

Botulinum Neurotoxin **10** in Tremors, Tics, Hemifacial Spasm, Spasmodic Dysphonia, and Stuttering

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INTRODUCTION

Therapeutic indications for the use of botulinum neurotoxins (BoNT) in movement disorders have steadily expanded since the first introduction in patients with dystonia in the 1980s.¹ The possibility of treating patients with hemifacial spasm (HFS) was identified early,² whereas the indications for tremors³ and spasmodic dysphonia (SD)⁴ were proposed later. BoNT treatment was also later proposed for the treatment of eyelid tics, usually manifested by bursts of blinking but, in some cases, becoming more sustained, resembling blepharospasm.⁵ With the exception of HFS, the indications reviewed in the present chapter have remained outside the mainstream of BoNT use, partly because of the limited number of patients affected, difficulty and risk in performing the treatment (as in the case of SD, particularly of the abductor type), and uncertain outcomes (as in the case of tremors).

HEMIFACIAL SPASM

HFS typically presents with unilateral, involuntary, intermittent and irregular clonic or tonic contractions of the cranial muscles supplied by the facial nerve.⁶ HFS is a sporadic disorder in most cases, but it can occasionally occur as a familial disorder. The twitching movements usually start in the orbicularis oculi, initially

involving the lower eyelid, gradually spreading to other ipsilateral facial muscles, frequently involving also the frontalis muscle, producing the “other Babinski sign” manifested by ipsilateral eye brow elevation.⁷ HFS spasm may also spread to involve the platysma. HFS is a chronic disorder, affecting women more than men.⁸ It is frequently attributed to the compression of the facial nerve at the root exit zone by an ectopic anatomic or pathologic structure, resulting in axono-axonal “ephaptic” transmission and increased excitability of the facial motor nucleus.⁸ Peripheral facial nerve injury or antecedent Bell palsy can also precede HFS; in such cases, the HFS often coexist with a mild ipsilateral facial weakness and synkinesis.⁹ Patients without an history of Bell palsy may still have abnormal electromyographic (EMG) findings suggesting a preceding facial nerve damage and subsequent pathologic regeneration.⁸ HFS is unilateral in most cases but may rarely occur bilaterally.¹⁰ In our experience, of 296 patients with HFS, two presented with a bilateral form, in which the two sides contracted asynchronously, but otherwise the HFS was typical without evidence of blepharospasm.

Treatment Options

HFS may have a severe impact on the patient’s appearance and causes social embarrassment.

Dr. Bentivoglio has received lecture fees and research grants from Allergan and Ipsen; Dr. Fasano does not report any conflicts of interest; and Dr. Albanese reports the following disclosures: The Neurotoxin Institute, Advisory boards for Allergan, Ipsen, and Merz.

Because it persists during sleep, it may lead to insomnia. Because spontaneous remissions are infrequent,¹¹ most patients need to be treated for many years, if not over their entire lifetime. Treatment options aim at reducing or stopping muscular twitches, and include BoNT injections, medications, neurosurgery and more recently, doxorubicin chemomyectomy.

Medications are often ineffective in the long-term management of HFS, although they may provide transient relief. Many drugs have been used, usually without substantial benefit. These include carbamazepine, a membrane-stabilizing drug that has been reported to alleviate HFS in approximately 50% of patients.¹² In addition, baclofen, clonazepam, phenytoin, orphenadrine, felbamate, gabapentin, latanoprost (a prostaglandin derivative), and levetiracetam have been reported to provide at least transient or mild symptom relief.

Surgical approach, using microvascular decompression, consists of placing surgical gauze or some other barrier, such as surgical or fibrin glue, between the facial nerve and the compressing vessel.^{13,14} The success rate of microvascular decompression is high (from 88% to 97%), but symptoms recur in as many as 25% of patients within 2 years after the surgery.¹⁵ Furthermore, complications occur in more than 20% of the patients, and sometimes are severe (e.g., permanent deafness or facial palsy).¹⁶ In the majority of cases, there is a durable resolution of HFS for up to 17 years, supporting the indication for surgery in younger patients.¹⁷⁻²⁰

Chemical myectomy or facial nerve block with doxorubicin is a possible alternative; the results reported so far are promising, and the most frequent adverse events consist in skin inflammation.^{21,22}

During the last 2 decades, BoNT treatment has emerged as the first-choice option for HFS.^{23,24} Two randomized controlled trials^{25,26} and more than 30 open-label studies, encompassing more than 2200 patients, have been published. The majority of these studies report on small series of patients, but several long-term observations of large cohorts confirm the safety and efficacy of this treatment.^{11,23,27-32} A recent evidence-based review by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology concluded that "BoNT is possibly effective with minimal side effects for the treatment of HFS (one Class II and one Class III study). Botox[®] and Dysport[®], after dosage adjustment, are possibly

equivalent in efficacy (one Class II study)" and recommended BoNT injection as a treatment option for HFS (Level C).³³

Botulinum Neurotoxin Treatment

BoNT injections are performed with the patient lying supine. The toxin is diluted to a minimum concentration of 10 to 25 Botox U/mL (Allergan, Irvine, CA), 50 to 100 U/mL Dysport (Ipsen, Milford, MA), or 5000 to 10,000 U/mL Neurobloc/Myobloc (Solstice Neurosciences, Malvern, PA) to minimize diffusion. The injections are performed using a 1-mL syringe with a 30-gauge needle. BoNT injections are placed subcutaneously because the orbicularis oculi, which is a superficial muscle, is easily reached by the local diffusion. EMG guidance is not necessary. The injections are placed in proximity of the pretarsal portion of the orbicularis oculi muscle, divided in two to three sites; most commonly the injection sites are close to the medial and lateral epicanthi in the upper and lower eyelids, close to the orbital rim. The orbicularis oculi has two anatomic-functional divisions (Fig. 10-1): the palpebral portion that closes the eyelids and the orbital portion that squeezes the eyes shut. The palpebral portion is further subdivided in two parts: the preseptal and the pretarsal regions. It has been reported that ptosis is less frequent when BoNT is injected into the lateral portion of the pretarsal orbicularis oculi, and occurs more frequently when injections are performed into the preseptal or orbital divisions.^{29,34}

The sites of injection are determined by the observation of the involuntary twitches, which can be triggered by instructing the patient to contract their muscles while smiling or pursing their lips. Usually, in the first treatment session, only the periorcular regions are injected. Later, if required, additional sites are treated to control the spread of contractions: the medial eyebrow, the procerus, the corrugator, the frontalis muscle, or the paranasal portion of the zygomaticus major muscle. When HFS involves the lower face, at least in the first treatment session, BoNT injections are placed only in the upper face, because it has been recognized that this may be sufficient to control lower facial spasms.^{11,23} However, if lower facial muscles are particularly active or if there is residual mouth contraction following periorcular treatment, targeting the orbicularis oris, the levator angularis, risorius, buccinator, or depressor

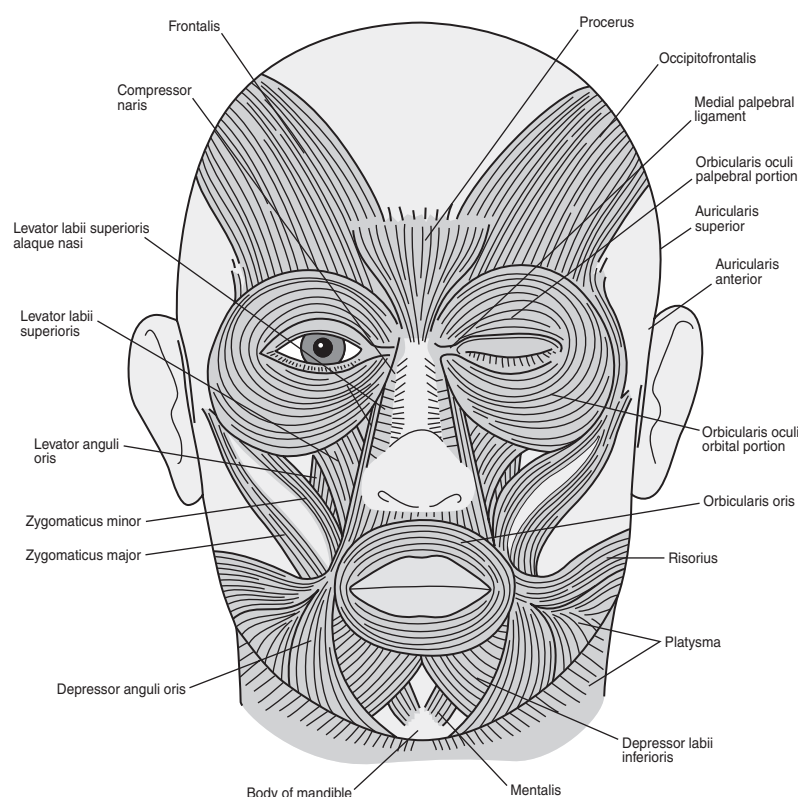


FIGURE 10-1. A number of facial muscles can be targeted with BoNT injections to reduce involuntary facial movements. Usually the muscles involved in the predominant involuntary movement are targeted during the first treatment session. The treatment can be refined and expanded in further sessions.

anguli oris may be considered, but only very small dosages should be used because injections into these areas can markedly distort facial expression, particularly when BoNT diffuses into the lips. The platysma muscles may also need to be injected if the HFS involves that part of the neck. The unaffected side of the face, mostly around the eye, may also require low doses of BoNT in order to avoid the appearance of asymmetric expressive facial lines.

The average dose used varies from 10 to 46 Botox U,^{23,35} from 53 to 160 Dysport U,³⁶ or from 1250 to 9000 Myobloc/NeuroBloc U^{37,38} (Table 10-1). Several reports indicate a lack of

correlation between the total dose injected and clinical outcome: the doses used in the “low-dose” Dysport protocol did not differ from standard dosages³⁹; furthermore, no significant difference in the response rate and duration of improvement were found in patients receiving 15 or 25 Botox U.⁴⁰ Similar discrepancies were reported also by others.⁴¹ In another paradigm, Botox doses were increased to provide a sustained effect with subsequent treatments.^{31,32} Alternatively, a slight, albeit not significant (from 17.5 to 15.9 Botox U) dose reduction was reported after 10 years.³⁰ In two studies using Dysport,

TABLE 10-1 Suggested Doses for the Treatment of Hemifacial Spasm³⁶

Drug Name	Orbicularis Oculi	Frontalis	Corrugator	Zygomaticus Major	Buccinator	Depressor Angularis Oris
Botox U	15–20	10	1	1	2	1
Dysport U	45–60	30	3	3	6	3
Myobloc/ NeuroBloc U	1000	500	50	50	100	50

a dose reduction was observed after the seventh consecutive treatment²⁹ and a 25% reduction was reported after 5 years.³⁹

In patients with HFS, improvement occurs soon after the first treatment,³⁹ with a latency varying from 2.6⁴² to 5.4 days.⁸ The clinical benefit generally lasts longer than in patients treated with BoNT for focal dystonia despite the use of smaller doses.^{31,35,42-44} This longer lasting improvement may be due to a subclinical denervation present in HFS.

The success rate of BoNT treatment has been estimated to be between 75%²⁸ and 100%,^{23,45} with a truly reliable estimate around 95%, as reported in two long-term studies.^{30,31} Patients with HFS have the lowest incidence of resistance to treatment, probably due to the low dosages used.⁴⁶ No secondary failures were reported in one series,⁴⁷ and an incidence of 0.9% per year was reported in another series³¹; furthermore, no evidence of immunoresistance was reported in a series of 110 patients.⁸ Primary failures were estimated to be 0.02%²⁹ or 1.4% per year,³¹ the lowest among different movement disorders treated with BoNT.

The mean duration of benefit was estimated between 75⁴⁸ and 196 days,⁴⁹ with a mean duration of approximately 90 days; this may increase,^{30,32,50} decrease⁴¹ or remain unchanged^{27,29,43,47,51} with repeated treatments. It has been hypothesized that disuse atrophy may occur in the facial muscles with repeated BoNT injections; but histologic studies failed to provide evidence to support this possibility.⁵²

Spontaneous prolonged remissions (up to 10 years) have been reported in a small number of patients treated with BoNT: 3% of patients in two series,^{30,40} 4% in another.¹¹ These remissions occurred after a variable number of treatment sessions (from 1 to 6).

Side effects occur in approximately 30% of patients and consist of erythema or ecchymosis of the injected region, dry eyes, mouth droop, ptosis, edema, or facial weakness. These complications are transient and usually resolve within 1 to 4 weeks. Earlier studies reported a high frequency of ptosis (up to 53%) with an overall mean of approximately 12%,^{43,51,53} likely due to diffusion of the toxin to the levator palpebrae superioris muscle. Mild symptoms of exposure keratitis (lacrimation and irritation of conjunctiva, occurring respectively in 3.6% and 2.3% of all treatments) are presumably an aftermath of decreased blink rate and incomplete eye closure from a partial

paralysis of the orbicularis oculi muscles. In several series, the most frequently reported side effect was facial weakness, involving 75%,⁴⁸ 95%,⁴⁰ or 97% of cases.²⁶ Facial weakness is more common when BoNT injections are placed in mid and low facial sites.⁵⁴ In a published series on blepharospasm,⁴³ 11.6% of the patients with facial weakness had received injections in the lower face, whereas a negligible portion of patients treated in the orbicularis oculi muscle had this complication. Because most patients report marked improvement of peribuccal spasms even when lower facial muscles are not directly injected,^{44,47} which is probably due to local diffusion of the drug, caution must be taken before injecting these sites. A positive correlation between dose and occurrence of side effects has been reported.^{30,39,40}

In our series of 665 BoNT treatments in 108 patients with HFS over the past 10 years, an average of 6.2 ± 5.5 (1–30) injections were performed in each patient. Botox was injected in 492 occasions and Dysport in 173 (unpublished data). The patients had a mean disease duration of 7.9 ± 5.4 years (1–26 years) with a mean follow up of 4.7 ± 3.0 years (0–11 years). At the last medical evaluation, the mean age of patients was 65.4 ± 14 years (29–92 years). The mean dose used per session was 11.2 ± 4.9 Botox U (1–50 U) and 46.5 ± 18.9 Dysport U (8–130 U). The analysis of repeated consecutive treatment revealed an increase of dose for either Botox ($\beta = 0.35$, $P < 0.001$) or Dysport ($\beta = 0.16$, not significant [n.s.]). Mean latency of clinical effect after the injection was 5.4 ± 5.3 days (0–40 days) for Botox and 4.9 ± 4.6 days (0–30 days) for Dysport, with no between-treatment differences. The duration of effect was longer for Dysport than for Botox: 105.9 ± 54.2 days (0–480 days) compared with 85.4 ± 41.6 days (0–330 days; $P < 0.001$). With repeated treatments, the duration of clinical benefit slightly increased with Botox ($\beta = 0.12$; $P < 0.01$), but remained constant for Dysport (Fig. 10-2).

A successful outcome was reported in 94% of treatment sessions (93.5% with Botox, 95.4% with Dysport, n.s.). There were no cases of primary or secondary resistance to BoNT. Side effects occurred in 116 of 665 sessions (17.4%), with comparable incidence with the two toxins. The most common side effects were palpebral ptosis and lacrimation. No correlation was found between the dose injected and the occurrence of side effects, either with Botox or with Dysport. No patient

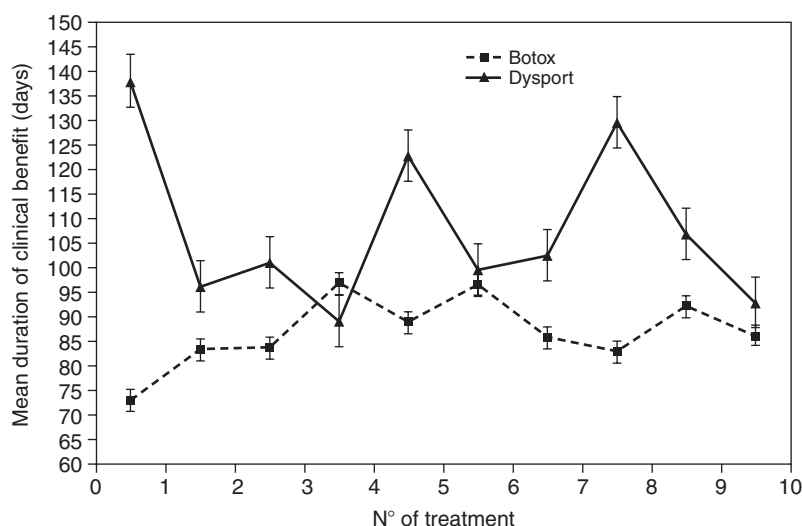


FIGURE 10-2. A series of 665 BoNT treatments in 108 patients with hemifacial spasm over 10 years. Longitudinal analysis of the mean duration of clinical benefit shows that the duration of clinical benefit is more predictable with Botox than with Dysport, probably due to variations in toxin diffusion.

discontinued treatment because of side effects, suggesting that the treatment was well tolerated.

New Botulinum Toxins

A new BoNT/A has been recently introduced in China (Prosigne, Lanzhou Institute of Biological Products, Shanghai, China), but the experience with this product is still limited. Its equivalency in terms of efficacy and safety with Botox has been suggested by a retrospective clinical study⁵⁵ and in a double-blind crossover trial in which 18 patients with HFS were randomized to Botox or Prosigne at a ratio of 1:1.⁵⁶ No data is currently available on the efficacy of Xeomin in HFS, but a controlled study is currently ongoing. BoNT/B has also been used for the treatment of HFS: clinical effects lasted about 8.5 weeks in the two patients treated with Myobloc over six sessions.³⁷ BoNT/C has also proven efficacious in two patients with HFS.⁵⁷

SPASMODIC DYSPHONIA

SD is a focal laryngeal dystonia characterized by action-induced spasms of the vocal folds, which are normal at rest, but during phonation develop contractions that cause abnormal movements and muscle spasms and typically result in dysphonia while speaking.⁵⁸ Historically SD was wrongly called "spastic dysphonia" and considered a disorder of uncertain

origin, often classified as psychogenic in nature. The dystonic nature of SD is suggested by its frequent occurrence in patients with cranial-cervical dystonia and by the improvement with "sensory tricks" such as yawn, laugh, cough, whisper, hum, or use of falsetto when starting to speak or while singing. Patients commonly report that their symptoms are worse when they are under emotional stress and are often better upon waking in the morning or after an alcoholic drink. Many can laugh and sing normally and, if able to speak different idioms, they find that their voice is better when speaking one language versus another. Symptoms usually worsen when the patients speak on the telephone.

The categorization of SD as a form of focal, laryngeal dystonia, was suggested by Marsden and Sheehy, who noted that "all evidence points to the conclusion that blepharospasm and oromandibular dystonia seen in Meige disease is another manifestation of adult-onset torsion dystonia, [and] since dysphonia may occur in the same syndrome, it is quite likely that dysphonia itself may be the sole manifestation of dystonia."⁵⁹ Later it was recognized that the characteristics of "spastic dysphonia" were similar to the dysphonia found in some patients with generalized and multifocal dystonia, and the clinical and EMG features of these patients revealed that most cases of dysphonia clinically diagnosed as "spastic dysphonia" were in fact focal forms of cranial dystonia.⁶⁰ Later, it became accepted that laryngeal dystonia may occur as a focal form of dystonia or in association with other affected sites in the

context of a segmental or more widespread dystonia.

Different types of SD have been recognized.

1. The **adductor type** is the most common (more than 80% of cases published in large series) and presents spasms of the vocal muscle (thyroarytenoid muscle) (Fig. 10-3). This causes a strain-strangled voice that is harsh, often tremulous, with inappropriate pitch or pitch breaks, breathiness, and glottal fry. The intermittent voice stoppage or breaks (phonatory breaks) is due to overadduction of the vocal folds, which results in a staccato-like voice.
2. The **abductor type** is less common and is due to involuntary spasms of the posterior cricoarytenoid muscles (see Fig. 10-3), causing a prolonged abduction of vocal folds during voiceless consonants. This produces a breathy, effortful, hypophonic voice with abrupt termination of voicing, or whispered speech.

3. The **mixed adductor-abductor type** presents with an admixture of breathy breaks and tight harsh sounds.

It has been proposed that adductor and abductor features coexist in all patients and that the symptoms depend on whether there is more adductor or abductor activity.⁶¹ Three other clinical variants have been reported⁶²:

1. The **compensatory abductor dysphonia** is occasionally present in patients with the adductor form of SD that produces a breathy voice by whispering or not contracting the vocal folds to prevent spasms and broken speech patterns.
2. The **compensatory adductor dysphonia** is much rarer, seen in patients with abductor SD who try to prevent breathiness by attempting to speak with their vocal folds tightly contracted.
3. In **adductor breathing dystonia**, the patients develop adductor spasms during breathing, producing paradoxical vocal fold motion.

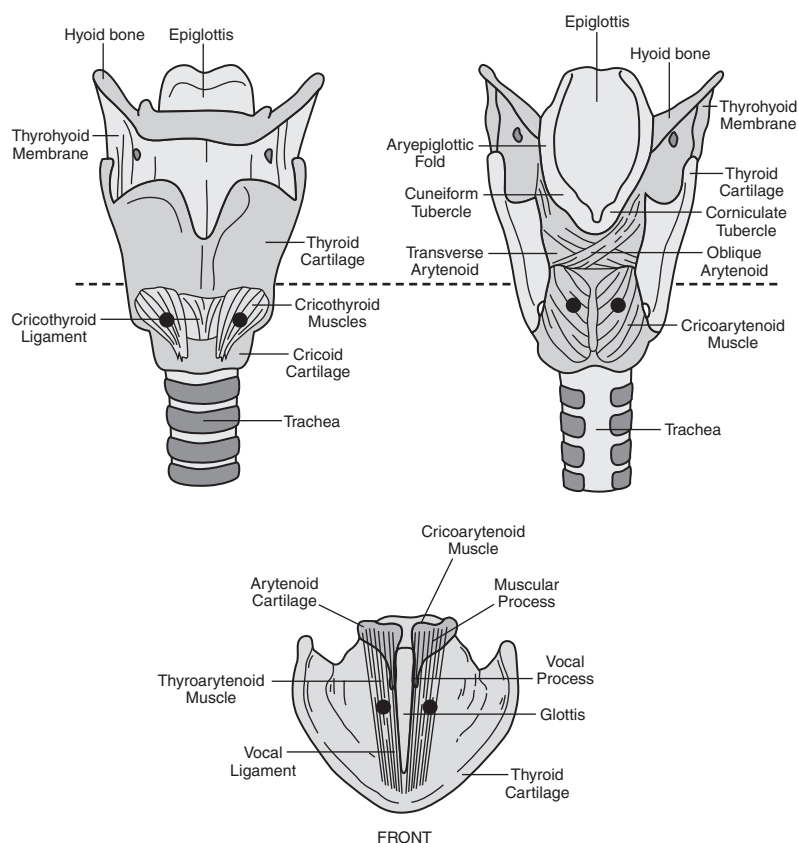


FIGURE 10-3. Anatomy of laryngeal muscles. Anterior view (*left*); posterior view (*middle*) and transverse section (*right*) of the larynx at the level of the dotted line. The *closed circles* indicate the muscles injected with BoNT in different forms of spasmodic dysphonia.

Symptoms of SD develop gradually over several months to years. SD typically affects patients in their mid-40s and is more common in women.^{63,64}

Clinical and Instrumental Evaluation

All patients with SD should undergo a detailed head and neck examination, particularly focusing on any presence of dystonia in the head or neck.

The Unified Spasmodic Dysphonia Rating Scale is a standardized, validated, vocal rating scale that includes two sections, one for reading and conversational speech and the other for voice and speech tasks.⁶⁵ Another scale, the Global Rating Scale, has also been used to evaluate voice function, scored as a percentage of normal from 0 (maximum degree of impairment) to 100% (normal voice).⁶⁶

Fiber optic laryngoscopy and stroboscopy allow to observe glottal function during phonation and to look for disruptions, spasms, breathy breaks, and tremor while the patient speaks. These movements can be video recorded and analyzed with slow speed and stop-action. Such examination cannot be reliably performed with indirect laryngoscopy, because anterior tongue traction limits speaking ability. Laryngostroboscopic examination of vocal function during speech segments is important for the diagnosis. The stroboscope can help define the nature of the associated tremor. Sometimes, a speech pathologist also makes acoustic and aerodynamic measures to evaluate for tremor, fundamental frequency, pitch and amplitude perturbation, harshness, fluency breaks, and breathiness. In patients with abductor dysphonia, laryngostroboscopic examination reveals a synchronous abduction of the true vocal fold that causes an extremely wide open glottic chink. Abductor spasms are triggered by consonant sounds, particularly when they are in the initial position in words. Having a patient say "taxi" or "Harry's hat" will often lead to an abnormal breathy break in speech. Laryngeal EMG helps evaluate tremor and areas of hyperactivity.

Treatment Options

Speech therapy has limited benefit and does not yield marked improvement in voice quality. When combined with BoNT, speech

therapy may be useful in developing coping strategies treat the compensatory behaviors superimposed on SD.⁶⁷ Psychotherapy may help patients manage the associated problems with social interactions and other activities requiring voice, which can be considerable, and thereby minimize the stress-related deterioration of voice. There is no evidence, however, that psychotherapy or psychological intervention can relieve the symptoms of SD.

Occasionally, the patients may improve with benzodiazepines (i.e., clonazepam, lorazepam), or with baclofen and those with superimposed voice tremor may benefit from anticonvulsants (i.e., gabapentin, primidone), or beta-adrenergic antagonists (i.e., propranolol).

Until the introduction of BoNT, surgical interventions have been the only truly efficacious options, but side effects and disappointing long-term results limited its applicability.⁶⁸ Surgical interventions included unilateral recurrent nerve resection, unilateral superior laryngeal nerve resection, and anterior laryngoplasty. EMG and clinical evidence suggests that recurrence of symptoms is due to reinnervation following these surgical ablations. Recurrent laryngeal nerve avulsion is a technique introduced as a modification of standard nerve section to prevent neural regrowth to the hemiparalyzed larynx and subsequent recurrence of SD.⁶⁹ An alternative surgical approach aimed at preventing reinnervation is the selective section of the distal branches of the recurrent nerve, leading to the thyroarytenoid and sometimes the lateral cricoarytenoid muscle, followed by immediate reinnervation using a non laryngeal nerve, generally the sternohyoid branch of the ansa cervicalis.^{70,71} There are other variants of these surgical procedures, including the use of transoral bilateral laser myoneurectomy of thyroarytenoid muscles.⁷²

Notwithstanding all these surgical options, BoNT is currently recognized as the first-choice treatment for SD,⁷³ and surgery is recommended in cases in which BoNT is not efficacious. There are also reports of patients treated with both BoNT and surgery, in order to obtain maximal benefit.^{74,75} A recent report, however, suggests caution on the use of this combined treatment.⁷⁶

Botulinum Neurotoxin Treatment

The first BoNT treatment for SD was performed in 1984 on a patient with adductor SD⁷⁷; patients with abductor SD were treated starting from 1988.⁷⁴ These observations were later confirmed by a double-blind study.⁷⁸

A meta-analysis of 30 series (uncontrolled trials in most cases) indicated a moderate overall improvement of adductor dysphonia following BoNT treatment.⁷⁹ The Cochrane Collaboration concluded that, although only one double-blind trial was available, most studies reported comparable successful outcome on the length of treatment effect, degree of improvement, patient satisfaction, and observed side effects.⁸⁰ Furthermore, a systematic review on the diagnosis and treatment of dystonia concluded that BoNT/A (or BoNT/B if there is resistance to type A) are the first-line treatment for SD.⁸¹ A recent evidence-based review recommended BoNT as a treatment option for adductor-type SD with a level B evidence, whereas the data was considered to be insufficient to evaluate the efficacy and safety of BoNT in the other variants of SD.³³

Adductor Spasmodic Dysphonia

The most commonly used technique is the percutaneous injection of the laryngeal adductor muscles. The patient lies in the supine position with the neck extended. The needle is curved slightly to allow for a more anterior placement, and is inserted through the space between the cricoid and thyroid cartilages, pointing toward the thyroarytenoid muscle (Fig. 10-4). BoNT is injected using an insulated needle connected to an EMG recorder. The patient is asked to phonate, and EMG activity is recorded; the toxin is injected when the needle tip is located in an active area of the muscle. The patient is instructed to try not to cough or swallow when the needle is in the airway or in the thyroarytenoid muscle. Patients with uncontrollable cough can be treated with 0.3 mL of 1% lidocaine injected through the cricothyroid membrane into the subglottic space or into the underneath airway. The anesthetic is not given routinely because it diminishes the EMG interference pattern, reducing the precision of muscle targeting.

Other approaches have also been proposed.

- The indirect laryngoscopic technique uses the transoral approach, which is more familiar to the otolaryngologists and requires no EMG equipment. The vocal folds are visualized directly and the injections are performed using an L-shaped syringe, a device originally designed for collagen injections. The advantage of the this approach is the visual individuation of the target area that reduces soft tissue traumas; a drawback is the waste of the

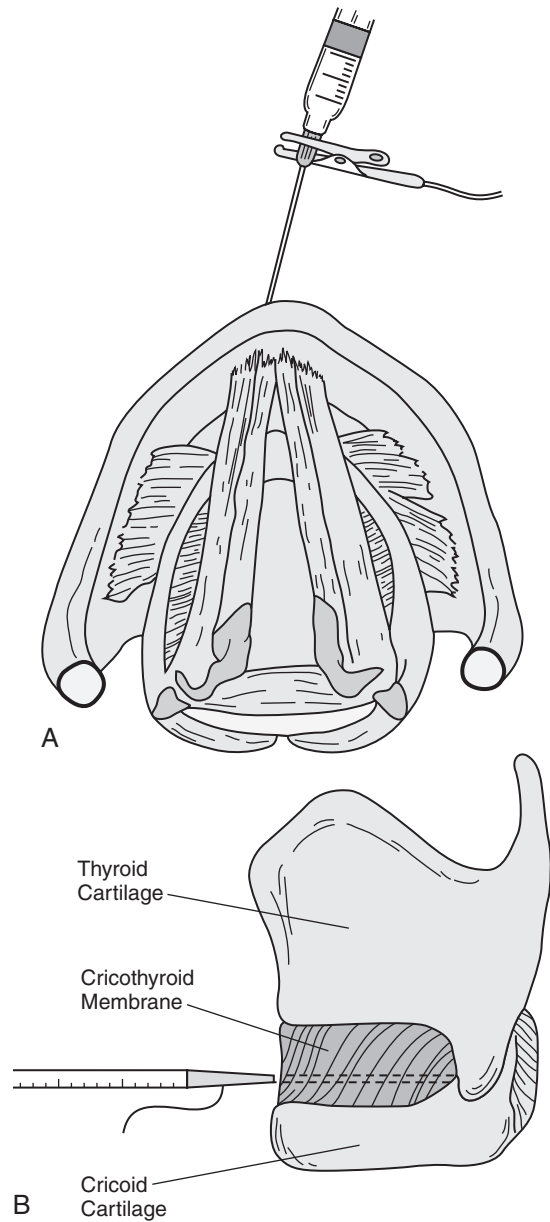


FIGURE 10-4. Percutaneous injection of the laryngeal adductor muscles: schematic view from above (A) and lateral view (B).

toxin due to the large dead volume in the long L-shaped needle.⁸²

- The injection can be performed using a needle placed into the operative channel of a flexible fiber optic laryngoscope (transnasal approach).⁸³
- The point-touch injection uses a needle inserted through the surface of the thyroid cartilage halfway between the thyroid

notch and inferior edge of the thyroid cartilage. The toxin is then given once the needle is passed into the thyroarytenoid muscle.⁸⁴

There are no comparative data on the efficacy and tolerability of these different techniques; however, EMG-guided percutaneous injections are considered the method of preference.

Unilateral or bilateral protocols have been proposed for BoNT injections into the thyroarytenoid muscle. Some authors have proposed to treat patients with relatively large doses (20–30 Botox U) given unilaterally, to simulate the effects of the recurrent nerve section, avoiding adverse events, such as breathiness or hoarseness.^{85,86} A comparison of outcome between 16 patients treated with unilateral injections and 33 patients who received bilateral injections concluded that unilateral injections have a better efficacy/tolerability profile⁸⁷: patients receiving unilateral injections had a significantly longer benefit and a higher rate of successful sessions. Others found that bilateral injections significantly prolonged the duration of benefit in men but not in women,⁸⁸ whereas others did not find substantial differences between the two techniques.⁸⁹ Blitzer and colleagues⁷⁵ suggested to use from 2.5 U to 7.5 Botox U in just one vocal fold. This would cause a vocal fold paresis, a period of breathy dysphonia, and eventually a 90% improvement in vocal function. Thereafter, the same authors considered that dystonia would exacerbate in the untreated vocal fold after unilateral paresis and shifted toward a bilateral injection protocol. They considered that such technique permits the use of smaller doses and produces better voicing. Yet another paradigm has been proposed for those patients who are exquisitely

sensitive to BoNT injections and do not have benefit from small bilateral doses but who have unacceptable breathiness at larger doses. In such patients, it has been proposed to stagger larger BoNT doses, by performing a unilateral injection, and then give a contralateral injection 2 weeks apart. Finally, some patients prefer more frequent, smaller (0.1–0.5 Botox U) unilateral doses. Although the duration of benefit in these patients is only from 6 to 8 weeks, it avoids the risk of breathiness. Frequent injections, however, increase the exposure to the immune system and potentially increase the risk of formation of blocking antibodies. Although this is much more of a concern in patients receiving higher doses for other indications, such as cervical dystonia, nevertheless frequent, “booster,” injections should be avoided whenever possible. It has been estimated that up to 20% of patients obtain no benefit from injection nor its side effects, suggesting the possibility that BoNT does not reach the appropriate vocal muscles in these cases.⁹⁰

BoNT injections can be placed just into the thyroarytenoid muscles or also in the lateral cricoarytenoid and interarytenoid muscles.⁹¹ It has been reported that simultaneous unilateral injections into both the thyroarytenoid and the lateral cricoarytenoid muscles gives the best overall improvement, the longest lasting benefit, and the shortest duration for undesirable breathiness.⁹²

The BoNT doses used in SD vary depending on the toxin brand and the technique used (Table 10-2). In the earlier series, the total doses varied from 3.75 to 7.5 Botox U for bilateral injections,^{78,93-95} and up to 15 U for unilateral injections.^{85,86} Remarkably, much larger doses (up to 50 Botox U in each vocal cord) have also been used.³⁵ More recent data,

TABLE 10-2 Suggested Doses in the Treatment of Adductor-Type Spasmodic Dysphonia

Drug Name	Muscle Injection type	Vocal Cord (Thyroarytenoid Muscle)		Lateral Cricothyroid
		Unilateral	Bilateral	Bilateral
Botox	Starting dose (U)	5–10	1.25–2.5	2.5–5
	Dilution	50 U/mL	25 U/mL	50 U/mL
Dysport	Starting dose (U)	20	5	10–20
	Dilution	200 U/mL	100 U/mL	100 U/mL
Myobloc/ Neurobloc	Starting dose (U)	200–500	50–100	100–200

however, recommended the use of lower doses.⁹⁶ In the 12-year experience reported by Blitzer and colleagues,⁷⁵ the dose range was between 0.005 and 30 Botox U (average: 3.09 U $\pm$ 3.1). The average starting dose was 1 Botox U in each thyroarytenoid muscle. Others injected between 0.6 and 2.5 Botox U bilaterally and then adjusted the dose according to the clinical improvement; alternatively, 5 or Botox U were injected unilaterally. Truong and colleagues⁶⁸ suggested to start with 0.5 Botox U or 1.5 Dysport U when injecting bilaterally; then to adjust the dose as needed (the estimated average dose being 0.75–1 Botox U or 2–3 Dysport U).

The clinical effects become visible from 1 hour to 3 days after the injection, and the patients may then experience transient breathiness for up to 2 weeks. On average, patients treated with BoNT experience a 97% improvement of voice.⁹⁵ After few months, as the clinical effect of BoNT wears off, SD slowly recurs. The duration of improvement is dose related. In a long-term series of 747 patients, the average latency of effect was 2.4 days, with the peak effect at 9.0 days and a duration of benefit of 15.1 weeks.⁷⁵

The treatment is generally well tolerated. In a double-blind controlled trial, it was reported that breathiness has higher incidence in the active drug-treated group.⁷⁸ A retrospective study reported mild breathiness in 35% and choking in 15% of the patients treated.⁹³ Compared with bilateral injections, alternating unilateral injections cause a significantly less breathy voice^{87,97} and stronger voice intervals. A slightly higher incidence of aspiration, dysphagia, and breathiness was reported in the bilaterally injected group of patients, who required significantly lower doses of toxin to attain benefit.⁸⁸

Abductor Spasmodic Dysphonia

Abductor SD is less frequent and more difficult to treat than the adductor form of SD. The posterior cricoarytenoid muscles, the cricothyroid muscles, or both, are usually injected in these patients. Using the EMG-guided percutaneous technique, the injections are performed by manually rotating the larynx away from the side of the intended injection. The posterior cricoarytenoid muscle is identified by EMG recording, using a needle inserted posterior to the posterior edge of the thyroid lamina. The needle is advanced through the inferior constrictor muscle to the cricoid cartilage and then moved out under EMG guidance to find

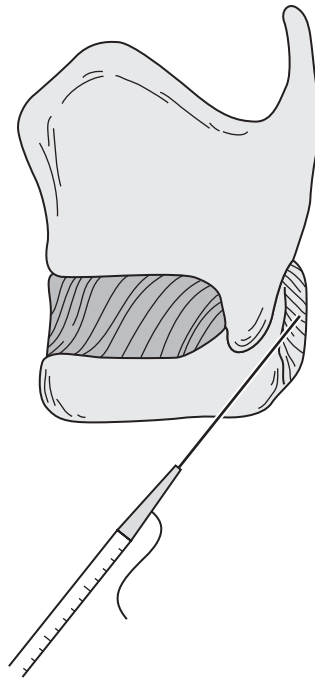


FIGURE 10-5. Percutaneous injection of the laryngeal abductor muscles (posterolateral approach) seen from a lateral view.

the posterior cricoarytenoid muscle (posterolateral approach) (Fig. 10-5). The patient is asked to sniff in order to activate this muscle and to swallow to stop its activity.⁷⁴

An alternative technique includes the anterior approach, consisting of the suprascricoid placement of the EMG needle under flexible transnasal laryngoscopic surveillance.⁹⁸ The needle is directed along the superior border of the posterior cricoid lamina and between the arytenoids. For anatomic reasons, the toxin is injected at the area above, to allow diffusion down into the muscle.

A refined simpler technique has the advantage of directing the injection into the muscle, and is particularly indicated in young individuals with soft cartilage. A small amount of 1% lidocaine is instilled in the subglottis before placing the EMG needle through the cricothyroid membrane just above the cricoid cartilage anteriorly. The needle is advanced along this plane and then directed laterally, until it hits the rostrum of the cricoid cartilage. The cartilage is impaled and, as the needle exits, there is often an appreciable burst of muscle activity from the posterior cricoarytenoid muscle (anterior transcricoid approach). In older patients, this approach is made difficult by the calcification of the cartilage.⁹⁹

Bilateral injections are dangerous, because side effects include stridor and airway obstruction. Therefore, unilateral injections with 2.5 to 25 U of Botox are performed initially, by choosing the most active side of contraction, as determined by fiber optic laryngoscopy. A common technique is to inject 5 U Botox into the more active posterior cricoarytenoid muscle. If there is no subjective improvement in voice quality after 2 weeks, and if no airway symptoms have occurred, then the opposite muscle is injected with an additional Botox 5 U.^{100,101} Another suggestion is: 2 to 4 U of Botox or 12 U of Dysport, with 1 U of Botox or 3 U of Dysport on the opposite side.⁶⁸ A lower dose protocol proposes 1.25 to 1.75 U of Botox in one muscle and 0.9 U on the opposite side (Table 10-3).⁹⁹ Generally, if a high dose is required on both sides, the second side can be injected with a delay of 2 weeks to avoid compromising the airway.

A review of the safety of simultaneous bilateral posterior cricoarytenoid muscle injections in 21 patients treated over 6 years demonstrated that this treatment is safe. The total BoNT dose injected bilaterally in each session was between 2.5 and 7.5 U of Botox, with an average total dose per session of 4.7 U. There were no life-threatening complications (intubations, tracheotomies, or admissions for airway observation); minor complications were self limited and included a 5% incidence of significant dyspnea and a 2% incidence of dysphagia.¹⁰²

In a 12-year experience on 154 patients, the overall improvement was around 70%, the average onset of improvement was 4.1 days, and the benefit lasted for 10.5 weeks.⁷⁵ In approximately 20% of patients, weakening or paralyzing just one posterior cricoarytenoid muscle produced significant

voice improvement; 80% needed a dose of 0.625 to 2.5 U of Botox into the contralateral posterior cricoarytenoid. The highest percent improvement was in the group with focal laryngeal involvement without tremor.⁷⁵ Of 154 treated patients, adverse effects included exertional wheezing in four patients and dysphagia in 10 patients, none of them requiring being intubated or tracheotomized related to treatment.⁷⁵

One additional issue to be considered in patients with abductor dysphonia is that spasmodic activity may also take place in the adductor muscle, explaining some cases of poor treatment outcome.¹⁰³

The cricothyroid muscle can also be injected, under EMG guidance, by percutaneous access. This muscle bends the vocal fold, antagonizing the posterior cricoarytenoid muscle.¹⁰⁰ In one series of SD patients, nine received bilateral injections (2.5 U of Botox on each side) in the cricothyroid muscles in addition to the posterior cricoarytenoid.⁷⁵ These patients still had breathy breaks or tremor despite significant limitation of abduction. Five of the nine injected patients had benefit consisting in a louder voice with fewer breaks. One patient got worse after the additional injection.

Mixed-Type Spasmodic Dysphonia

In the mixed adductor-abductor type of SD there is an admixture of breathy breaks and tight harsh sounds. The treatment aims at improving the most disturbing features, which in most patients, is the adductor component; in such cases, the treatment is directed at weakening the thyroarytenoid muscles. Sometimes in the mixed type, there are compensatory contractions that do not require treatment. However, in the truly mixed type both components occur, and if isolated adductor or

TABLE 10-3 Suggested Doses in the Treatment of Abductor-Type Spasmodic Dysphonia

Drug Name	Muscle Injection	Posterior Cricothyroid	Posterior Cricothyroid	Lateral Cricothyroid
		Unilateral	Bilateral (Lower Dose on the Less Active Side)	Bilateral
Botox	Starting dose (U) Dilution	1.25–5 U 25 U/mL	1.5–3.0 and 1 U 20 U/mL	2.5–5 50 U/mL
Dysport	Starting dose (U) Dilution	20 U 200/mL	10 and 5 100/mL	10–20 100 U/mL
Myobloc/ Neurobloc	Starting dose (U)	50–200	50–150 and 50	100–200

abductor type of treatment is performed, the untreated component gets much worse. In such cases, adductor and abductor muscles both require treatment.

Botulinum Neurotoxin Type B

Resistance to BoNT injections for SD is uncommon, and there are no reported cases of secondary resistance to BoNT/A in a large series (901 patients treated with 6300 injections for more than ten years).⁷⁵ Secondary resistance has been reported in 2 patients after several years of regular treatments for SD, who failed to have the expected voice improvement after receiving their standard treatment.¹⁰⁴ In one of them, antibodies to BoNT/A were detected by mouse neutralization bioassay. It is conceivable that repeating injections at close intervals, as in the case of shortly spaced unilateral injections, may favor the development of immune response to BoNT.

BoNT/B stands as an alternative to BoNT/A in immunologically resistant patients. The experience with BoNT/B in SD is limited to the treatment of adductor type SD. In two patients who failed to respond to BoNT/A, 250 to 1000 U of Myobloc were injected in each vocal fold, with beneficial effects lasting for 4 months.¹⁰⁵ It has been reported that eight out of 10 treated patients who received 200 U of Myobloc on each side had a clinical improvement lasting for 8 weeks.¹⁰⁶ Three patients, who failed to respond to BoNT/A and subsequently received BoNT/B (up to 1000 U Myobloc on each side), were reported to improve for approximately 2 months.⁶⁸

A direct comparison of BoNT/A and BoNT/B was performed on 32 patients with adductor SD who had been treated with stable doses of BoNT/A and were followed for 1 year with BoNT/B.¹⁰⁷ The conversion rate for laryngeal injections was 52.3:1 (B:A). BoNT-B was associated with more rapid onset of action (2.09 vs. 3.2 days) and a shorter duration of benefit (10.8 vs. 17 weeks) but no difference in safety profile.

SPASMODIC LARYNGEAL DYSPNEA

Spasmodic laryngeal dyspnea (SLD), or adductor breathing dystonia, causes a dystonic stridor. SLD has been typically described in the context of neurodegenerative disorders, such as multiple system atrophy, but it also occurs

as a primary disorder in some patients. In SLD, the spasmodic vocal fold contraction is activated by breathing (primarily inspiration) rather than by speaking (as in the case of SD). SLD causes dyspnea by intermittently obstructing the glottic and supraglottic airway due to laryngeal and supralaryngeal pharyngeal muscle spasms. The patients present with stridor and tirage and, albeit rarely, may develop hypoxia. SLD abates during sleep and may improve with speaking.^{108,109} Some of these patients may also have dystonic movements in other body districts or respiratory or breathing incoordination, with paradoxical movements of the diaphragm or of the chest wall.¹¹⁰

The treatment is generally similar to that of adductor SD. Localized unilateral injections are placed into the thyroarytenoid muscle and, if necessary, into the ventricular folds. The clinical improvement lasts from 9 weeks to 6 months.¹¹¹

In a series of 12 patients a dose of 0.625 to 3.75 U, Botox was injected into each thyroarytenoid muscle, depending on the severity of the spasms.⁷⁵ The average preinjection function was 27% of normal, and pulmonary function tests showed abnormal flow volume loops with intermittent interruptions of airflow during inspiration or expiration in 20 of 24 patients. The average best postinjection function was 82% of normal. The mean duration of relief from the stridor was 14 weeks. A breathy voice lasting for 1 to 2 weeks was reported in 50% of the patients. Mild choking on fluids also occurred in five patients and lasted for 1 week. In 3 of 4 patients with severe stridor and multiple system atrophy (MSA), treated with 10 U of Botox injected into the right thyroarytenoid muscle, an improvement was documented one month after the injection.⁷⁶

STUTTERING

Stuttering is an action-induced speech disorder with involuntary, audible, or silent repetitions or prolongations in the utterance of short speech elements (sounds, syllables) and words. Symptomatic treatment programs frequently have initial success; persistent benefit is variable and many patients remain disabled. Stuttering has many characteristics similar to SD, often including the presence of adductor laryngeal spasms that obstruct airflow (glottal block).

On this basis, it has been proposed that relief of the spasmodic dysphonic glottal

blocks in stutterers would modify the stuttering phenomenon and increase fluency. Unilateral BoNT injections (doses ranging from 10 to 78 U of Botox) into the vocal fold improved fluency and speech in seven stuttering patients.¹¹² Fourteen adult patients were treated with 1.25 U of Botox injected into each thyroarytenoid muscle.¹¹³ Improvement in fluency was documented at 2 and 6 weeks, with a functional relapse around 12 weeks. BoNT injections could be useful in the management of stuttering with glottal block after failure of speech interventional therapy.

VOCAL TREMORS

Patients with vocal tremor have a tremulous sound of their voice, which is especially audible while they pronounce prolonged vocals. There are different types of vocal tremors. SD may be associated with a tremor of the vocal folds: EMG studies found that almost 25% of patients with SD have an irregular 4- to 8-Hz tremor on phonation, whereas another 6% has a regular tremor similar to that of essential tremor (ET).⁶⁰ Vocal tremor in SD may be similar to that found in patients with ET, being synchronous with pharyngeal, lingual, velar, mandibular, facial, thoracic, and diaphragmatic tremor.¹¹⁴

The involvement of the thyroarytenoid muscle is predominant in SD cases without tremor, whereas the lateral cricoarytenoid muscle is equally involved when tremor is a relevant feature. It has been shown that the interarytenoid muscle may be involved in rare cases of tremulous SD.⁹¹ In the majority of patients, the thyroarytenoid muscle alone has been injected and this may explain the poorer response rate to BoNT treatment of patients with SD and associated vocal tremor compared with patients with isolated SD. In a series of 81 patients with tremulous SD, the best outcome was achieved when the lateral cricoarytenoid muscle was also injected.¹¹⁵

Some patients with ET affecting the head and hands also present with voice tremor. Rarely, patients with Parkinson's disease may also display low-frequency (4–6 Hz) voice tremor. Many of these patients benefit from beta-adrenergic antagonists or other drugs used to treat ET, but sometimes this benefit is partial, particularly when high doses cannot be used. Objective acoustic measures have shown efficacy of BoNT in only a small number of treated patients, although the majority of

them reported a subjective reduction in vocal effort.¹¹⁶ Subjective evaluations reported a benefit in 67% of patients with essential voice tremor treated with BoNT/A, whereas acoustic analysis showed a nonsignificant decrease in the fundamental frequency and a decrease in the fundamental frequency during sustained vowel phonation.¹¹⁷ An improvement in voice tremor was reported in another study following BoNT/A injection into the vocal cord.¹¹⁸ The average doses used in each vocal muscle are 1.25 to 3.75 U of Botox or 4 to 12 of U Dysport. No experience with BoNT/B has been reported in the treatment of essential voice tremor.

TREMOR

Tremor is defined as a rhythmic, involuntary oscillatory movement of a body part; it is etiologically and physiologically heterogeneous.¹¹⁹ BoNT has been tested on various tremor disorders in open-label and small controlled studies, and it has been proposed as a treatment for essential hand tremor.^{3,20} Intramuscular BoNT injections may reduce tremor by weakening the muscles or by blocking gamma motor efferents and muscle spindle afferents.

In open-label trials of BoNT-A for ET affecting the hands, an improvement was reported in 6 of 10 patients and unwanted hand weakness was reported.³ In a study of 16 patients followed for more than 6 weeks, a significant improvement occurred on the Webster tremor scale and on a global disability scale.¹²⁰ However, tremor amplitude decreased by no more than 25% and weakness of the digit extensors was a common side effect. A single-masked placebo-controlled study found that the treatment was better than placebo in more than half the patients; many had clinically significant weakness of the hands, which resolved over time.¹²¹

In a controlled study, 25 patients were randomized to receive 50 U of Botox or placebo into wrist extensors and flexors.¹²³ If patients did not respond, they were eligible to receive another injection of 100 U 4 weeks later. A significant improvement was observed after 4 to 16 weeks in the tremor severity rating scale. However, there were no significant changes in the functional rating scales. Patients treated with the active drug reported finger weakness.

Evidence of efficacy was observed in a multicenter, randomized, controlled study in which

133 ET patients were randomized to a low-dose (50 U of Botox) or a high-dose (100 U of Botox) regimen or to placebo treatment.¹²⁴ Injections were made under EMG guidance into the wrist flexors (flexor carpi radialis and ulnaris) and extensors (extensor carpi radialis and ulnaris). The study showed improvement of postural, but not kinetic, hand tremor, providing an explanation for limited functional improvement, since it is accepted that kinetic rather than postural tremor causes disability. A dose-dependent hand weakness was the most reported side effect. As a result of the extensor muscle weakness, which was observed in both controlled trials, injections into the wrist extensor muscles are now only rarely employed, and as a result, the frequency of extensor hand or finger weakness has disappeared without a compromise in the efficacy. BoNT should be considered as a treatment option for essential hand tremor in those patients in whom treatment with oral agents (Level B) has failed.³³

A recent open-label trial enrolled five patients with primary writing tremor, a form of dystonic hand tremor. Four patients had significant improvement of symptoms after receiving low doses of BoNT/A for at least 1 year. The treatment schedule was flexible and involved the flexor carpi ulnaris, the extensor carpi ulnaris or radialis, the extensor digitorum communis, and the abductor pollicis longus. Each muscle was injected with a dose ranging from 10 to 12.5 U of Botox.¹²⁵

Jaw tremor in Parkinson disease does not respond well to conventional antiparkinsonian medication and causes social embarrassment.

It has been reported that BoNT injections may improve jaw tremor without relevant side effects. Three patients received injections into both masseter muscles with a mean dose of 53 U of Dysport (range: 30–100 U).¹²⁶

Palatal tremor with associated ear click may also be treated with BoNT.¹²⁷ A recent review concluded that BoNT should not be reserved for refractory cases but should be considered a safe and effective first-line therapy.¹²⁸ The tensor veli palatini, levator veli palatine, or both have been injected with doses ranging from 5 to 20 U of Botox or from 5 to 60 U of Dysport. The treatment is generally safe; rarely have velopharyngeal insufficiency or nasal speech been recorded. In the rare cases of hereditary chin tremor and isolated high-frequency jaw tremor, BoNT/A can be injected into the active muscles with marked reduction in the amplitude of the tremor.^{129,130}

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 or individual patients that cannot be adequately treated with systemic drugs or accepted surgical procedures, such as deep brain stimulation. BoNT can be helpful particularly with atypical presentations or when the tremor is confined to few muscles (Table 10-4). In the authors' experience head tremors are particularly suitable for BoNT treatment, which usually results in a satisfying outcome. The treatment paradigms follow the wide experience collected for cervical dystonia. Finally, very scanty data are available on BoNT-B treatment of tremors.³⁷

TABLE 10-4 Suggested Doses in the Treatment of Upper Limb Tremor

Injection Site	Botox Dose (U)	Dysport Dose (U)	Myobloc/Neurobloc Dose (U)
Pronator teres	25–75	80–100	1000–2500
Pronator quadratus	10–50	80–100	1000–2500
Flexor carpi radialis	25–100	150	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

Modified from Albanese A, Bentivoglio AR. Botulinum toxin in movement disorders. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:605–619.

TICS

BoNT/A has been used to treat motor or vocal tics in patients with chronic tic disorders. The first anecdotal observations were performed in patients with Tourette syndrome and dystonic tics affecting the eyelids and the neck.⁵ BoNT treatment reduced the frequency and the intensity of tics and ameliorated the associated premonitory sensory urge; the benefit lasted for several weeks.

In another series, 35 patients (30 men, 5 women) were treated with BoNT in the sites of their most problematic tics¹³¹: cervical or upper thoracic area (17 patients), upper face (14), lower face (7), vocal cords (4), upper back and/or shoulder (3), scalp (1), forearm (1), leg (1), and rectus abdominis (1). The response to BoNT was scored on a 0 to 4 clinical rating scale (0, no improvement, to 4, marked improvement in both severity and function). The mean peak effect recorded in 115 sessions was 2.8; the mean duration of benefit was 14.4 weeks; and the mean latency of benefit onset was 3.8 days. Twenty-one (84%) of 25 patients who reported premonitory sensations reported a marked relief.

A controlled trial has confirmed the efficacy of BoNT/A for the treatment of simple motor tics, yielding a 39% reduction in their number (compared with a 6% increase in the placebo group) and a significant reduction of the urge score.¹³² The patients, however, did not report a consistent subjective benefit.

BoNT can also be indicated for vocal tics thereby ameliorating quality of life.^{133,134} A series of 30 patients received 2.5 U of Botox in both vocal cords and were followed up for 12 months.¹³⁵ Vocal tics improved after treatment in 93% patients, with 50% being tic free. The mean response time was 5.8 days, and the mean duration of response was 102 days. Quality of life improved, and premonitory experiences dropped from 53% to 20%. Hypophonia was the only side effect of note (80% of patients).

In summary, it is worth trying BoNT/A in patients who have simple and repetitive motor or vocal tics, particularly if systemic medication is contraindicated or inefficacious. However, the long-term outcome in patients with tic disorders remains to be established. According to the evidence-based evaluation criteria the clinical studies available so far allow to state that BoNT is possibly effective for the treatment of motor tics, with a level C evidence, whereas there are insufficient

data to determine the effectiveness of BoNT in phonic tics.³³

References

1. Frueh BR, Felt TH, Wojno TH, Musch DC. Treatment of blepharospasm with botulinum toxin: a preliminary report. *Arch Ophthalmol*. 1984;102:1464-1468.
2. Mauriello JA. Blepharospasm, Meige syndrome, and hemifacial spasm: treatment with botulinum toxin. *Neurology*. 1985;35:1499-1500.
3. Jankovic J, Schwartz K. Botulinum toxin treatment of tremors. *Neurology*. 1991;41:1185-1188.
4. Blitzer A, Brin MF. Laryngeal dystonia: a series with botulinum toxin therapy. *Ann Otol Rhinol Laryngol*. 1991;100:85-89.
5. Jankovic J. Botulinum toxin in the treatment of dystonic tics. *Mov Disord*. 1994;9:347-349.
6. Digre K, Corbett JJ. Hemifacial spasm: differential diagnosis, mechanism, and treatment. *Adv Neurol*. 1988;49:151-176.
7. Stamey W, Jankovic J. The other Babinski sign in hemifacial spasm. *Neurology*. 2007;69:402-404.
8. Wang A, Jankovic J. Hemifacial spasm: clinical findings and treatment. *Muscle Nerve*. 1998;21:1740-1747.
9. Martinelli P, Giuliani S, Ippoliti M. Hemifacial spasm due to peripheral injury of facial nerve: a nuclear syndrome? *Mov Disord*. 1992;7:181-184.
10. Tan EK, Jankovic J. Bilateral hemifacial spasm: a report of five cases and a literature review. *Mov Disord*. 1999;14:345-349.
11. Mauriello JA, Leone T, Dhillon S, Pakeman B, Mostafavi R, Yezpey MC. Treatment choices of 119 patients with hemifacial spasm over 11 years. *Clin Neurol Neurosurg*. 1996;98:213-216.
12. Alexander GE, Moses H. Carbamazepine for hemifacial spasm. *Neurology*. 1982;32:286-287.
13. Ryu H, Yamamoto S. A simple technique for neurovascular decompression of the cranial nerves. *Br J Neurosurg*. 2000;14:132-134.
14. Kurokawa Y, Maeda Y, Toyooka T, Inaba K. Microvascular decompression for hemifacial spasm caused by the vertebral artery: a simple and effective transposition method using surgical glue. *Surg Neurol*. 2004;61:398-403.
15. Piatt JH, Wilkins RH. Microvascular decompression for tic douloureux. *Neurosurgery*. 1984;15:456.
16. Loeser JD, Chen J. Hemifacial spasm: treatment by microsurgical facial nerve decompression. *Neurosurgery*. 1983;13:141-146.
17. Chung SS, Chang JH, Choi JY, Chang JW, Park YG. Microvascular decompression for hemifacial spasm: a long-term follow-up of 1,169 consecutive cases. *Stereotact Funct Neurosurg*. 2001;77:190-193.
18. Badr-El-Dine M, El-Garem HF, Talaat AM, Magnan J. Endoscopically assisted minimally invasive microvascular decompression of hemifacial spasm. *Otol Neurotol*. 2002;23:122-128.
19. Goto Y, Matsushima T, Natori Y, Inamura T, Tobimatsu S. Delayed effects of the microvascular decompression on hemifacial spasm: a retrospective study of 131 consecutive operated cases. *Neurol Res*. 2002;24:296-300.
20. Samii M, Gunther T, Iaconetta G, Muehling M, Vorkapic P, Samii A. Microvascular decompression to treat hemifacial spasm: long-term results for a consecutive series of 143 patients. *Neurosurgery*. 2002;50:712-718.
21. Wirtschafter JD, McLoon LK. Long-term efficacy of local doxorubicin chemomyectomy in patients with

- blepharospasm and hemifacial spasm. *Ophthalmology*. 1998;105:342-346.
22. Ito M, Hasegawa M, Hoshida S, Miwa T, Furukawa M. Successful treatment of hemifacial spasm with selective facial nerve block using doxorubicin (adriamycin) under local anesthesia. *Acta Otolaryngol*. 2004;124:217-220.
 23. Flanders M, Chin D, Boghen D. Botulinum toxin: preferred treatment for hemifacial spasm. *Eur Neurol*. 1993;33:316-319.
 24. Jost WH, Kohl A. Botulinum toxin: evidence-based medicine criteria in blepharospasm and hemifacial spasm. *J Neurol*. 2001;248(Suppl 1):21-24.
 25. Park YC, Lim JK, Lee DK, Yi SD. Botulinum a toxin treatment of hemifacial spasm and blepharospasm. *J Korean Med Sci*. 1993;8:334-340.
 26. Yoshimura DM, Aminoff MJ, Tami TA, Scott AB. Treatment of hemifacial spasm with botulinum toxin. *Muscle Nerve*. 1992;15:1045-1049.
 27. Taylor JD, Kraft SP, Kazdan MS, Flanders M, Cadera W, Orton RB. Treatment of blepharospasm and hemifacial spasm with botulinum A toxin: a Canadian multicentre study. *Can J Ophthalmol*. 1991;26:133-138.
 28. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol*. 1992;239:5-8.
 29. Jitpimolmard S, Tiamkao S, Laopaiboon M. Long term results of botulinum toxin type A (Dysport) in the treatment of hemifacial spasm: a report of 175 cases. *J Neurol Neurosurg Psychiatry*. 1998;751-757.
 30. Defazio G, Abbruzzese G, Girlanda P, Vacca L, Curra A, De Salvia R, et al. Botulinum toxin A treatment for primary hemifacial spasm: a 10-year multicenter study. *Arch Neurol*. 2002;59:418-420.
 31. Hsiung GY, Das SK, Ranawaya R, Lafontaine AL, Suchowersky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. *Mov Disord*. 2002;17:1288-1293.
 32. Mejia NI, Vuong KD, Jankovic J. Long-term botulinum toxin efficacy, safety, and immunogenicity. *Mov Disord*. 2005;20:592-597.
 33. Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, et al. Botulinum neurotoxin for the treatment of movement disorders: an evidence-based review. *Neurology*. 2008;70:1699-1706.
 34. Cakmur R, Ozturk V, Uzunel F, Donmez B, Idiman F. Comparison of preseptal and pretarsal injections of botulinum toxin in the treatment of blepharospasm and hemifacial spasm. *J Neurol*. 2002;249:64-68.
 35. Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. *J Neurol Neurosurg Psychiatry*. 1990;53:633-639.
 36. Frei K, Truong DD, Dressler D. Botulinum toxin therapy of hemifacial spasm: comparing different therapeutic preparations. *Eur J Neurol*. 2006;13(Suppl. 1):30-35.
 37. Wan XH, Vuong KD, Jankovic J. Clinical application of botulinum toxin type B in movement disorders and autonomic symptoms. *Chin Med Sci J*. 2005;20:44-47.
 38. Tousi B, Perumal JS, Ahuja K, Ahmed A, Subramanian T. Effects of botulinum toxin-B (BTX-B) injections for hemifacial spasm. *Parkinsonism Relat Disord*. 2004;10:455-456.
 39. Van den Bergh P, Francart J, Mourin S, Kollmann P, Laterre EC. Five-year experience in the treatment of focal movement disorders with low-dose Dysport botulinum toxin. *Muscle Nerve*. 1995;18:720-729.
 40. Chen RS, Lu CS, Tsai CH. Botulinum toxin A injection in the treatment of hemifacial spasm. *Acta Neurol Scand*. 1996;94:207-211.
 41. Ainsworth JR, Kraft SP. Long-term changes in duration of relief with botulinum toxin treatment of essential blepharospasm and hemifacial spasm. *Ophthalmology*. 1995;102:2036-2040.
 42. Shorr N, Seiff SR, Kopelman J. The use of botulinum toxin in blepharospasm. *Am J Ophthalmol*. 1985;99:542-546.
 43. Dutton JJ, Buckley EG. Long-term results and complications of botulinum A toxin in the treatment of blepharospasm. *Ophthalmology*. 1988;95:1529-1534.
 44. Ruusuvaara P, Setälä K. Long-term treatment of involuntary facial spasms using botulinum toxin. *Acta Ophthalmol (Copenh)*. 1990;68:331-338.
 45. Chong PN, Ong B, Chan R. Botulinum toxin in the treatment of facial dyskinesias. *Ann Acad Med Singapore*. 1991;20:223-227.
 46. Biglan AW, May M. Treatment of facial spasm with Oculinum (C. botulinum toxin). *J Pediatr Ophthalmol Strabismus*. 1986;23:216-221.
 47. Mauriello JA, Coniaris H, Haupt EJ. Use of botulinum toxin in the treatment of one hundred patients with facial dyskinesias. *Ophthalmology*. 1987;94:976-979.
 48. Yu YL, Fong KY, Chang CM. Treatment of idiopathic hemifacial spasm with botulinum toxin. *Acta Neurol Scand*. 1992;85:55-57.
 49. Borodic GE. Hemifacial spasm: evaluation and therapy. In: Jankovic J, Hallett M, eds. *Textbook of Botulinum Toxin Therapy*. New York: Marcel Dekker; 1994:331-353.
 50. Frueh BR, Musch DC. Treatment of facial spasm with botulinum toxin. An interim report. *Ophthalmology*. 1986;93:917-923.
 51. Carruthers J, Stubbs HA. Botulinum toxin for benign essential blepharospasm, hemifacial spasm and age-related lower eyelid entropion. *Can J Neurol Sci*. 1987;14:42-45.
 52. Borodic GE, Ferrante R, Pearce LB, Smith K. Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic botulinum A toxin injections. *Mov Disord*. 1994;9:31-39.
 53. Savino P, Sergott R, Bosley T, Schatz N. Hemifacial spasm treated with botulinum A toxin injection. *Arch Ophthalmol*. 1985;103:1305-1306.
 54. Elston JS. Botulinum toxin treatment of hemifacial spasm. *J Neurol Neurosurg Psychiatry*. 1986;49:827-829.
 55. Tang X, Wan X. Comparison of Botox with a Chinese type A botulinum toxin. *Chin Med J (Engl)*. 2000;113:794-798.
 56. Rieder CR, Schestatsky P, Socal MP, Monte TL, Fricke D, Costa J, et al. A double-blind, randomized, crossover study of Prosigne versus Botox in patients with blepharospasm and hemifacial spasm. *Clin Neuropharmacol*. 2007;30:39-42.
 57. Eleopra R, Tugnoli V, Rossetto O, Montecucco C, De Grandis D. Botulinum neurotoxin serotype C: a novel effective botulinum toxin therapy in human. *Neurosci Lett*. 1997;224:91-94.
 58. Blitzer A, Brin MF, Fahn S, Lovelace RE. Localized injections of botulinum toxin for the treatment of focal laryngeal dystonia (spastic dysphonia). *Laryngoscope*. 1988;98:193-197.
 59. Marsden CD, Sheehy MP. Spastic dysphonia, Meige disease and torsion dystonia. *Neurology*. 1982;32:1202-1203.

60. Blitzer A, Lovelace RE, Brin MF, Fahn S, Fink ME. Electromyographic findings in focal laryngeal dystonia. *Ann Otol Rhinol Laryngol*. 1985;94:591-594.
61. Cannito MP, Johnson JP. Spastic dysphonia: a continuum disorder. *J Commun Disord*. 1981;14:215-233.
62. Blitzer A, Brin MF, Fahn S, Lovelace RE. Clinical and laboratory characteristics of focal laryngeal dystonia: study of 110 cases. *Laryngoscope*. 1988;98:636-640.
63. Adler CH, Edwards BW, Bansberg SF. Female predominance in spasmodic dysphonia. *J Neurol Neurosurg Psychiatry*. 1997;63:688.
64. Schweinfurth JM, Billante M, Courey MS. Risk factors and demographics in patients with spasmodic dysphonia. *Laryngoscope*. 2002;112:220-223.
65. Stewart CF, Allen EL, Tureen P, Diamond BE, Blitzer A, Brin MF. Adductor spasmodic dysphonia: standard evaluation of symptoms and severity. *J Voice*. 1997;11:95-103.
66. Brin MF, Fahn S, Blitzer A, Ramig LO, Stewart C. Movement disorders of the larynx. In: Blitzer A, Brin MF, Sasaki CT, Fahn S, Harris K, eds. *Neurological Disorders of the Larynx*. New York: Thieme; 1992: 240-248.
67. Murry T, Woodson GE. Combined-modality treatment of adductor spasmodic dysphonia with botulinum toxin and voice therapy. *J Voice*. 1995;9:460-465.
68. Truong DD, Bhidayasiri R. Botulinum toxin therapy of laryngeal muscle hyperactivity syndromes: comparing different botulinum toxin preparations. *Eur J Neurol*. 2006;13(Suppl 1):36-41.
69. Weed DT, Jewett BS, Rainey C, Zeale DL, Stone RE, Ossoff RH, et al. Long-term follow-up of recurrent laryngeal nerve avulsion for the treatment of spastic dysphonia. *Ann Otol Rhinol Laryngol*. 1996;105:592-601.
70. Berke GS, Blackwell KE, Gerratt BR, Verneil A, Jackson KS, Sercarz JA. Selective laryngeal adductor denervation-reinnervation: a new surgical treatment for adductor spasmodic dysphonia. *Ann Otol Rhinol Laryngol*. 1999;108:227-231.
71. Allegetto M, Morrison M, Rammage L, Lau DP. Selective denervation: reinnervation for the control of adductor spasmodic dysphonia. *J Otolaryngol*. 2003;32:185-189.
72. Su CY, Chuang HC, Tsai SS, Chiu JF. Transoral approach to laser thyroarytenoid myoneurectomy for treatment of adductor spasmodic dysphonia: short-term results. *Ann Otol Rhinol Laryngol*. 2007;116:11-18.
73. Clinical use of botulinum toxin. *NIH Consensus Statement*. 1990;8:1-20.
74. Blitzer A, Brin MF, Stewart C, Aviv JE, Fahn S. Abductor laryngeal dystonia: a series treated with botulinum toxin. *Laryngoscope*. 1992;102:163-167.
75. Blitzer A, Brin MF, Stewart CF. Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia): a 12-year experience in more than 900 patients. *Laryngoscope*. 1998;108:1435-1441.
76. Sulica L, Behrman A. Management of benign vocal fold lesions: a survey of current opinion and practice. *Ann Otol Rhinol Laryngol*. 2003;112:827-833.
77. Blitzer A, Brin MF, Fahn S, Lange D, Lovelace RE. Botulinum toxin for the treatment of spastic dysphonia. *Laryngoscope*. 1986;96:1300-1301.
78. Truong DD, Rontal M, Rolnick M, Aronson AE, Mistura K. Double-blind controlled study of botulinum toxin in adductor spasmodic dysphonia. *Laryngoscope*. 1991;101:630-634.
79. Boutsen F, Cannito MP, Taylor M, Bender B. Botox treatment in adductor spasmodic dysphonia: a meta-analysis. *J Speech Lang Hear Res*. 2002;45:469-481.
80. Watts C, Nye C, Whurr R. Botulinum toxin for treating spasmodic dysphonia (laryngeal dystonia): a systematic Cochrane review. *Clin Rehabil*. 2006;20:112-122.
81. Albanese A, Barnes MP, Bhatia KP, Fernandez-Alvarez E, Filippini G, Gasser T, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. *Eur J Neurol*. 2006;13:433-444.
82. Ford CM, Bless DM, Lowery JD. Indirect laryngoscopic approach for injection of botulinum in spasmodic dysphonia. *Otolaryngol Head Neck Surg*. 1990;103:752-758.
83. Rhew K, Fiedler DA, Ludlow CL. Technique for injection of botulinum toxin through the flexible nasolaryngoscope. *Otolaryngol Head Neck Surg*. 1994;111:787-794.
84. Green DC, Ward PH, Berke GS, Gerratt BR. Point-touch technique of botulinum toxin injection for the treatment of spasmodic dysphonia. *Ann Otol Rhinol Laryngol*. 1992;101:883-887.
85. Miller RH, Woodson GE, Jankovic J. Botulinum toxin injection in the vocal fold for spasmodic dysphonia. A preliminary report. *Arch Otolaryngol Head Neck Surg*. 1987;113:603-605.
86. Ludlow CL, Naunton RF, Sedory SE, Schulz GM, Hallett M. Effects of botulinum toxin injections on speech in adductor spasmodic dysphonia. *Neurology*. 1988;38:1220-1225.
87. Bielamowicz S, Stager SV, Badillo A, Godlewski A. Unilateral versus bilateral injections of botulinum toxin in patients with adductor spasmodic dysphonia. *J Voice*. 2002;16:117-123.
88. Maloney AP, Morrison MD. A comparison of the efficacy of unilateral versus bilateral botulinum toxin injections in the treatment of adductor spasmodic dysphonia. *J Otolaryngol*. 1994;23:160-164.
89. Zwirner P, Murry T, Woodson GE. A comparison of bilateral and unilateral botulinum toxin treatments for spasmodic dysphonia. *Eur Arch Otorhinolaryngol*. 1993;250:271-276.
90. Galardi G, Guerriero R, Amadio S, Leocani L, Teggi R, Melloni G, et al. Sporadic failure of botulinum toxin treatment in usually responsive patients with adductor spasmodic dysphonia. *Neurol Sci*. 2001;22:303-306.
91. Klotz DA, Maronian NC, Waugh PF, Shahinfar A, Robinson L, Hillel AD. Findings of multiple muscle involvement in a study of 214 patients with laryngeal dystonia using fine-wire electromyography. *Ann Otol Rhinol Laryngol*. 2004;113:602-612.
92. Inagi K, Ford CN, Bless DM, Heisey D. Analysis of factors affecting botulinum toxin results in spasmodic dysphonia. *J Voice*. 1996;10:306-313.
93. Brin MF, Fahn S, Moskowitz C, Friedman A, Shale HM, Greene PE, et al. Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. In: Fahn S, Marsden CD, Calne DB, eds. *Dystonia 2*. New York: Raven; 1988:599-608.
94. Brin MF, Blitzer A, Fahn S, Gould W, Lovelace RE. Adductor laryngeal dystonia (spastic dysphonia): treatment with local injections of botulinum toxin (Botox). *Mov Disord*. 1989;4:287-296.
95. Whurr R, Nye C, Lorch M. Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review

- of 22 studies. *Int J Lang Commun Disord.* 1998;33(Suppl):327-329.
96. Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope.* 2001;111:218-226.
 97. Koriwchak MJ, Netterville JL, Snowden T, Courey M, Ossoff RH. Alternating unilateral botulinum toxin type A (BOTOX) injections for spasmodic dysphonia. *Laryngoscope.* 1996;106:1476-1481.
 98. Rontal M, Rontal E, Rolnick M, Merson R, Silverman B, Truong DD. A method for the treatment of abductor spasmodic dysphonia with botulinum toxin injections: a preliminary report. *Laryngoscope.* 1991;101:911-914.
 99. Meleca RJ, Hogikyan ND, Bastian RW. A comparison of methods of botulinum toxin injection for abductor spasmodic dysphonia. *Otolaryngol Head Neck Surg.* 1997;117:487-492.
 100. Ludlow CL, Naunton RF, Terada S, Anderson BJ. Successful treatment of selected cases of abductor spasmodic dysphonia using botulinum toxin injection. *Otolaryngol Head Neck Surg.* 1991;104:849-855.
 101. Bielamowicz S, Squire S, Bidus K, Ludlow CL. Assessment of posterior cricoarytenoid botulinum toxin injections in patients with abductor spasmodic dysphonia. *Ann Otol Rhinol Laryngol.* 2001;110:406-412.
 102. Stong BC, DelGaudio JM, Hapner ER, Johns MM, III. Safety of simultaneous bilateral botulinum toxin injections for abductor spasmodic dysphonia. *Arch Otolaryngol Head Neck Surg.* 2005;131:793-795.
 103. Cyrus CB, Bielamowicz S, Evans FJ, Ludlow CL. Adductor muscle activity abnormalities in abductor spasmodic dysphonia. *Otolaryngol Head Neck Surg.* 2001;124:23-30.
 104. Smith ME, Ford CN. Resistance to botulinum toxin injections for spasmodic dysphonia. *Arch Otolaryngol Head Neck Surg.* 2000;126:533-535.
 105. Guntinas-Lichius O. Injection of botulinum toxin type B for the treatment of otolaryngology patients with secondary treatment failure of botulinum toxin type A. *Laryngoscope.* 2003;113:743-745.
 106. Adler CH, Bansberg SF, Krein-Jones K, Hentz JG. Safety and efficacy of botulinum toxin type B (Myobloc) in adductor spasmodic dysphonia. *Mov Disord.* 2004;19:1075-1079.
 107. Blitzer A. Botulinum toxin A and B: a comparative dosing study for spasmodic dysphonia. *Otolaryngol Head Neck Surg.* 2005;133:836-838.
 108. Grillone GA, Blitzer A, Brin MF, Annino DJ Jr., Saint-Hilaire MH. Treatment of adductor laryngeal breathing dystonia with botulinum toxin type A. *Laryngoscope.* 1994;104:30-32.
 109. Zwirner P, Dressler D, Kruse E. Spasmodic laryngeal dyspnea: a rare manifestation of laryngeal dystonia. *Eur Arch Otorhinolaryngol.* 1997;254:242-245.
 110. Braun N, Abd A, Baer J, Blitzer A, Stewart C, Brin M. Dyspnea in dystonia: a functional evaluation. *Chest.* 1995;107:1309-1316.
 111. Zwirner P, Murry T, Woodson GE. Effects of botulinum toxin on vocal tract steadiness in patients with spasmodic dysphonia. *Eur Arch Otorhinolaryngol.* 1997;254:391-395.
 112. Ludlow CL. Treatment of speech and voice disorders with botulinum toxin. *JAMA.* 1990;264:2671-2675.
 113. Brin MF, Stewart C, Blitzer A, Diamond B. Laryngeal botulinum toxin injections for disabling stuttering in adults. *Neurology.* 1994;44:2262-2266.
 114. Aronson AE, Brown JR, Litin EM, Pearson JS. Spastic dysphonia. II. Comparison with essential (voice) tremor and other neurologic and psychogenic dysphonias. *J Speech Hear Disord.* 1968;33:219-231.
 115. Maronian NC, Waugh PF, Robinson L, Hillel AD. Tremor laryngeal dystonia: treatment of the lateral cricoarytenoid muscle. *Ann Otol Rhinol Laryngol.* 2004;113:349-355.
 116. Warrick P, Dromey C, Irish JC, Durkin L, Pakiam A, Lang A. Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor: a crossover design study of unilateral versus bilateral injection. *Laryngoscope.* 2000;110:1366-1374.
 117. Hertegard S, Granqvist S, Lindestad PA. Botulinum toxin injections for essential voice tremor. *Ann Otol Rhinol Laryngol.* 2000;109:204-209.
 118. Adler CH, Bansberg SF, Hentz JG, Ramig LO, Buder EH, Witt K, et al. Botulinum toxin type A for treating voice tremor. *Arch Neurol.* 2004;61:1416-1420.
 119. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord.* 1998;13(Suppl. 3):2-23.
 120. Trosch RM, Pullman SL. Botulinum toxin A injections for the treatment of hand tremors. *Mov Disord.* 1994;9:601-609.
 121. Henderson JM, Ghika JA, Van Melle G, Haller E, Einstein R. Botulinum toxin A in non-dystonic tremors. *Eur Neurol.* 1996;36:29-35.
 122. Pullman S, Greene PF, Fahn S. Approach to the treatment of limb disorders with botulinum toxin A. Experience with 187 patients. *Arch Neurol.* 1996;53:617-624.
 123. Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord.* 1996;11:250-256.
 124. Brin MF, Lyons KE, Doucette J, Adler CH, Caviness JN, Comella CL, et al. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology.* 2001;56:1523-1528.
 125. Papapetropoulos S, Singer C. Treatment of primary writing tremor with botulinum toxin type A injections: report of a case series. *Clin Neuropharmacol.* 2006;29:364-367.
 126. Schneider SA, Edwards MJ, Cordivari C, Macleod WN, Bhatia KP. Botulinum toxin A may be efficacious as treatment for jaw tremor in Parkinson's disease. *Mov Disord.* 2006;21:1722-1724.
 127. Deuschl G, Lohle E, Heinen F, Lucking C. Ear click in palatal tremor: its origin and treatment with botulinum toxin. *Neurology.* 1991;41:1677-1679.
 128. Penney SE, Bruce IA, Saeed SR. Botulinum toxin is effective and safe for palatal tremor: a report of five cases and a review of the literature. *J Neurol.* 2006;253:857-860.
 129. Gordon K, Cadera W, Hinton G. Successful treatment of hereditary trembling chin with botulinum toxin. *J Child Neurol.* 1993;8:154-156.
 130. Gonzalez-Alegre P, Kelkar P, Rodnitzky RL. Isolated high-frequency jaw tremor relieved by botulinum toxin injections. *Mov Disord.* 2006;21:1049-1050.
 131. Kwak CH, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. *Arch Neurol.* 2000;57:1190-1193.
 132. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized,

- double-blind, controlled clinical trial. *Neurology*. 2001;56:605-610.
133. Scott BL, Jankovic J, Donovan DT. Botulinum toxin injection into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. *Mov Disord*. 1996;11:431-433.
134. Salloway S, Stewart CF, Israeli L, Morales X, Rasmussen S, Blitzer A, et al. Botulinum toxin for refractory vocal tics. *Mov Disord*. 1996;11:746-748.
135. Porta M, Maggioni G, Ottaviani F, Schindler A. Treatment of phonic tics in patients with Tourette's syndrome using botulinum toxin type A. *Neurol Sci*. 2004;24:420-423.
136. Albanese A, Bentivoglio AR. Botulinum toxin in movement disorders. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*. ed 5th. Philadelphia: Lippincott Williams & Wilkins; 2007:605-619.