe starting dose for children treated with Neurobloc/Myobloc is considered to be 400 U/kg weight, to be gradually up-titrated, with a maximum total dose of 10,000 U (37).

Observational and controlled studies have shown that BoNT-A improves function and symptoms in adult patients with poststroke upper or lower limb spasticity. Controlled studies on patients with increased flexor tone in the upper limbs, due to a previous stroke, have reported improvement of tone and of other features (dressing ability, hygiene, limb posture, and pain) 6 to 12 weeks following treatment with BoNT-A. Not as much evidence of efficacy has been

TABLE 44.3
RECOMMENDED DOSES OF BOTULINUM
NEUROTOXINS IN CHILDREN
WITH SPASTICITY

Injection Site	Botox Dose (U/kg)	Dysport Dose (U/kg)
Upper Limb		
Subscapularis	1–2	
Teres major	2	
Latissimus dorsi	2	
Pectoralis complex	2	
Triceps		
Biceps	2	
Brachialis	2	
Brachioradialis	1	
Pronator teres	1	
Pronator quadratus	0.5–1	
Flexor carpi radialis	1–2	
Flexor carpi ulnaris	1–2	
Flexor digitorum superficialis	1–2	
Flexor digitorum profundus	1–2	
Flexor pollicis longus	0.5–1	
Opponens pollicis		
Adductor pollicis		
Lumbricals	0.5–1	
Lower limb		
Quadriceps mechanism	3–6	
Hamstrings	3–6	6.5
Hip adductor group	3–6	
Gastrocnemius	3–6	10
Soleus	2–3	11
Tibialis posterior	1–2	
Tibialis anterior	1–3	
Extensor hallucis longus	1–2	
Flexor hallucis longus	1–2	
Flexor digitorum longus	1–2	
Flexor digitorum brevis	1–2	

collected for the lower limbs (spastic toe, in particular). The efficacy of BoNT-B on poststroke upper limb spasticity has been observed in open-label series but not confirmed by controlled trials.

Cerebral palsy is a disorder caused by perinatal brain injury that combines athetosis, dystonia, and spasticity in various degrees. Involvement of the lower limbs is responsible for early difficulties in gait and balance control. In children the most dynamic development can be observed during the first 6 years of life; accordingly, all therapeutic interventions on spasticity or movement disorders in this early period of life are evaluated against the background of a dramatically changing and developing motor system. To achieve an optimal therapeutic result, early intervention is required to tap into the developmental potential of the child. The trials of BoNT in children with cerebral palsy are limited by the small sample size

TABLE 44.4**RECOMMENDED DOSES OF BOTULINUM TOXIN IN ADULTS WITH SPASTICITY**

Injection Site	Botox Dose (U)	Dysport Dose (U)	Myobloc/Neurobloc Dose (U)
Upper limb			
Subscapularis	50–100	150–200	1000–3000
Teres major	25–100	60–150	1000–3000
Latissimus dorsi	50–150	200–400	2500–5000
Pectoralis complex	75–150	300–500	2500–5000
Triceps	50–200	300–500	2500–5000
Biceps	50–200	100–400	2500–5000
Brachialis	40–100	200–300	1000–3000
Brachioradialis	25–75	150–200	1000–3000
Pronator teres	25–75	80–100	1000–2500
Pronator quadratus	10–50	80–100	1000–2500
Flexor carpi radialis	25–100	100–200	1000–3000
Flexor carpi ulnaris	20–70	100–150	1000–3000
Flexor digitorum superficialis	20–60	150–300	1000–3000
Flexor digitorum profundus	20–60	150–200	1000–3000
Flexor pollicis longus	10–30	30–60	1000–2500
Opponens pollicis	5–25	30–60	500–1500
Adductor pollicis	5–25	30–60	500–2500
Lumbricals	10–50 per hand	30–80 per hand	1500–4500 per hand
Lower limb			
Quadriceps mechanism	50–200	500–1000	5000–7500
Hamstrings	50–200	350–500	2500–7500
Hip adductor group	200–400	150–500	5000–10,000
Gastrocnemius	50–250	250–1000	3000–7500
Soleus	50–200	200–500	2500–5000
Tibialis posterior	50–150	200–500	3000–7500
Tibialis anterior	50–150	250–400	2500–5000
Extensor hallucis longus	50–100	150–250	2000–4000
Flexor hallucis longus	25–75	100–200	1500–3500
Flexor digitorum longus	25–100	150–300	2500–5000
Flexor digitorum brevis	20–40	100–200	2500–5000

and differ for methodology and outcome measures; this is probably the main reason why the available evidence has not been considered sufficient to prove efficacy by some recent meta-analyses. Notwithstanding the evident methodological difficulties, efficacy and safety of BoNT-A in the management of lower limb spasticity associated with cerebral palsy have been reported in controlled trials. This remains, notwithstanding, an open field for future research.

Common side effects observed in patients with adult spasticity or cerebral palsy include muscle soreness, pain at injection site, skin rash, fatigue, excessive weakness, influenzalike symptoms, infection, and allergic reaction. Autonomic side effects (especially dry mouth) are particularly common following treatment with BoNT-B and are dose dependent.

BoNT also has been used to treat spasticity in patients with motor neuron disease or multiple sclerosis. There is insufficient documentation to assess the efficacy and safety of BoNT treatment in these conditions.

Tics

BoNT-A has been used to treat motor or vocal tics in patients with chronic tic disorders. The first anecdotal observations were made in patients with Gilles de la Tourette's syndrome with dystonic tics (38). BoNT-A treatment reduced the frequency and the intensity of tics and ameliorated the associated premonitory sensory urge; this benefit lasted for several weeks. A trial of BoNT on vocal tics also yielded symptomatic improvement and ameliorated quality of life. A controlled trial has confirmed the efficacy of BoNT-A for the treatment of simple motor tics with a 39% reduction in the number of tics per minute on a videotape segment (compared to a 6% increase in the placebo group) and a significant reduction of the urge score. The patients, however, did not report a comparable subjective benefit from this treatment.

It is possible to try BoNT-A in patients who have simple and repetitive motor or vocal tics, particularly if there is no indication to prescribe a systemic medication. More

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studies are required to identify the long-term outcome of BoNT in patients with tic disorders.

Tremor

BoNT-A has been used to treat hand tremor of different origin with controversial results. Evidence of efficacy has been collected by a controlled study, showing improvement of postural, but not kinetic, hand tremor in patients with essential tremor (39). This study showed limited functional improvement and dose-dependent hand weakness as a side effect. Improvement of voice tremor was demonstrated using objective acoustic measures in 3 of the 10 patients who received bilateral BoNT-A injections (2.5 Botox U in each thyroarytenoid muscle).

The evidence collected is insufficient to indicate a primary role of BoNT in the symptomatic treatment of tremors; however, there may be an indication for some specific forms of tremor that cannot be adequately treated with systemic drugs or deep-brain stimulation. BoNT can be helpful, particularly with atypical presentations or when tremor is confined to a few muscles.

Other Movement Disorders

Some cases of myoclonus have been treated with BoNT injections. Tinnitus associated with palatal myoclonus has proven to be responsive to BoNT-A (4–10 Botox U or 30–60 Dysport U) injected in the tensor veli palatini muscle (or alternatively in the levator veli palatini). Other forms of myoclonus treated with BoNT-A are secondary to head trauma or spinal cord infarcts.

Tardive dyskinesias are a potentially persistent and disabling abnormal involuntary movement disorder secondary to the use of neuroleptic drugs. Tardive dyskinesias can be relieved by BoNT (40). Their clinical features are variable, but most often they present as orolingual and facial movements that usually are choreic or dystonic in nature. Tardive dystonia responds as well as primary dystonia to BoNT treatment, depending on the sites affected. It may present as blepharospasm, cervical dystonia, or orolingual dystonia. In a series of 300 patients with cervical dystonia, 6% were of tardive etiology. The range of doses overlaps with that used to treat primary dystonia.

Anecdotal reports indicate that akathisia and bruxism also can be treated with BoNT injections. Bruxism is grinding, gnashing, or clenching of the teeth during sleep or situations that evoke tension or anxiety. In some cases, bruxism may be associated with contractures of the temporalis muscle. It occurs most often in the early part of the night, and it may be idiopathic or a symptom of several neurological conditions. BoNT-A has been reported to be effective in bruxism, and it has been confirmed that satisfactory clinical control is achieved regardless of the etiology. The dose range is wide (25–100 Botox U).

Fixed Contractures

Patients with movement disorders may present fixed contractures that usually involve one or more limb joints and can be proximal or distal. Primary contractures occur in fixed dystonia or in spasticity; secondary contractures occur in Parkinson's disease (PD) or other parkinsonian syndromes. The use of BoNT to treat fixed contractures is a logical approach if there is no evidence of joint deformities or of tendon or muscle abnormalities that might impede an increase in range of motion following chemical denervation of the muscle. In some patients, the appropriate muscle selection can be performed by assessing passive joint mobility under general anesthesia.

Children who could not open the mouth due to focal spasticity of the masticatory muscles have been treated with BoNT-A bilaterally in the masseter and the temporalis (150 and 75 Dysport U, respectively, on each side) with satisfactory outcome lasting for 90 days. BoNT injections are also performed to reduce neck, jaw, or limb contractures in the advanced stages of parkinsonian syndromes (see the following). The problem with a clenched fist is hand hygiene. The hand becomes dirty and the nails cut the palm skin. Dirtiness and infections create a vicious circle that can be resolved by treatment with BoNT. Clenched fist can be relieved by injections to allow cleaning and drying the hand, and lockjaw (or trismus) can be treated to help feeding or to warrant mouth hygiene.

COMPREHENSIVE APPROACH TO PARKINSONIAN PATIENTS

Patients with parkinsonian syndromes can benefit from BoNT treatment for many symptoms associated with their conditions. Some indications are better established than others, but, in principle, a BoNT consultation should be available at every clinic devoted to parkinsonian syndromes (Table 44.5). Motor symptoms that are treatable with BoNT include dystonia, contractures, and possibly freezing of gait; nonmotor symptoms include sialorrhea, bladder hyperreflexia, constipation, and benign prostatic hyperplasia.

Off-Period Dyskinesias

Dyskinesias are a frequent finding in PD patients. Focal dystonia is the most common off-period dyskinesia observed in PD patients and in patients with Parkinson's-plus syndromes, such as corticobasal ganglionic degeneration. *Off-period* dystonia is often painful: It may occur in the morning (early morning dystonia) or during the daily off periods. In addition, *on-period* dystonia is also observed. Dystonia involves more frequently the limbs, the neck, or the face, mainly the periorcular muscles, and can be painful, particularly off-period foot dystonia (41). BoNT-A is efficacious for treating off-period dystonia in limb muscles that must be

TABLE 44.5
INDICATIONS FOR BoNT TREATMENT
IN PARKINSONIAN SYNDROMES

Motor Symptoms

Dystonia

- Painful foot dystonia
- Outlet-type constipation
- Laryngeal and cervical dystonia
- Cranial dystonia

Contractures

- Upper limb
- Trismus

Freezing of gait

Nonmotor Symptoms

Sialorrhea

Urinary symptoms

- Bladder hyperreflexia
- Prostate hyperplasia

selected based on the coincidence of a dystonic cramp and localized pain. Dystonia and pain respond as well, but off-period pain unrelated to dystonia does not respond adequately. EMG guidance may be required to inject deep muscles, particularly in the legs. Off-period cervical dystonia, blepharospasm, and oromandibular dystonia can be managed the same way as the corresponding forms of primary dystonia, by administering a relatively low starting dose to be gradually up-titrated.

Parkinsonian syndromes are often complicated in the advanced disease stages by neck or head contractures. The flexed PD posture (camptocormia) may give rise to fixed antecollis. A typical feature of multiple system atrophy, instead, is disproportionate antecollis, in which a flexed neck makes contact with a nonflexed trunk; in addition, there is often a certain degree of torsion. In progressive supranuclear palsy (PSP), there may be an extended neck with fixed retrocollis. In late stages, parkinsonian syndromes may be complicated by contractures of the masseters that impede oral hygiene and chewing. Swallowing also may become impaired in later stages of parkinsonian syndromes. Little experience has been reported abouthandling such late-stage complications with focal injections of BoNT, but we have successfully treated a few such patients.

It has been postulated that freezing of gait, a parkinsonian symptom poorly responsive to dopaminergic medication, improves following treatment with BoNT-A. A woman affected by hemiparkinsonism was treated for leg dystonia with injections in the gastrocnemius-soleus and in the extensor hallucis longus (42). An open-label trial with BoNT-A (total dose: 100–300 Botox U) produced some improvement of freezing of gait that lasted for 2 to 12 weeks.

This observation could not be confirmed by later open-label or controlled studies with BoNT-A and BoNT-B. The pathophysiology of freezing of gait in PD is poorly known, and there is no solid basis for understanding the principles by which BoNT should be helpful for this symptom.

Constipation

Chronic constipation occurs in more than one-half of PD patients and is caused mainly by a reduction of motility in the colon caused by peripheral dysautonomia and aggravated by antiparkinsonian medication. In 13% of PD patients, constipation also is caused by inability to evacuate stools at straining, associated with lack of relaxation of the puborectalis muscle (so-called *outlet-type constipation* or *pelvic floor dysfunction*) (43). Failure of the puborectalis muscle to relax (or its paradoxical contraction instead) during efforts to defecate have been considered a focal dystonia (44). With an effort to evacuate the rectum, the puborectalis muscle normally relaxes to straighten the anorectal canal. If this does not occur appropriately, patients are unable to defecate and stools accumulate in the rectum. The diagnosis of outlet-type constipation is supported by the observation of an abnormal anorectal angle during attempted evacuation of barium paste and by EMG of the puborectalis muscle during straining. BoNT-A injections into the puborectalis muscle improve defecation in patients with outlet-type constipation. A total of 30–100 Botox U or 90–300 Dysport U can be injected in the puborectalis muscle during transrectal ultrasonography. The procedure is simple and well tolerated. The effects last for less than 2 months, and the treatment can be repeated. Side effects are mild and consist mainly of transient incontinence.

Sialorrhea

Sialorrhea (or drooling) is commonly associated with PD or other parkinsonian syndromes, due to a reduction of automatic swallowing in patients with akinesia. Injections of BoNT into the salivary glands reduce the production of saliva, thereby reducing drooling. Reduced swallowing also occurs in other neurological conditions, such as motor neuron disease, cerebral palsy, encephalopathies, or stroke; by contrast, increased salivation can be caused by lesions or by foreign bodies introduced into the mouth, by rabies infection, by mercurial poisoning, or as a side effect of antiepileptic drugs or of atypical neuroleptics (e.g., clozapine). Traditional treatments of sialorrhea (e.g., anticholinergics, surgical gland resection, transposition of the excretory ducts, tympanic neurectomy, or local irradiation) are poorly efficacious and often irreversible. The advantage of using BoNT is that the total dose and the injection schedule can be modified according to the patient's needs and to variations of antiparkinsonian medication.

The idea of injecting the parotid glands with BoNT-A to treat sialorrhea was first developed in patients with motor

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neuron disease. Further open-label studies have investigated the possibility of controlling drooling by injecting the parotid glands (which are responsible for 20% of total saliva production, at the time of eating) or the submandibular glands (which are responsible for 70% of basal saliva production). Doses injected in the parotid gland varied from 5–40 Botox U and from 20–150 Dysport U; Neurobloc was injected at a dose of 1000 U. In the submandibular gland, instead, the doses varied among 5–15 Botox U, 80 Dysport U, or 250 Neurobloc U. Treatment of the submandibular gland alone is much less effective than is the combined treatment.

The reported duration of benefit of BoNTs varies from 3 to 30 weeks. No systemic side effects have been reported. Some patients experienced local side effects, such as excessive dryness of the mouth, worsening of dysphagia, chewing difficulties, jaw dislocation, weakness of nearby muscles, local pain at injection site, or hematomas.

In all studies, BoNT injections were placed percutaneously, with or without ultrasound guidance. In one pilot study, direct retrograde injections were placed through Stenon's duct and the lingual ducts using a small catheter; this technique was associated with serious side effects and was not tolerated by the patients. Ultrasound guidance improves the efficacy and safety of treatments and helps to avoid vascular and nervous structures, as well as the masseter muscle.

To prevent the potential side effects of BoNT treatment, it is appropriate to start with low doses only in the parotid gland, depending on the amount of drooling. There is an inverse relation between the extent of drooling before treatment and the duration and degree of clinical benefit. If the starting dose is ineffective, higher doses can be tested in the parotid glands; then the submandibular glands also may be injected. The reduction of saliva flow can increase dental caries and requires adequate dental supervision if the treatment is prolonged over time.

BoNT-A also has been used to treat sialorrhea in children and secondary sialorrhea caused by clozapine administration. Overall, BoNT is effective, especially when administered in more than just one salivary gland. Up to two-thirds of patients subjectively experience a marked to moderate improvement following treatment, resulting in amelioration in their quality of life. The reduction of drooling can be estimated with objective measures and is often substantial; the duration of clinical improvement lasts as long as for dystonia and spasticity.

Micturition Disturbances

PD patients typically present an overactive urinary bladder causing urgency and other urinary symptoms. In PD, urethral sphincter function is preserved and incontinence is an uncommon late occurrence. More severe symptoms may occur in other parkinsonian syndromes. Moderate-to-severe bladder dysfunction, consisting of urgency, hesitancy,

nycturia, incontinence, or retention requiring catheterization, is observed in up to 80% of patients with multiple system atrophy. Urinary symptoms of multiple system atrophy result from a combination of detrusor hyperreflexia and urethral sphincter weakness. These pathophysiological features account for the early appearance of incontinence after an initial period of urgency due to bladder hyperreflexia. In later stages of multiple system atrophy, the detrusor may become hypotonic, producing difficulty of voiding and incontinence due to the associated sphincter weakness.

Detrusor overactivity occurs in patients with neurogenic bladder. These patients can benefit from BoNT injections into the detrusor muscle, even if they respond inadequately to (or do not tolerate) anticholinergic medication. In patients with spinal cord injuries, it has been observed that BoNT-A injection (200–400 Botox U or 300 Dysport U) into the detrusor muscle increases the maximum cystometric bladder capacity and decreases the maximum detrusor voiding pressure. This improvement could still be detected 36 weeks after treatment. Anticholinergic medication could be reduced or abolished. Similar observations have been performed in children with neurogenic detrusor overactivity due to myelomeningocele. Experience with lower urinary tract dysfunction can be extrapolated to the micturition disturbances observed in parkinsonian syndromes. No study has specifically addressed parkinsonian patients, but unpublished evidence suggests that micturition disturbance in PD is amenable to treatment with BoNT (Brisinda et al., unpublished observation).

BoNT-A is effective in reducing urethral resistance and facilitating voiding efficiency in patients with urinary retention caused by cauda equina lesions, peripheral neuropathy, detrusor failure, or nonrelaxing urethral sphincter. The injections are made into the external urethral sphincter (100 Botox U, 300 Dysport U). Patients who used to void by means of Valsalva's maneuver improved after treatment and gave up using a catheter. Similar results were achieved in patients with dysuria or urinary retention due to detrusor underactivity and a nonrelaxing urethral sphincter. These results have not been confirmed by other series, indicating that further studies are necessary.

Benign prostatic hyperplasia is a nonmalignant enlargement of the prostate that involves both the stroma and the epithelium of the gland. Symptoms related to benign prostatic hyperplasia add up to other urinary symptoms associated with PD and lead to incomplete bladder emptying or complications, such as acute urinary retention. Benign prostatic hyperplasia is rarely detected before age 40 years, and its incidence increases with age. More than half of the men are symptomatic in their sixties and as many as 90% are symptomatic in their seventies or eighties. Prostate resection is the gold-standard treatment for symptomatic benign prostatic hyperplasia; however, approximately 25% percent of patients who undergo surgical treatment do not have a satisfactory long-term outcome. Patients with urinary symptoms due to neurogenic bladder dysfunction

have a worse outcome after surgery. Direct BoNT-A injections into the prostate have been the object of a 2003 randomized controlled study (45). A dose of 200 Botox U was injected in 2 sites, 1 in each lobe. BoNT-A caused a reduction in prostate volume, inducing a decrease in the mean residual urinary volume.

OTHER INDICATIONS FOR BOTULINUM NEUROTOXINS

Secretory Disorders

Secretory disorders may be primary conditions but often are secondary to neurological diseases, such as sialorrhea in PD or in motor neuron disease, gustatory sweating after facial nerve injuries, or pathological tearing in blepharospasm. It has long been recognized that botulism has autonomic effects that are more pronounced following intoxication with BoNT-B (46). The denervation of peripheral cholinergic parasympathetic terminals, and possibly also of terminals containing other neurotransmitters, is responsible for the autonomic symptoms.

Hyperhidrosis is an idiopathic condition of exaggerated sweat production by the eccrine glands that affects approximately 1% of the population. Hyperhidrosis may be focal or generalized. Focal hyperhidrosis affects the axillae, palms or soles, and, less commonly, the face. The disease may be primary (caused by overactivity of sweat glands in specific areas) or secondary to spinal cord injuries or neuropathies. There is class-A evidence on the efficacy of BoNT-A in axillary hyperhidrosis and class-B evidence for the treatment of palmar and gustatory sweating (47). The doses used in each axilla are 50 Botox U or 100–200 Dysport U; more limited experience suggests that the dose of BoNT-B is as low as 250 Myobloc or Neurobloc U or by contrast much higher (2000–4000 U). The treatment is safe, and clinical efficacy lasts for 6 months or more, yielding a substantial improvement in quality of life. The doses used for palmar hyperhidrosis are between 50 and 100 Botox U in each hand or 200–400 Dysport U, or 5000 Myobloc/Neurobloc U. BoNT-A is effective in treating palmar hyperhidrosis in more than 70% of cases, yielding a substantial improvement for up to 6 months. The treatment is safe, although mild weakness of hand muscles repeatedly has been reported with all BoNT serotypes, and dry mouth has been noted with BoNT-B. The injection technique is based on the performance of multiple intradermic injections in the hyperhidrotic areas revealed by Minor's iodine test; direct injections are painful and usually require local anesthesia. As an alternative, iontophoretic delivery, not requiring anesthesia, has been used.

Gustatory sweating (Frey syndrome) is due to the aberrant sprouting of cholinergic secretomotor fibers after a parotid gland lesion; this condition also can be associated

with diabetes and other neuropathies. Sweating occurs on the cheek in response to salivation or expectancy of food. Several uncontrolled studies have documented the efficacy and safety of BoNT-A injection into the affected skin areas detected by means of Minor's iodine test. The doses used are between 16 and 80 Botox U, 70–175 Dysport U, or 6000–7500 Myobloc/Neurobloc U. The procedure is well tolerated.

Pathological Tearing and Rhinorrhea

Secretomotor fibers of the facial nerve innervate the lacrimal gland through the greater superficial petrosal nerve. Following injuries to the proximal part of the facial nerve, the visceromotor fibers, originally innervating the salivary glands, aberrantly connect to the fibers of the lacrimal gland. This causes a hyperlacrimation whenever the patient salivates (crocodile tears). Local BoNT-A injections directly into the lacrimal gland or around the eye may correct this symptom. The doses used are 20–30 Botox U or 20–75 Dysport U.

A potential therapeutic role in treating rhinitis and rhinorrhea was postulated following experimental studies on animals. One controlled and several uncontrolled clinical trials have been performed. The submucosal injection into the turbinates of 20–30 Botox U on each side relieves rhinorrhea, nasal obstruction, sneezing, and itching.

Substitute for Avoidable Surgical Procedures

BoNT can be employed to avoid unnecessary surgery and general anesthesia in patients who have medical conditions, such as rectocele, anal fissure, or prostatic diseases.

Rectocele is a hernia of the anterior rectal wall into the lumen of the vagina. It has been suggested that in some instances the rectocele is caused by failure of relaxation or paradoxical contraction of the puborectalis muscle occurring during attempted evacuation, but the reason for its establishment is not clear. Injections are performed on either side of the puborectalis muscle and in the anterior third of the external anal sphincter. A total dose of 30–100 Botox U is employed.

A chronic fissure is a painful cut or crack in the anal canal or anal verge that can be seen as the buttocks are parted; it is associated with a spasm of the internal anal sphincter and has been treated traditionally with internal sphincterotomy. Controlled and uncontrolled studies have provided class-A evidence on the efficacy of BoNT-A injections into the internal anal sphincter, with doses ranging from 10–40 Botox U or 100–150 Dysport U. The external anal sphincter also can be targeted. The procedure is safe, and fissure healing is usually attained following a single or a few repeated treatment sessions.

BoNT-A has been used to treat some common situations confronting the practicing urologist: nonbacterial

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prostatitis and benign prostatic hyperplasia. The injections are made directly into the prostate by ultrasound guidance, as previously reported.

CHRONIC PAIN DISORDERS

BoNT improves chronic pain disorders, probably due to a direct antinociceptive effect. Although the mechanism of the analgesic action of BoNT remains obscure, there is a growing body of evidence of a direct influence on pain that is not mediated by muscle spasm (5,48). In keeping with this hypothesis, it has been observed repeatedly that pain relief precedes motor improvement in patients with dystonia or spasticity. The antinociceptive action of BoNT may be mediated by neurotransmitters other than acetylcholine.

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