# Chapter 3
# Clinical Use of Botulinum Neurotoxin: Neuromuscular Disorders

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**Abstract** The original clinical application of botulinum neurotoxin was in the treatment of strabismus by local chemical denervation of the neuromuscular junction and relaxation of the muscle with a duration of several months. This initial application has been followed by use of the neurotoxin to treat a wide range of disorders of muscle hyper-contraction. Botulinum neurotoxin is now a major clinical product for the treatment of spasticity and muscle hyperactivity. Muscle relaxation also underpins the cosmetic use of the neurotoxin. This chapter will review and assess the clinical utility of the various botulinum products in neuromuscular disorders.

**Keywords** Botulinum neurotoxin · Dystonia · Blepharospasm · Spasticity · Tremor · Dyskinesias

## 3.1 Introduction

In the late 1970s, a botulinum neurotoxin (BoNT) was introduced as a therapeutic agent for the treatment of strabismus [1]. This pioneering indication has paved the way to the use of BoNT products as therapeutic agents for a wide range of disorders with muscle hyper-contraction. The list of potential applications of BoNT in clinical practice has rapidly expanded to encompass dystonia syndromes, tremor, tics, spasticity and other neuromuscular disorders (Table 3.1). We review here this wealth of information and highlight the therapeutic role of BoNT in neuromuscular disorders.

Several BoNT preparations are now licensed for clinical use [2]. Three branded products contain BoNT/A (onabotulinumtoxinA marketed as Botox®, abobotulinumtoxinA marketed as Dysport®, incobotulinumtoxinA marketed as Xeomin®) and one contains BoNT/B (rimabotulinumtoxinB marketed as Myobloc® in Canada, the USA and Korea and as NeuroBloc® in the European Union, Norway and Iceland). These products are dosed using noninterchangeable proprietary units and switching from

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**Table 3.1** BoNT indications in neuromuscular disorders: first introduction

| Year | Disease | First report |
|---|---|---|
| 1980 | Strabismus | [1] |
| 1985 | Blepharospasm | [24] |
| 1985 | Cervical dystonia | [57] |
| 1986 | Hemifacial spasm | [144] |
| 1986 | Spasmodic dysphonia | [240] |
| 1989 | Oromandibular dystonia | [88] |
| 1989 | Focal hand dystonia | [241] |
| 1989 | Spasticity | [242] |
| 1992 | Cosmetic use | [243] |
| 1990 | Tardive dyskinesias | [212] |
| 1993 | Cerebral palsy in children | [181] |
| 1994 | Dystonic tics | [202] |
| 1994 | Axial dystonia | [244] |
| 1995 | Focal lower limb dystonia | [127] |
| 1997 | Freezing of gait | [236] |

one to another requires expert clinical management. Licensing varies among products and between countries, particularly within Europe, and expands continuously on indications (Table 3.2).

There is no consensus on how to perform BoNT injections in different neuromuscular disorders. Variables such as dosing, dilutions, number of injections per site, targeting (visual, electromyography (EMG)- or ultrasound-guided) influence outcome and reduce comparability of data among different centers. BoNT injections can be intramuscular, subcutaneous, intradermic or intraglandular and are part of a comprehensive treatment plan.

## 3.2 Neurological Indications

### *3.2.1 Dystonia*

Dystonia is characterized by sustained muscle contractions, frequently causing repetitive twisting movements or abnormal postures resulting in a combination of dystonic movements and postures [3]. This was the first hyperkinetic movement disorder treated with BoNT [4]. Localized injections provide a transient symptomatic relief in primary and non-primary dystonia syndromes, as demonstrated by several randomized controlled studies and by a large number of uncontrolled studies. Experience on the use of BoNT treatment, in focal dystonias, dates back to almost 30 years ago. Due to this long-lasting experience, treatment of dystonia is currently standardized across movement disorder clinics.

BoNT is the first-choice treatment for most types of focal dystonia. It is established that BoNT/A products, in properly adjusted doses, are effective and safe treatments of primary cranial (excluding oromandibular) and cervical dystonia and are effective on writing dystonia [5]. RimabotulinumtoxinB is also an efficacious treatment for cervical dystonia, but the larger doses required (compared to BoNT/A), pain at

**Table 3.2** Approved indications for BoNT use in neuromuscular disorders

| Product name/Toxin type | US approved uses | EU approved uses |
|---|---|---|
| OnabotulinumtoxinA | Cervical dystonia | Cervical dystonia |
| | Blepharospasm | Blepharospasm |
| | Hemifacial spasm | Hemifacial spasm |
| | Strabismus | Strabismus |
| | Upper limb spasticity | Focal spasticity |
| | Glabellar rhytides | Cerebral palsy |
| | | Glabellar rhytides |
| AbobotulinumtoxinA | Cervical dystonia | Cervical dystonia |
| | Neck pain | Blepharospasm |
| | Glabellar rhytides | Hemifacial spasm |
| | | Hyperhidrosis |
| | | Strabismus |
| | | Focal spasticity |
| | | Cerebral palsy |
| | | Glabellar rhytides |
| IncobotulinumtoxinA | Cervical dystonia | Cervical dystonia |
| | Blepharospasm | Blepharospasm |
| | | Upper limb spasticity |
| | | Glabellar rhytides |
| RimabotulinumtoxinB | Cervical dystonia | Cervical dystonia |

injection sites and shorter duration of action make it a second-choice option in treating dystonia [6], [7]. BoNT/A is also effective for focal upper limb and laryngeal dystonia, but the results are not as convincing as those collected in cases of cranial and cervical dystonia [8]. The level of evidence for efficacy on focal lower limb dystonia is even lower [8].

Given the long-standing experience in performing treatments, in recent years several long-term studies on the efficacy and safety of onabotulinumtoxinA and abobotulinumtoxinA have been published confirming their safety and efficacy [9]–[11]. IncobotulinumtoxinA has been introduced in Europe and North America only recently and long-term data on this product are not available. Few studies on rimabotulinumtoxinB have been performed in cervical dystonia and blepharospasm, and very few ones in oromandibular and upper limb dystonia. The results of these studies have confirmed the efficacy of rimabotulinumtoxinB but have not responded to the concern about antigenicity and systemic anticholinergic adverse effects. Shared experience on rimabotulinumtoxinB is insufficient compared to the large amount of information published on BoNT/A serotypes [12], [13].

There is informal agreement, albeit no consensus, on the practicalities of BoNT injections for dystonia. Overactive muscles can be identified by direct inspection or by EMG-guided targeting. As mentioned above, direct inspection is usually sufficient to target a superficial muscle, such as most facial and some cervical muscles. In these regions, EMG- or, less commonly, ultrasound-guided targeting provides a second-line approach whenever improvement of muscle selection is needed. In other body regions, such as the sublingual muscles, larynx and limbs, targeting is performed using EMG guidance rather than inspection.

### 3.2.2 *Blepharospasm*

Blepharospasm is a focal dystonia involving the orbicularis oculi and periocular muscles; when associated with oromandibular involvement, it is referred to as "Meige syndrome." In blepharospasm, there is excessive (intermittent or persistent) involuntary closure of the eyelids, usually bilateral, though it may sometimes be unilateral at onset. Eye closure is produced by phasic or tonic contractions of the ocular muscles. Over time, these may become more frequent and continuous, leading to sustained eyelid closure and functional blindness [14]. Blepharospasm typically begins insidiously between the fifth and the seventh decades. The estimated prevalence increases with age, ranging from as little as 16 cases per million to as many as 133 per million [15], suggesting that in many cases blepharospasm remains underdiagnosed. It affects twice as many women as men [16].

Initially, blinking may increase in response to bright light, accompanied by a sensation of eye discomfort. Symptoms then progress very slowly and the eyes may involuntary shut for long intervals, interrupting the patient's daily activities, such as driving or reading. In its most severe form, blepharospasm results in depression and social isolation. Spasms are absent during sleep. The condition generally takes several years to worsen and it may progress very mildly in some patients. Spontaneous remission occurs rarely, most often within the first 5 years [17]. Patients who develop blepharospasm may experience spread of the dystonia to other body parts. In a recent update on blepharospasm, studies that evaluated spread to other body regions were reviewed [18]. A series of 602 patients with primary dystonia showed that in patients with blepharospasm, spread of the dystonia to other body parts was more likely than in those with others focal forms [19]. Most spread occurred during the first 2 years after onset of blepharospasm, whereas the risk of spread remained roughly constant over time for other dystonias. This is in keeping with other observations that the time from onset to initial spread is shorter in patients with blepharospasm [20], [21].

In the majority of cases, no identifiable cause of blepharospasm is found, and secondary cases account for only 10 % of patients [22]. Therefore, primary (essential) blepharospasm is cured symptomatically. A commonly shared hypothesis is that blepharospasm is related to hyperexcitability of brainstem neurons, as a result of basal ganglia dysfunction. Recently, it has been proposed that an abnormal corneal input induced by excessive blinking may exacerbate increased long-term potentiation type of plasticity, thus leading to blepharospasm [23]. Secondary blepharospasm can occur in response to provocative, irritating mechanical or light stimuli, commonly because of a number of ocular disorders, such as blepharitis, trichiasis, dry eye syndrome and corneal disorders. Additionally, blepharospasm can be observed in a variety of neurodegenerative disorders.

BoNT/A has been quickly recognized as the treatment of choice for blepharospasm (14). Prior to its innovative introduction [24], medical and surgical treatments were rarely successful. Although there is no high-quality, randomized, controlled efficacy data to support the use of BoNT in blepharospasm, several open-label studies on large series indicate that it is an efficacious and safe treatment [25]. The Food and

Drug Administration (FDA) approved BoNT for the treatment of blepharospasm in 1989. Its efficacy has been confirmed by more than 50 open-label studies (accounting for > 2,500 patients), and by a few controlled studies. Data compiled by American Society of Ophthalmology showed that BoNT/A successfully treats approximately 90 % of blepharospasm patients [26]. In keeping with this, guidelines produced by the American Academy of Neurology and the European Federation of Neurological Societies provide 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 [5], [8]. Other studies have also evidenced improvement in quality of life after BoNT treatment [27].

Injections are typically well tolerated, with dry eye, eyelid ptosis, and mild facial weakness reported as the most frequent adverse events [26], occurring in less than 10 % of treated patients, and normally of short duration (less than 2 weeks). Treatment commonly starts with small doses that are increased as needed at successive treatment sessions. The upper limit is found when motor improvement lasting for 2–3 months without appreciable side effects is obtained. The site of injection greatly influences the outcome. Best results are obtained when low doses of BoNT are placed at pretarsal, rather than orbital, sites [28]–[31].

Common doses are 20–40 onabotulinumtoxinA U, 75–175 abobotulinumtoxinA U or 2,500 rimabotulinumtoxinB U. Higher doses are reported in some publications, indicating that the therapeutic window for BoNT may be quite wide. Very high doses of onabotulinumtoxinA (> 100 U) have been used in selected cases to treat refractory blepharospasm [32], [33]. The average latency from the time of injection to the onset of improvement varies from 3 to 5 days; a benefit lasting for 2–3 months is observed in almost all patients. The effect of BoNT/A is reversible and in most cases injections are repeated approximately every 3–4 months. Common reasons for lack of efficacy include underdosing and improper injection technique (particularly placement). Secondary resistance to BoNT is rare and can often be managed [34]; the doses used are lower than in other dystonia types and injections are performed less frequently.

Several studies have compared different formulations of BoNT in the treatment of blepharospasm. No differences were found between onabotulinumtoxinA and abobotulinumtoxinA with regard to duration of effect and adverse events in a single-blind, randomized comparison [35]. Based on these data, a 4:1 conversion rate was suggested for blepharospasm and hemifacial spasm (HFS). A double-blind, crossover study on 212 subjects compared abobotulinumtoxinA and onabotulinumtoxinA, using the same 4:1 ratio [36]. The duration of effect was identical in the two groups, but onabotulinumtoxinA caused fewer side effects, particularly ptosis. Another study reported different results about the duration of these two BoNT/A brands. A class IV trial found that onabotulinumtoxinA is more efficacious than abobotulinumtoxinA in blepharospasm and has a longer duration of effect [37]. More recently, we compared a large series of patients with blepharospasm who had been treated with abobotulinumtoxinA or onabotulinumtoxinA for more than 15 years [9]. In this long follow-up, abobotulinumtoxinA had a longer duration of improvement and produced more side effects than onabotulinumtoxinA. Both BoNT/A brands were

effective and safe in patients with blepharospasm but had marked differences related to patient management. It has been anecdotally reported that abobotulinumtoxinA is potentially effective in secondary nonresponders to onabotulinumtoxinA, but this has not been confirmed by controlled trials [38].

IncobotulinumtoxinA, which has been licensed recently, has been reported to be not inferior to onabotulinumtoxinA for the treatment of blepharospasm. IncobotulinumtoxinA was compared to onabotulinumtoxinA in a 1:1 dose ratio in two randomized, double-blind paralleled studies and no inferiority of efficacy or difference in tolerability was found [39], [40]. Another double-blind, parallel-group, multicenter study also reported that incobotulinumtoxinA is effective in blepharospasm and does not differ from onabotulinumtoxinA in terms of potency, duration or adverse reaction profile [41].

Another BoNT/A brand (called Prosigne®) is available in China and few other countries. This has not been widely investigated, and few data are available. In a small crossover study on 8 patients with blepharospasm, this toxin brand provided equivalent improvement, with latency, duration and side effects similar to onabotulinumtoxinA [42]. A prospective, randomized, double-blind study has compared this product to onabotulinumtoxinA in blepharospasm and HFS. The mean duration of efficacy was comparable (11.3 weeks for either toxin in blepharospasm). Pain and burning during the injection and the result of the treatment were similar in both groups. No systemic adverse events were reported; local side effects were similar in terms of intensity and frequency. Therefore, it has been concluded that onabotulinumtoxinA and the Chinese product have similar efficacy, safety and tolerability profiles, so that a dose equivalence of 1:1 may be considered for blepharospasm treatments [43]. These results need to be replicated in larger series, as the quantity and quality of data supporting the observation are limited.

In addition to BoNT/A, rimabotulinumtoxinB has also been used successfully in the treatment of blepharospasm [44], but double-blind controlled studies in this disorder are lacking. In a retrospective review of 16 patients resistant to BoNT/A and treated with BoNT/B, the mean effect equaled 7.3 weeks and was rated as fair to excellent in the majority. However, in this study, side effects were common and included pain at the site of injection, ptosis and dry mouth. Switching to an alternative BoNT serotype may benefit "secondary nonresponder" patients (those who have initial clinical benefit from BoNT injections that wanes over time) [45].

Understanding the muscular anatomy is critical to ensure optimal results. Various BoNT injection techniques have been advocated to optimize response and minimize adverse effects. The standard treatment techniques involve injection into four sites around each eyes, two in the upper lid, one medially, and one laterally near the canthus. Two additional injection sites in the lower lid, one at the lower lateral canthus and one near the lower lid midline, seem to produce a longer duration of effects than those in the eyebrows, inner orbital and outer orbital [46]. Blepharospasm may differentially affect the three 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 [29]. In a retrospective study of 25 patients with blepharospasm, compared to preseptal

placements, pretarsal BoNT/A injections produced a better response rate with a longer duration and lower incidence of ptosis, the most common side effect [31]. It was concluded that pretarsal placement is sufficient to provide optimum results, leaving the option to add preseptal or orbital injections if necessary. Furthermore, patients with a predominant pretarsal involvement may have prevalently tonic eye closure and find it difficult to voluntarily open the eyelids (so-called eyelid-opening apraxia). In such cases, EMG recordings show 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 the ones used in the orbital part of the muscle [28]. Other muscles that may also be involved in blepharospasm include the corrugator supercilii, the frontalis and the procerus.

### *3.2.3 Cervical Dystonia*

Cervical dystonia is the most common form of primary focal dystonia, also referred to as "spasmodic torticollis"; its incidence has been estimated in 5–9/100,000 [47] and prevalence in 20–200 per million [48]. It is a neurologic condition that causes abnormal movements and postures of the neck. The phenomenology of cervical dystonia is complex; it can variably combine tonic (slow and sustained) and phasic (fast and intermittent) movements. Overlying spasms can induce slow and rapid head jerks. Cervical dystonia arises from involuntary activation of muscles causing turning (torticollis), tilting (laterocollis), flexion (antecollis) or extension (retrocollis) of the head; sometimes these are combined with elevation or anterior shifting of the shoulder. Each of these postures is associated with specific patterns of muscle overactivity in each patient, with variability from patient to patient. Pain affects approximately 60 % of cervical dystonia patients and can be the most disabling feature. Cervical dystonia most commonly presents as a sporadic disorder of adulthood, but up to 12 % of patients may report a positive family history [49].

Commonly, cervical dystonia starts in the 40s; it is a lifelong condition; permanent remissions are rare, although temporary remissions lasting days to years may occur [50]. Although not life threatening, cervical dystonia can cause disability and impair quality of life [51]. Moreover, several disabling conditions (cervical arthritis, radiculopathy, and myelopathy) may occur concomitantly [52]. Secondary cases of cervical dystonia have also been described following cervical or brain traumatic injury, or in association with neurodegenerative diseases or cerebral palsy (CP). The assessment and treatment of secondary forms of cervical dystonia have not been subject to the same rigorous studies as primary focal cervical dystonia.

Several treatment options are available for cervical dystonia, including oral pharmacological agents, soft tissue surgery, surgical denervation and deep brain stimulation (DBS). Oral medications (anticholinergic agents, baclofen and benzodiazepines) may be of limited benefit; their use is limited by common side effects. Although the use of DBS in patients with dystonia is recent, there is growing evidence

that globus pallidus DBS is an option for patients with severe symptoms [53], [54]. Among the therapeutic interventions available, BoNT is regarded as the first-choice treatment, due to its efficacy and positive cost/benefit ratio. Up to 85 % of patients get benefit from BoNT treatment, particularly as it concerns ameliorating head posture, reducing pain and improving range of motion. For these reasons, this has long been considered the treatment of choice in cervical dystonia patients [55], [56].

Since the first report of the efficacy of the original North American BoNT/A batch (Oculinum®) [57], more than 80 studies (mostly uncontrolled or consisting of small series) have evaluated BoNT in cervical dystonia. Among these, eight prospective, double-blind, randomized controlled clinical studies provided class I evidence of the efficacy of BoNT in ameliorating head posture and neck pain (8). Other studies documented the improvement of health-related quality of life and disability after BoNT. One study compared abobotulinumtoxinA injections with oral administration of trihexyphenidyl and found that BoNT/A is more efficacious with fewer adverse events [58].

All commercially available BoNT brands have proven efficacious in randomized controlled trials (RCTs) on cervical dystonia. Notwithstanding this evidence, several questions remain unresolved. The first is whether the three BoNT/A brands are equivalent and the second is what place the BoNT/B formulation has in the treatment algorithm. These products are not identical, in either formulation or dose [2] and there are suggestions of potential differences in efficacy and safety profiles among BoNT preparations.

In clinical practice, when shifting from one brand of BoNT/A to another or from BoNT/A to BoNT/B, there is no clear dosing equivalency [59]. Dosing in cervical dystonia patients varies depending on serotype and brand. Two prospective studies compared onabotulinumtoxinA to abobotulinumtoxinA. In one blinded, parallel-arm study, a fixed dose ratio of 1 onabotulinumtoxinA U to 3 abobotulinumtoxinA U showed similar efficacy, adverse effect profile and duration [60]. However, a subsequent study from the same group did not confirm this observation and reported that the dose equivalency of onabotulinumtoxinA and abobotulinumtoxinA was less than 1:3 [61]. Furthermore, a retrospective study analyzing patients switched from abobotulinumtoxinA to onabotulinumtoxinA or vice versa found a variable dosing ratio ranging from 3 to 5:1 [62]. This suggests that different brand units cannot be converted linearly. It is therefore recommended that each BoNT/A brand be administered according to the dosing suggestion of the information package and the patient's needs. In cervical dystonia, onabotulinumtoxinA doses vary between 70 and 370 U. Doses $< 100$ U are usually sufficient to relieve cervical pain in the majority of patients [63]. As for abobotulinumtoxinA, it has been recommended to start with a dose of 500 U that provides benefit in most patients with minimal risk of adverse events [64]. A study comparing 250, 500 and 1,000 abobotulinumtoxinA U in cervical dystonia reported that the magnitude and duration of improvement was greatest after injections of 1,000 U, at the cost of significantly more adverse events [65]. IncobotulinumtoxinA has been compared to onabotulinumtoxinA in a non-inferiority trial reporting that this BoNT/A brand is as efficacious and safe at a

1:1 dose ratio as onabotulinumtoxinA [66]. Direct comparison of onabotulinumtoxinA and rimabotulinumtoxinB was performed in two studies that established a dose ratio between 1:40 and 1:66.6 U. Both studies showed comparable efficacy. In the first study, the onabotulinumtoxinA-treated group had a modestly longer duration of benefit (approximately 2 weeks) and fewer occurrences of dysphagia and dry mouth than the rimabotulinumtoxinB group (6). In the second study, there was no difference in duration or adverse events [67].

A Chinese BoNT/A brand (Prosigne®) has been compared to onabotulinumtoxinA® in a prospective, randomized, double-blind study. Average duration of effect and incidence of adverse events were similar; social aspect, pain and quality of life improved in both groups; the authors concluded that these two BoNTs were equivalent in terms of efficacy, safety and tolerability profiles, with a dose equivalence ratio for cervical dystonia of 1:1 [43]. As for blepharospasm, more experience and higher quality trials are needed for this toxin brand. BoNT/F has also been shown to improve cervical dystonia symptoms in secondary nonresponders. However, the benefit duration is much shorter, lasting for approximately 8 weeks [68]. Increasing the dose prolongs the duration of clinical benefit at the cost of increased adverse effects [69]. It has also been observed that after repeated injections approximately 33 % of these patients developed resistance to serotype F [68].

In clinical practice, the average total dose injected in patients with cervical dystonia is 100–300 onabotulinumtoxinA U or incobotulinumtoxinA U, 400–800 abobotulinumtoxinA U, or 10,000–20,000 rimabotulinumtoxinB U. These doses can vary considerably as the recommended range has to be adjusted depending on the individual patient's features. It is also generally accepted that larger doses are associated with an increased risk of adverse events [70]. The initial treatment should be targeted to the most active muscles contributing to dystonic movements and postures. Most studies report that the average latency of clinical action is around 1 week. The benefit duration is reported to last between 8 and 16 weeks, although it may be as long as 5–6 months, especially with repeated sessions. However, on average the patients need re-treatment every 3–4 months. Duration of benefit has been observed to last longer in patients with moderate cervical dystonia [71]; efficacy on pain reduction is more marked than that on involuntary movements.

Adverse events are generally mild or moderate and transient, including pain at injection site, neck weakness, flu-like symptomatology, hoarseness, dry mouth and dysphagia [72]. Systemic events include general tiredness and muscle weakness (occurring even in the placebo arm of controlled studies) [73]. Differences in adverse-event rate among BoNT preparations may be important for selecting a treatment and setting expectations. After injection of cervical muscles, the most severe side effect and dose-limiting factor is dysphagia, caused by migration of BoNT out of the injected muscle. According to some studies, abobotulinumtoxinA is more efficacious than onabotulinumtoxinA in controlling pain and dystonia [61], but has a higher incidence of side effects (dysphagia, dysphonia, asthenia, neck weakness), probably because of a higher diffusion around the injection sites [74]. Dysphagia and dysphonia are considered the two most important side effects related to BoNT diffusion

to the underlying pharyngeal and laryngeal muscles after injection in the sternocleidomastoid muscle. Particular care should be taken to avoid diffusion outside the sternocleidomastoid towards deeper structures, limiting the doses [65] and choosing the appropriate dilutions and injection sites. There is evidence that autonomic dysfunction is more common with BoNT/B compared to BoNT/A [75]. This has been confirmed by two class I studies [6], [67]. Dry mouth is commonly associated with BoNT/B injection and seems unrelated to the doses injected, presumably because BoNT/B blocks the cholinergic release in postganglionic parasympathetic fibers to the salivary glands (Table 3.3).

Patients with cervical dystonia who do not improve after BoNT treatment are called primary nonresponders; those who do not improve following a previous successful treatment are called secondary nonresponders. Primary failure occurs in approximately 15–30 % of patients and has several causes, including contractures, inadequate dosing, inaccurate muscle selection, inaccessibility of the muscles involved or patient's immunization. For example, in patients with antecollis, BoNT injections may be unsuccessful because of the involvement of prevertebral muscles that are not accessible for injection. Retrospective studies suggest that secondary failure to BoNT affects approximately 10–15 % of patients with cervical dystonia [72], [76]. The occurrence of antibodies to BoNT, revealed by the mouse neutralization assay, has been reported in one third of secondary nonresponding patients [76]. In patients who develop resistance to one serotype, treatment with another serotype may restore clinical efficacy [77]. It is advisable that the frequency of repeated treatments is reduced as much as possible to minimize the risk of immunization.

## 3.3 Other Focal Dystonias

### *3.3.1 Oromandibular and Lingual Dystonia*

Oromandibular dystonia (OMD) is a focal form that mainly involves the masticatory muscles and also affects the lower facial, labial and tongue muscles. Masticatory muscles spasms can induce jaw closing or opening, lateral deviation, protrusion, retraction, or a combination of different movements. Involuntary biting of the tongue, cheek, or lips and difficulty in speaking and chewing is often socially embarrassing and cosmetically disfiguring. Lingual dystonia often occurs in association with other OMD forms, but can be isolated as well. It is rare and disabling, impacting daily activities (e.g., speaking, chewing, swallowing) and causes social disability.

OMD affects women more than men. The mean age at onset is between 50 and 60 years [78]. The picture tends to remain stable, but fluctuations are observed in individual cases. Although spontaneous improvement may occur with time, complete remissions are exceptionally rare. Dystonia in OMD is commonly worsened by action, in particular with specific motor tasks, such as eating or praying [79].

Most patients with OMD have a primary condition, while tardive dystonia represents the most common cause of secondary OMD. Trauma or procedures involving

**Table 3.3** Class I studies on BoNT treatment in neuromuscular disorders (classification based on American Academy of Neurology criteria)

| Disease | Study design | BoNT type | Dose (U total) | Patients (*n*) | Reference |
|---|---|---|---|---|---|
| Blepharospasm | Double-blind randomized, non-inferiority | OnabotulinumtoxinA vs. IncobotulinumtoxinA | 40.4 U (mean) | 300 | [39] |
| Cervical dystonia | Double-blind, randomized, placebo controlled | OnabotulinumtoxinA | 150–165 U | 55 | [245] |
| Cervical dystonia | Double-blind, randomized, controlled, prospective | AbobotulinumtoxinA vs. Trihexyphenidyl | 554 U vs. 16.5 mg (mean) | 66 | [58] |
| Cervical dystonia | Double-blind, placebo-controlled | RimabotulinumtoxinB | 2,500/5,000/10,000 U | 122 | [246] |
| Cervical dystonia | Double-blind, randomized, placebo controlled | AbobotulinumtoxinA | 250/500/1,000 U | 75 | [65] |
| Cervical dystonia | Double-blind, randomized, parallel | OnabotulinumtoxinA vs. AbobotulinumtoxinA | 159 U vs. 477 U (mean) | 73 | [60] |
| Cervical dystonia | Double-blind, placebo-controlled, randomized | RimabotulinumtoxinB | 5,000/10,000 U | 109 | [247] |
| Cervical dystonia | Double-blind, placebo-controlled | RimabotulinumtoxinB | 10,000 U | 77 | [77] |
| Cervical dystonia | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 500 U | 80 | [248] |
| Cervical dystonia | Double-blind, randomized, parallel-group | OnabotulinumtoxinA vs. RimabotulinumtoxinB | 250 U vs. 10,000 U | 139 | [6] |
| Cervical dystonia | Double-blind, randomized | OnabotulinumtoxinA vs. RimabotulinumtoxinB | 150 U vs. 10,000 U | 111 | [67] |
| Writer's cramp | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 178 U (mean) | 40 | [122] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | OnabotulinumtoxinA | 75/150/300 U | 39 | [249] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 1,000 U | 24 | [250] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 500/1,000/1,500 U | 25 | [251] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 1,000 U | 40 | [252] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 500/1,000/1,500 U | 82 | [253] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 1,000 U | 59 | [254] |
| Upper limb spasticity | Double-blind, placebo-controlled | OnabotulinumtoxinA | 200–240 U | 122 | [161] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | OnabotulinumtoxinA | 90/180/360 U | 91 | [255] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | RimabotulinumtoxinB | 10,000 U | 15 | [172] |
| Upper limb spasticity | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 350/500/1,000 U | 50 | [256] |
| Upper and lower limb spasticity | Double-blind, randomized, placebo-controlled | OnabotulinumtoxinA | 141.25 U (upper limb), 284.75 U (lower limb), (mean) | 52 | [257] |

**Table 3.3** (continued)

| Disease | Study design | BoNT type | Dose (U total) | Patients (*n*) | Reference |
|---|---|---|---|---|---|
| Lower limb spasticity (hip adductor) | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 500/1,000/1,500 U | 74 | [177] |
| Lower limb | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 500/1,000/1,500 U | 234 | [258] |
| Spastic equines (CP) | Double-blind, randomized, placebo-controlled | OnabotulinumtoxinA | 4 U/Kg | 20 | [259] |
| Spastic equines (CP) | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 15/25 U/Kg | 40 | [260] |
| Spastic equines (CP) | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 10/20/30 U/Kg | 126 | [261] |
| Adductor spasticity (CP) | Double-blind, randomized, placebo-controlled | OnabotulinumtoxinA | 8 U/Kg | 16 | [262] |
| Adductor spasticity (CP) | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 30 U/Kg (max 1,500 U) | 61 | [263] |
| Lower limb spasticity (CP) | Double-blind, randomized, placebo-controlled | OnabotulinumtoxinA | 12 U/Kg (max 400 U) | 33 | [264] |
| Upper limb spasticity (CP) | Double-blind, randomized, controlled | OnabotulinumtoxinA | 4.6 vs. 9.2 U/Kg | 39 | [265] |
| Leg spasticity (CP) | Double-blind, randomized, placebo-controlled | AbobotulinumtoxinA | 15–30 U/Kg | 64 | [266] |

the face or oral and dental structures have been suggested to be causative [80]. Occasionally, OMD has been observed as an accompanying manifestation of neurodegenerative disorders, focal brain lesion or brainstem lesion [81]. Finally, OMD can lead to secondary complications, such as tension-type headache, increased dental wear, temporomandibular joint syndrome or temporomandibular joint dislocation. In order to prevent these complications, early diagnosis and appropriate treatment are crucial.

The presentation of OMD is highly variable and treatments need to be individualized. Pharmacological therapy is only partially effective [82]. Oral medications, including anticholinergics, tetrabenazine, baclofen or clonazepam, can be used. Tetrabenazine, in particular, is helpful in lingual protusion dystonia [83], [84]. Muscle afferent block by intramuscular injection of lidocaine and alcohol has been shown to be helpful, but further experience and evaluation are needed to determine its long-term efficacy and benefit [85]. Lastly, pallidal DBS has been performed in a few patients with positive results and may be considered as an option in some patients with intractable OMD [86], [87].

#### 3.3.1.1 BoNT Treatment in OMD and Lingual Dystonia

BoNT has become the therapy of choice for OMD, and its use in jaw-opening, jaw-closing and jaw-deviation OMD has been documented [88], [89], although most data derive from open studies. The best responses have been reported on jaw-closing OMD [78].

In jaw-closing and jaw-deviation dystonia, BoNT is injected into both masseters and temporalis muscles. Typical doses in the masseters are 25 onabotulinumtoxinA or 100 abobotulinumtoxinA units; in the temporalis muscles typical doses are 20 and 80 units, respectively. If these injections are not sufficient to control dystonic movements, the internal pterygoid can be injected (with 15 onabotulinumtoxinA U or 60 abobotulinumtoxinA U). Scanty data are available on rimabotulinumtoxinB [90], [91]. Suggested doses are 2,500 units in each masseter muscle and 1,000 units in the pterygoids [92]. There is no experience with incobotulinumtoxinA.

The treatment of patients with jaw-opening dystonia is more challenging; in this situation, the most important muscle to treat is the external pterygoid that can be approached transorally or laterally through the mandibular incisure. Notwithstanding, the digastric and other muscles can play a role. The external pterygoid is injected with 15 onabotulinumtoxinA units or 60 abobotulinumtoxinA units and the digastric muscle with 10 and 40 units, respectively. This combination is usually effective. In some patients, injecting the platysma with 20 onabotulinumtoxinA U, 60 abobotulinumtoxinA U or 1,000 rimabotulinumtoxinB U can provide additional improvement.

In jaw-deviation dystonia (often combined with protrusion), the contralateral external pterygoid muscle is the most important muscle to treat; when jaw-protrusion dystonia is dominating, both external pterygoids are often involved. Pterygoid muscle injections have to be performed with EMG guidance, as the muscles are not

easily accessible to palpation. The use of EMG is often helpful for other jaw muscles (digastric, masseter, temporalis). BoNT may also 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 in less than 20 % of treatment sessions. BoNT treatment may be disappointing in severely disabled patients for whom other solutions, such as DBS of the globus pallidum internum, have to be considered.

Lingual dystonia is difficult to treat and significant adverse effects have been reported. The need to preserve functional activity limits the amount of toxin that can be used. Especially in patients with severe tongue protrusion, results are disappointing [93]. Injections of 10 onabotulinumtoxinA U or 40 abobotulinumtoxinA U into the intrinsic tongue muscles can be used in lingual dystonia. More recently, it has been suggested that lingual protrusion dystonia may be successfully treated by injecting the genioglossus muscles. However, the risk of dysphagia is high, so it is recommended to start with very low doses (5 onabotulinumtoxinA U) in each genioglossus muscle and then increase by 2.5 U up to 15 U per treatment session until the patient achieves a reasonable response. Despite this prudent approach, dysphagia may still occur [94].

There is no reported experience with rimabotulinumtoxinB or incobotulinumtoxinA in lingual dystonia.

### *3.3.2 Spasmodic Dysphonia*

Spasmodic dysphonia (SD) is a laryngeal dystonia, most often focal, that sometimes may occur in association with cranial or generalized dystonia. The vocal folds are normal at rest, but during phonation they develop action-induced, task-specific contractures causing abnormal movements and muscle spasms during speaking and resulting in dysphonia [95].

Different types of SD have been identified. The adductor type, caused by spasmodic activity of the vocal muscle (thyroarytenoid), is the most common; it induces hyperadduction of the vocal folds during speaking, producing a “strain-strangled” voice that is harsh, often tremulous, with inappropriate pitch or pitch breaks, breathiness and glottal fry. The abductor form is less common; it is due to spasms of the posterior cricoarytenoid muscles, causing a prolonged, inappropriate abduction of vocal folds during voiceless consonants. This results in a breathy, effortful, hypophonic voice with abrupt termination of voicing, aphonic or whispered segments of speech. Some retain that all patients have mixed adductor/abductor involvement with predominance of either of the two. There are also patients with compensatory or pseudoabductor forms, who whisper to compensate for the tight adductor spasms they experience. In some cases, the presentation at onset may change with time; particularly, adductor may turn to abductor.

In another rare type, the adductor breathing dystonia, there are adductor spasms during respiration. The paradoxical motion creates stridulous noises during inspiration, but usually does not produce hypoxia. Other laryngeal activities are normal.

Also a "singer's laryngeal dystonia" has been identified. In this form, the vocal abnormalities occur during singing. SD typically affects patients in their mid-40s and is more common in women [96], [97]; most often SD symptoms develop gradually over several months to years.

For many years, the only treatment options for these patients were speech therapy or psychotherapy, with poor results overall. Speech therapy alone does not yield significant improvement but combined with BoNT allows treatment of the compensatory behaviors superimposed to SD [98]. Although psychotherapy may help the patients manage the associated social stress and minimize the emotion-related voice deterioration, there is no evidence that psychotherapy or psychological intervention can relieve SD.

Occasionally 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 had been the only truly efficacious options, but side effects and disappointing long-term results limited its usefulness.

#### 3.3.2.1 BoNT Treatment in SD

The first BoNT treatment was performed in 1984 on a patient with adductor SD [99]. Following this pioneering series on adductor SD, patients with abductor SD were also treated starting in 1988 [100]. In the past two decades, enough evidence has been produced to conclude that BoNT/A (or BoNT/B if there is resistance to type A) are the first-line treatment for SD [101]. Currently, BoNT is considered the treatment of choice for this disorder; most investigators report a 75–95 % 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.

Most commonly, adductor SD is treated by injecting percutaneously the laryngeal adductor muscles under EMG guidance. Unilateral or bilateral protocols have been proposed for BoNT injections into the thyroarytenoid muscle. Some groups have proposed treatment with large doses (20–30 onabotulinumtoxinA U) given unilaterally to minimize adverse events [102]. When bilateral treatments were compared with unilateral ones, the latter showed a more favorable efficacy/tolerability profile [103]. The most experienced injectors, however, retain that after an initial unilateral treatment of 2.5–7.5 onabotulinumtoxinA U, application of a bilateral protocol in subsequent treatment session prevents exacerbation of laryngeal dystonia in the untreated side [104]. Similar experience has been gathered with abobotulinumtoxinA [105]. In a prospective study, 31 patients with adductor SD were treated for five consecutive times, either unilaterally or bilaterally. Low-dose unilateral injections into the thyroarytenoid muscles produced comparable results to bilateral treatment, regarding duration, voice improvement and complications; moreover, unlike bilateral injections, unilateral ones were not associated with complete voice loss [106].

The doses of BoNT used in SD can vary depending on the toxin brand and the technique used. In the earlier literature, the doses varied from 3.75 to 7.5 onabotulinumtoxinA U for bilateral injections [107], [108] to 15 U for unilateral injections [102]. Remarkably, up to 50 onabotulinumtoxinA U in each vocal cord have been used [109]. Lower doses were later recommended [110]. Truong and colleagues suggested to start with 0.5 onabotulinumtoxinA U or 1.5 abobotulinumtoxinA U when injecting bilaterally, then to adjust the dose as needed (the estimated average dose being 0.75–1 onabotulinumtoxinA U or 2–3 abobotulinumtoxinA U) [111]. The duration of improvement is dose related. In the long term, the average latency of effect was 2.4 days with a peak at 9 days and a duration of 15.1 weeks [104]. This treatment is generally well tolerated; breathiness was often reported as transient or mild. Alternating unilateral injections caused significantly less breathy voice than bilateral injections [103]. 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 [112].

The experience with BoNT/B in SD is limited to the treatment of adductor-type dysphonia. In one patient who failed to respond to BoNT/A, 250 rimabotulinumtoxinB U were injected in each vocal fold with beneficial effects lasting for 3.5 months [113]. RimabotulinumtoxinB was found to be safe and effective in a class IV single-site, open-label study. It has been reported that 8 out of 10 treated patients, who received 200 rimabotulinumtoxinB U on each side, had a clinical improvement lasting for 8 weeks [114]. Three patients, who failed to respond to BoNT/A and subsequently received BoNT/B (up to 1,000 rimabotulinumtoxinB U per side), were reported to show improvement for approximately 2 months [111]. A direct comparison of BoNT/A and BoNT/B was performed on 32 patients with adductor SD who had been treated with stable BoNT/A doses and were followed up for 1 year with BoNT/B [115]. The conversion rate for laryngeal injections was considered to be 52.3:1. RimabotulinumtoxinB had more rapid onset and shorter duration of action (10.8 vs. 17 weeks). The safety profile was comparable.

Abductor SD is a difficult-to-treat condition. Usually the posterior cricoarytenoid muscles, the cricothyroid muscles or both are involved, but generally only the posterior cricoarytenoid muscle is injected under EMG guidance.

Bilateral injections are dangerous, as side effects include stridor and airway obstruction. Therefore, unilateral injections with 2.5–25 onabotulinumtoxinA U are performed on the most active side, as determined by fiberoptic laryngoscopy. A common procedure is to inject 5 onabotulinumtoxinA U 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 5 onabotulinumtoxinA U [116]. The following procedure has also been proposed: 2–4 onabotulinumtoxinA U on the most active side with 1 U in contralateral muscles, or 12 abobotulinumtoxinA U on the most active side and 3 abobotulinumtoxinA U on the opposite side [111]. A lower dose protocol with 1.25–1.75 onabotulinumtoxinA U in one muscle and 0.9 U on the opposite side has also been implemented [117]. 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. Simultaneous bilateral posterior cricoarytenoid muscle injections have also been considered to be safe [118]. The total BoNT dose injected in each session was between 2.50 and 7.50 onabotulinumtoxinA U, with an average total dose per session of 4.70 U. There were no life-threatening complications.

In a 12-year long experience on 154 patients, approximately 20 % of them had significant voice improvement associated to weakening or paralysis of one posterior cricoarytenoid muscle. The remaining 80 % needed an additional dose of 0.625–2.5 onabotulinumtoxinA U into the contralateral posterior cricoarytenoid. The overall improvement was around 70 %; the onset of efficacy was on an average 4.1 days and the benefit lasted for 10.5 weeks. Side effects were observed in 2 % of patients, consisting of mild exertional wheezing and 6 % mild transient dysphagia to solids [119]. The cricothyroid muscle can also be injected, under EMG guidance, by percutaneous access. In a large series of SD patients, nine received bilateral injections (2.5 onabotulinumtoxinA U on each side) in the cricothyroid muscles in addition to treatment in the posterior cricoarytenoid. These patients still had breathy breaks despite significant limitation of abduction. Five of the nine injected cases had benefit consisting in a louder voice with fewer breaks. One patient got worse after the additional injection [104]. Therefore, BoNT is probably effective for the treatment of adductor SD but there is less evidence to support its use in abductor SD.

In summary, laryngeal dystonia is a heterogeneous condition that can be improved by BoNT. Different treatment schemes and doses are required to fit the many varieties of presentations.

### *3.3.3 Focal Limb Dystonia*

Albeit BoNT represents the treatment of choice for focal limb dystonias, functional outcome of treatments is disappointing compared to that of blepharospasm or cervical dystonia, particularly because hand movements involve the subtle tuning of many forearm and hand muscles. Still, there are no effective alternative medical or surgical treatments. Writer's cramp (WC) in particular affects the sophisticated function of writing. As for other occupational cramps, it is difficult to obtain the requested quality of voluntary movement without weakness.

#### 3.3.3.1 Upper Limb

The upper extremity is affected more commonly than the lower limb. Focal upper limb dystonia usually begins in the hand and is task specific; with progression, task specificity is gradually lost. Typical upper limb dystonias include musician's cramps and WC, where BoNT has been reported to be effective [120], [121].

Most studies on WC are open-label reports of clinical experiences. A class I randomized, double-blind, placebo-controlled trial in 40 patients with WC treated with abobotulinumtoxinA showed BoNT/A efficacy based on subjective and objective

clinical scales [122]. Temporary weakness and pain at the injection site were the only reported adverse events. This observation has been replicated in three class II double-blind trials on upper limb injections of onabotulinumtoxinA [123], [124]. Pain is the symptom most frequently improved after treatment, often independently of motor function. The desired goals of BoNT treatment vary in each patient. The most immediate goal is to correct abnormal hand posture and relieve discomfort. The primary goal of restoring normal hand function is extremely difficult to achieve, as a consequence, despite initial improvement, some patients do not continue injections. Other patients are dissatisfied with the degree of benefit because BoNT does not fully correct all the symptoms, in particular loss of speed and coordination that is especially problematic for professional musicians. Secondary resistance due to antibody formation has been described in approximately 10 % of patients treated with the original onabotulinumtoxinA batch for focal hand dystonia [120]. Type A-resistant patients have been effectively treated with BoNT/F (68).

The first step in treatment planning is to identify the muscles most severely affected, separating out dystonic from compensatory movements. After initial inspection, EMG muscle selection usually allows to refine the choice of targets [121]. Injections can be performed using EMG- or ultrasound-based targeting.

The dose of BoNT is based on muscle size. Injections are repeated about every 3 months. In WC, the muscles injected usually include finger flexors and extensors and, if needed, also wrist pronators and flexors. Dose ranges are: 10–50 onabotulinumtoxinA U or 30–120 abobotulinumtoxinA U per muscle [125]. The importance of EMG-guided targeting is supported by the observation that only 37 % of needle placements based on surface anatomy were appropriately localized in the target muscle [126].

#### 3.3.3.2 Lower Limb Dystonia

Foot dystonia can be either idiopathic, in the context of a generalized dystonia, or symptomatic as in Parkinson's disease (PD) or in juvenile CP. Successful treatments with BoNT have been reported but no controlled trials are available [127–129]. BoNT use is still recommended since therapeutic alternatives are lacking. Higher doses may be given than in hand dystonia because motor control is less refined.

Lower limb dystonias often present with foot inversion, toe dorsiflexion and/or ankle plantar flexion. The injected muscles may include tibialis posterior, extensor hallucis longus, gastrocnemius and long toe flexors.

## 3.4 Hemifacial Spasm

HFS, a form of segmental myoclonus, is characterized by involuntary, intermittent and irregular clonic twitches or tonic contractions of the muscles supplied by the facial nerve on one side of the face [130]. HFS is a sporadic disorder with occasionally familial occurrence. Some patients may be genetically predisposed to develop HFS,

but most cases are sporadic [131]. It occurs more commonly in women (2:1) with an overall prevalence around 10/100,000, but in some populations, such as the Asians, the prevalence is much higher [132].

Most cases of HFS are attributed to an aberrant or ectopic artery (anterior inferior cerebellar, posterior cerebellar or vertebral) compressing the facial nerve at the root exit zone, resulting in an axono-axonal "ephaptic" transmission and a hyperexcitable facial motor nucleus. However, up to 25 % of unaffected individuals have vascular loops compressing the facial nerve, suggesting that this phenomenon alone may be insufficient to cause HFS [133]. Reports which have been associated to HFS include meningioma, schwannoma, neurinoma of the acoustic nerve, parotid gland tumor and pilocytic astrocytoma of the fourth ventricle. These space-occupying lesions should be excluded, in particular in patients with atypical features such as facial weakness or decreased corneal reflex, or any other evidence of cranial nerve dysfunction. Sometimes, peripheral facial nerve injury or prior Bell's palsy can also precede HFS; in those cases, hyperkinesias often coexist with a mild ipsilateral facial weakness [134]. Patients without history of Bell's palsy still may have abnormal EMG findings suggesting an old facial nerve damage and subsequent pathological regeneration [130].

Most patients present with unilateral contractions, but bilateral cases of HFS have been reported [135], [136]. Usually, the disorder starts in the orbicularis oculi muscle and gradually spreads to other muscles, such as the frontalis, procerus, zygomaticus, risorius, levator labii superioris, depressor labii inferioris, depressor anguli oris and sometimes also platysma. Although HFS is not a life-threatening condition, it may have a severe impact on the patient's aesthetics and causes social disability; moreover, it sometimes interferes with sleep. Rarely, patients with HFS may spontaneously remit; most require lifelong treatment.

Treatment options are aimed to reduce or stop muscular twitches and include medications, BoNT injections, neurosurgery and doxorubicin chemomyectomy.

Several symptomatic drugs have been tried. Anticonvulsant medications (such as carbamazepine, clonazepam, phenytoin, gabapentin or valproate) have been reported to improve HFS and to provide mild symptom relief. Among these, carbamazepine is the most frequently used; it has been reported to alleviate HFS in approximately 50 % of patients [137]. However, medications are often ineffective in the long-term management and side effects may be relevant [138].

A potentially curative approach is provided by microvascular decompression aimed at separating the aberrant artery from the facial nerve. This technique has a high success rate (from 88 to 97 %), and in the majority of cases resolution of HFS is durable, supporting the indication of surgery in younger patients [139], [140]. On the other hand, symptoms recur in as many as 25 % of patients within 2 years after surgery; moreover, complications occur in more than 20 % of the patients, sometimes serious, including permanent deafness, facial palsy, excessive bleeding and even death [141], [142]. Chemical rhizotomy of the facial nerve with doxorubicin is a potential alternative which has provided promising results. The most frequently reported adverse event is skin inflammation [143].

The introduction of BoNT as a therapeutic agent has represented a major milestone in the effective clinical management of HFS. AbobotulinumtoxinA was first used in HFS with appreciable results in 6 patients [144]. Based on the experience collected over the past two decades, BoNT has emerged as the first-choice option for the symptomatic management of HFS [26]. Although experience with BoNT mainly originates from open-label trials, there is no doubt on its efficacy and safety in the long term [34], [145]–[150]. Two RCTs [151], [152] and more than 30 open-label studies, encompassing overall more than 2,200 patients, are available on the use of BoNT/A in HFS. However, as pointed out from a recent Cochrane meta-analysis, the peculiarities of the different BoNT formulations, such as long-term efficacy, safety and immunogenicity, still need to be investigated [153].

A single-blind, randomized, parallel-design study comparing onabotulinumtoxinA and abobotulinumtoxinA failed to show differences in efficacy and tolerability using a 1:4 conversion rate in HFS [35]. It has been anecdotally reported that shifting from onabotulinumtoxinA to abobotulinumtoxinA may relieve HFS in secondary nonresponders [38], but this observation has not been confirmed by controlled trials. We recently performed a retrospective evaluation of outcome predictors, efficacy and safety of onabotulinumtoxinA and abobotulinumtoxinA in more than 100 HFS patients followed for a 10-year period and observed the following differences [154]. The mean duration of clinical improvement was higher after the injection of abobotulinumtoxinA than onabotulinumtoxinA by approximately 20 days ($105.9 \pm 54.2$ vs. $85.4 \pm 41.6$ days, respectively, $p < 0.01$). Over time, the duration of clinical benefit slightly increased with onabotulinumtoxinA, but remained constant with abobotulinumtoxinA; ptosis and lagophthalmos were more common with abobotulinumtoxinA treatments ($p < 0.005$). This supported the view that, although both brands bear the same indications for HFS, they should be considered as two different products.

There is also experience with BoNT/B in HFS. The clinical effects lasted for about 8.5 weeks in two patients treated with rimabotulinumtoxinB over six consecutive sessions [91]. Doses ranging from 200 to 800 BoNT/B U are considered appropriate in HFS [155], but further studies are needed as the experience with BoNT/B in HFS is quite limited.

In a recent study, 17 patients with HFS, who were previously treated with onabotulinumtoxinA, were blindly converted to incobotulinumtoxinA with a 1:1 conversion rate and treated continuously for 3 years without evidence of any differences in outcome or safety profile [156]. Small studies have also assessed the efficacy of the Chinese BoNT/A brand (Prosigne®) [42], [43] and BoNT/C [157].

The injection technique plays a critical role with regard to clinical response in HFS patients. Injections are placed subcutaneously and the orbicularis oculi is easily reached by the local diffusion of BoNT; EMG guidance is not needed. The injections are placed in the orbicular or pretarsal portion of the eyelids, divided into three to four sites. Most investigators favor targeting the pretarsal portion, considering that the outcome is better (higher response rate, longer duration of response and a lower frequency of side effects), compared with preseptal injections [31]. Treatment of the periocular region leads to improvement also in the lower facial muscles (probably

due to local diffusion of the toxin) [148]. At first, the extra-orbicular regions are not injected, but later, if required, these and other sites (e.g., the medial eyebrow, procerus, corrugator, frontalis muscle or the paranasal portion of the zygomaticus major muscle) can be treated. Still, if lower facial muscles are particularly active, or if there is residual contraction of the mouth following treatment in the orbicularis oculi, treating other muscles (e.g., the orbicularis oris, levator angularis, risorius, buccinator, depressor anguli oris or the platysma) should be considered.

In most studies, the average total dose used varies from 12.5 to 60 onabotulinumtoxinA U. from 10 to 160 abobotulinumtoxinA U or from 200 to 800 rimabotulinumtoxinB U. A prudent approach is necessary in cases of post-paralytic HFS. It is considered that a minimum threshold BoNT dose is necessary to obtain benefit, particularly for the first treatment session. In subsequent sessions, BoNT doses need to be increased or reduced based on the patient's response.

The patients usually improve soon after the first treatment session; primary or secondary failures are very uncommon. The average latency of clinical benefit varies from 2 to 6 days, and the overall response to treatment is satisfactory with a successful outcome in 66–100 % of patients. Patients with HFS have the lowest incidence of resistance to treatment, probably due to the low dosages used. The mean duration of benefit varies between 10 and 28 weeks. In most cases, the duration of efficacy increases with repeated treatments, more rarely it decreases or remains unchanged. It has also been observed that the duration of benefit is shorter in severe cases than in those of moderate severity. Prolonged remissions may spontaneously occur in a minority of patients, after a variable number of years of treatment [158].

The treatment is generally well tolerated; side effects occur in approximately 30 % of the patients and consist mainly of erythema, ecchymosis of the injected region, dry eyes, mouth droop, ptosis, facial weakness or edema. These are usually transient and resolve within 1–4 weeks. In several series, facial weakness is the most commonly reported side effect, occurring in 75–95 % of cases, mostly after injections in the mid-facial or lower facial muscles [158], [159]. Ptosis may occur following injections into the orbicularis oculi, particularly if the injection sites are too medial, abutting the levator palpebrae superioris muscle. Mild symptoms of exposure keratitis (lacrimation and irritation of conjunctiva) occur in less than 4 % of treatments, presumably due to a decreased blink rate and incomplete eye closure.

## 3.5 Spasticity

Spasticity is defined as a velocity-dependent increase in tonic stretch reflexes (muscle tone) that arises from abnormal processing of sensory afferent inputs to the spinal cord. Spasticity is a positive sign of the upper motor neuron (UMN) syndrome, that is a chronic motor disorder caused by UMN lesions. It is a consequence of an insult to the brain or spinal cord, which can lead to life-threatening, disabling and costly consequences. It is a central disorder of muscle tone characterized by increased resistance of an initially passive limb to externally imposed joint motion. Increased

tone is a reflection of the loss of descending inhibitory (reticulospinal) influences resulting in increased excitability of dynamic fusimotor (gamma) and alpha neurons.

Besides increased tone, spasticity presents typically with increased muscle stretch reflexes, muscle spasms and clonus, weakness (spastic paralysis), and impairment of voluntary movements. Spasticity leads to exaggerated reflexes, posturing (so-called spastic dystonia), and flexor or extensor spasms, often painful. Late consequences of spasticity include contracture, fibrosis, tendon shortening and muscle atrophy.

Spasticity is frequently classified by its distribution into generalized, multifocal and focal ones. Spasticity may occur in diffuse or focal pathological disorders of the brain and spinal cord, such as stroke, multiple sclerosis (MS), traumatic brain injury, spinal cord injury and CP.

The goal of spasticity treatment is to reduce motor overactivity in order to improve movement 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. The time elapsed between the acute event leading to spasticity and comprehensive patient management influences the long-term clinical picture. Successful spasticity management requires a multi-professional task force. All medical and surgical treatments need to be combined with physical interventions; therefore, BoNT injections cannot be regarded as a solo approach [160].

BoNT provides an important tool within a rich armamentarium (including physical therapy, orthosis, medication, etc.) to assemble individualized treatment plans for patients with UMN syndrome. BoNT is indicated not only to prevent and limit the functional impairment caused by spasticity, but also to provide functional improvement [161]. Safety and efficacy data lead BoNT injections to be considered as the pharmacological treatment of choice in focal spasticity, to improve limb position and functional ability and reduce pain [162].

Most studies of BoNT in limb spasticity used electrophysiological or ultrasound techniques to optimize muscle localization for injection, similarly to focal limb dystonia. A common approach is also to perform electrical stimulation or EMG targeting. EMG is not necessary for large, superficial, easily visible muscles, but is advisable for smaller and deep muscles and particularly applies to forearm and lower leg muscles, hip flexors (psoas major) and small inaccessible muscles around the jaw. The use of ultrasonography for locating both superficial and deep muscles is growing, as it is safe, noninvasive and less distressing than EMG.

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, the number of muscles involved, the patient's age, the severity of spastic contraction and the patient's weight [163]. BoNT doses used in spasticity are higher than those used to treat other movement disorders and the upper dose limits have raised caution, particularly in children. In children, doses of 6 onabotulinumtoxinA or incobotulinumtoxinA U/kg (body weight) should not be exceeded in each muscle, with a maximum total dose of 29 U/kg [164]. A safe upper limit for abobotulinumtoxinA is 30 U/kg, with a maximum total dose of 1,000 U per child [165]. The absolute maximum abobotulinumtoxinA doses for adult have not been established, but they should probably not exceed 2,000 units in each session. A safe starting dose for

children treated with rimabotulinumtoxinB is considered 400 U/kg weight that can be gradually increased to a maximum total dose of 10,000 U [166]. However, up to 17,500 rimabotulinumtoxinB U have been reported [167].

The duration of action may be appreciated 6 weeks after injection and for up to 9–12 weeks [168]. The exact timing between treatment sessions is variable; some information can be derived from experience in hyperkinetic movement disorders, but the clinical effects in spasticity may last longer than in dystonia, resulting in an average interval between treatments of approximately 3–5 months.

BoNT/A dilution affects treatment efficacy, although there are currently no recommendations on how to dilute different BoNT/A brands in spasticity. A controlled study has shown that treatment efficacy of onabotulinumtoxinA on biceps brachii spasticity may vary with changing dilutions [169]: A higher dilution results in larger injection volumes and greater neuromuscular block, probably because of more easy spread to neuromuscular endplates remote from the injection site.

BoNT has been used to treat spasticity associated with juvenile CP, cerebral stroke, brain trauma, amyotrophic lateral sclerosis or MS, but virtually every condition could be treated, as BoNT decontracts the muscles independently from the cause. The approved indications generally are, with differences from one country to the other, upper or lower limb spasticity (regardless of the etiology) and lower limb spasticity due to CP. Practical management may be as simple as injecting few muscles involved in adult-onset focal spasticity or involve a complex stepped approach as for some cases of childhood-onset spasticity requiring gradual tuning. In all cases, physical treatments are appropriately combined with BoNT injections.

Recent systematic reviews have concluded that BoNT is effective in reducing upper limb spasticity in adults and reduces muscle overactivity in a dose-dependent manner [170]. BoNT efficacy is better established for spasticity in the upper, rather than lower, limb. A limit of current evidence is that, particularly for the case of poststroke spasticity, functional improvement in patients treated with BoNT has not been investigated in detail [168]. It is believed that some disabilities related to upper limb passive and active function can improve, while the functional outcome after treatment of lower limb spasticity is poorly known. Spastic extension of the lower limb, in particular, supports standing and walking, functions that may be affected by BoNT treatments.

As with movement disorders, BoNT/A is well tolerated and safe in patients with spasticity: adverse events are limited and rare. Common side effects observed, in adults as well in children, include muscle soreness, pain at injection site, skin rash, fatigue, excessive weakness, influenza-like symptoms, infection and allergic reaction, but are generally reported to be mild and reversible. One study revealed that the most frequent problem in patients with poststroke spasticity is nausea, affecting only 2.2 % of cases [171].

There are limited data on the efficacy of BoNT/B in spasticity. One placebo-controlled trial failed to show efficacy [172] and revealed that dry mouth was a common side effect. This study also confirmed observations from treatment of dystonia patients that dose-dependent autonomic side effects are common following treatment with BoNT/B.

Future research will highlight some of the unanswered issues in spasticity treatment, such as long-term efficacy and safety and cost-effectiveness. There is also need for good quality studies on lower limb spasticity. Finally, the timing of BoNT treatment needs to be associated to treatment outcome and stratified by adjunct management strategies, such as physical and orthopedic interventions.

In adults, spasticity results from diverse etiologies, including stroke, trauma, MS, neoplasm involving the central nervous system (CNS) and amyotrophic lateral sclerosis. For the latter indication, there is insufficient documentation to assess the efficacy and safety of BoNT treatment.

### *3.5.1 Poststroke Spasticity*

In adults, stroke is the most common cause of UMN syndrome. These patients often present postural patterns characterized by shoulder adduction, elbow and wrist flexion in the upper limb, and hip adduction, knee extension and ankle plantar flexion in the lower limb.

Although most hemiparetic patients are able to reach different ambulatory levels with rehabilitation efforts, upper and lower limb spasticity can impede activities of daily living, personal hygiene, ambulation, and in some cases, functional improvement. Paresis and increased muscle tone can also cause joint stiffness leading to contractures.

Observational and controlled studies have shown that BoNT/A improves function and symptoms in adult patients with upper or lower limb spasticity following stroke. The efficacy of BoNT/B on poststroke upper limb spasticity has been observed in open-label series, but not confirmed by controlled trials. BoNT is employed as focal antispastic agents usually as part of complex rehabilitation regimes.

There is evidence that BoNT/A is superior to placebo in reducing upper and lower limb spasticity after stroke [173]. Notwithstanding the reduction in muscle tone, there was no overall effect on functional parameters of disability. The different studies are difficult to compare, as they use different outcome measures to assess functional parameters. Reduction of hypertonia is maintained for a longer time in distal than in proximal muscles, probably due to insufficient doses injected into the larger proximal muscles [168].

A recent Japanese study on a new BoNT brand assessed the treatment of lower limb poststroke spasticity in a large, placebo-controlled clinical trial. One hundred twenty patients were randomized to a single treatment with BoNT/A or placebo, injected into lateral and medial head of the gastrocnemius, soleus and tibialis posterior muscles. This is the first large-scale large-scale trial to indicate that BoNT/A significantly reduced poststroke lower limb spasticity for 12 weeks [174].

### *3.5.2 Spasticity in MS*

MS is the most common disabling chronic central nervous system disease among young adults and it is often complicated by spasticity. MS is a common cause of diffuse or regional muscle overactivity. In MS, it is particularly difficult to differentiate what part of functional disability is due to spasticity, and the administration of symptomatic short-lasting treatments like BoNT may contribute to define this aspect [175]. In this condition, BoNT has been used to treat thigh adductor spasticity, pes equines, striatal toe or shoulder adduction. BoNT treatment can also help patients who are bedridden or wheel-chaired and may prevent the occurrence of decubital ulcers and pain. This view has been confirmed by observational and controlled studies. Using a randomized crossover design, 400 onabotulinumtoxinA U were injected into the thigh adductor muscles; after 6 weeks, reduction of spasticity and improvement of hygiene scores have been observed without adverse events [176]. More recently, a placebo-controlled study with three different abobotulinumtoxinA doses (500, 1,000 and 1,500 U) has been performed in MS patients with hip adductor spasticity [177]. A risk–benefit assessment suggested that the optimal starting dose for treating hip adductor spasticity in MS is 500–1,000 abobotulinumtoxinA U, divided between the two legs, with subsequent dose titration as required.

Two studies evaluated the effect of BoNT/A on painful tonic spasm in MS patients. These trials showed that BoNT/A is effective in relieving pain (both the intensity and the number of painful spasms) [178]. Just as for the other indications, also in MS, physical therapy is recommended in association with BoNT treatment to improve the outcome [179]. In general, given the small numbers of MS patients studied, there is a need for further long-term studies on large cohorts. Furthermore, MS-related fatigue could be aggravated by BoNT, especially considering that large doses are needed for spasticity.

## 3.6 Cerebral Palsy

CP is a disorder, presenting early in life, due to prenatal, perinatal and postnatal brain injury that combines increased or decreased muscle tone, spasticity, muscle weakness, involuntary movements and loss of control of muscle coordination in various degrees. Muscle hypertonia in children combines with body growth leading to fixed contractures, torsional deformities of long bones and joint instability, which further impair the child's motor performance. Involvement of the lower limbs is responsible for early gait and balance impairment. The most dynamic developments can be observed during the first 6 years of life and all therapeutic interventions on spasticity and motor impairment must take into account the dramatic motor development taking place. Optimal therapeutic results are provided by early intervention that tap into the developmental potential of the child. Clinical manifestations may vary depending on the cause of brain injury, with spasticity being the commonest symptom.

The decision to use antispasticity medications in a child requires a careful assessment of the patient's impairment in all domains, including the occurrence of associated weakness or movement disorders, to choose the appropriate interventions. Reasons to treat spasticity include reduction of pain and muscle spasms, facilitate brace use, improve posture, minimize contractures and deformity, facilitate mobility and dexterity and improve patient ease of care as well as hygiene/self-care [180].

Pharmacologic treatment with myorelaxants and non-pharmacologic interventions such as physiotherapy and occupational therapy provide a basis to which BoNT is added. The first clinical trial with BoNT for spasticity in children with CP was reported almost 20 years ago [181]. Since then, growing evidence indicated that BoNT can decrease muscle tone and improve range in joints served by injected muscles. BoNT/A has later gained acceptance as an adjunct therapy for spasticity for children with CP. For the past 10 years, clinical experience from numerous case reports, retrospective and prospective open-label cohort studies and RCTs have described the potency of BoNT/A to treat upper and lower limb spasticity in children with CP. Additionally, several independent systematic reviews, meta-analyses and consensus statements from various groups have confirmed these observations [182].

BoNT/A combined with surgical and nonpharmacological interventions is currently the best treatment approach for children with CP. The goals of BoNT therapy go beyond a decrease in muscle tone to influence pain relief, prevention of contractures, psychological integration and global functional improvement. Scanty data are available on BoNT/B; they mostly derive from small open-label pilot studies including patients who were secondary nonresponders to BoNT/A. There is concern that, particularly in children, large BoNT doses may lead to a botulism-like symptomatology. In 2009, the US FDA ordered that the manufacturers of BoNT products add a boxed warning to the prescribing information for each product about the potential for serious side effects at sites distant from injection. The FDA also ordered the manufacturers to develop a Risk Evaluation and Mitigation Strategy, and to submit safety data on injections in children for treatment treatment of spasticity [183]. Pediatric cases involved treatment for spasticity and were described as botulism, or involved symptoms including difficulty breathing, difficulty swallowing, muscular weakness, drooping eyelids, constipation, aspiration pneumonia, speech disorder, facial drooping, double vision or respiratory depression. Serious case reports described hospitalizations involving ventilatory support and reports of death.

## 3.7 Tremor

Tremor is defined as a rhythmical, involuntary oscillatory movement of a body part produced by alternating or synchronous contractions of antagonistic muscles. It is the most common movement disorder and is etiologically and physiologically heterogeneous [184]. Essential tremor (ET) is the most common type of tremor and also the most commonly observed movement disorder. Propranolol and primidone

usually ameliorate mild or moderate ET, but pharmacotherapy is usually not sufficient to control tremors of high amplitude that impair daily living activities.

In some of these patients, local injections of BoNT might be proposed before considering more aggressive intervention such as thalamic DBS. There are no class I studies investigating BoNT efficacy on tremor, but it is well established that this treatment is not as successful as in dystonia or spasticity [185]–[188].

BoNT/A has been tested on various tremor disorders in small open-label and controlled studies and has been proposed as a treatment for essential hand tremor [185], [186], [188]–[191]. A difficulty with the interpretation of results on tremor is that in most trials BoNT was injected according to a predetermined, rigid protocol without individualization to each patient's need, pattern and severity of tremor phenomenology. A class II class II placebo-controlled study with onabotulinumtoxinA reported improvement in tremor severity without amelioration of function and finger weakness as a side effect [191]. Another class II multicenter, randomized, placebo-controlled trial showed significant improvement of postural, but not kinetic, hand tremor in patients with ET who received 50 or 100 onabotulinumtoxinA U into the wrist flexors and extensors (188). This study provided an explanation for limited functional improvement, as it showed that kinetic rather than postural tremor is related to disability. Scant data are available for BoNT/B [91].

Primary writing tremor, a task-specific hand tremor related to focal dystonia, improved in four out of five patients treated with low onabotulinumtoxinA doses (10–12.5 U) 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 [192].

Data on head and voice tremor are still inconsistent. Although a number of studies reported efficacy [193]–[195], a class II study on ten patients with head tremor denied benefit [196]. In essential voice tremor, BoNT has been injected into the thyroarytenoid muscles to reduce tremor amplitude and laryngeal resistance. A class IV study suggested subjective improvement on vocal strain when speaking (195). Another class IV open-label study showed a beneficial effect of onabotulinumtoxinA in 13 patients with isolated vocal tremor and no evidence of SD [197].

Jaw tremor in PD sometimes is not controlled by antiparkinsonian medication and can improve with BoNT injections. The experience is limited to few patients, who have been treated with a mean dose of 50 abobotulinumtoxinA U (range: 30–100 U) in both masseter muscles [198]. Another case report of intermittent rapid focal jaw tremor mentioned a successful BoNT/A treatment into the masseters [199].

Palatal tremor with associated ear click may also be treated with BoNT into the tensor veli palatini muscle [200]. In these cases, BoNT should not be reserved for refractory cases, but it should be considered a safe and effective first-line therapy [201]. Tensor veli palatini, levator veli palatini or both have been injected with doses ranging between 5 and 20 onabotulinumtoxinA U or 5 and 60 abobotulinumtoxinA U. The treatment is generally safe; velopharyngeal insufficiency or nasal speech has been rarely recorded.

## 3.8 Tics

Tics are relatively brief, intermittent movements (motor tics), or sounds (vocal or phonic tics), usually preceded by a premonitory sensation; the association of motor and vocal tics is the clinical hallmark of Tourette's syndrome. Antidopaminergic drugs (neuroleptics) are often used to treat troublesome multifocal tics, but the risk of side effects such as tardive dyskinesias (TDs), hepatotoxicity, prolonged QT intervals, sedation and depression is quite high. Patients with focal tics affecting the eyes, the head or the larynx may be treated with BoNT/A in the affected muscles.

The first anecdotal observations were performed in patients with Tourette's syndrome and dystonic tics affecting the eyelids and neck [202]. OnabotulinumtoxinA treatment reduced the frequency and intensity of tics and ameliorated the associated premonitory sensory urge; this benefit lasted for several weeks.

Single case reports [203], [204] and case series [205]–[207] have later confirmed the improvement. One class II, double-blind, crossover study has shown that BoNT/A reduced the frequency of simple motor tics and associated premonitory urge [208]. Despite these objective improvements, the patients did not report a comparable subjective benefit from treatment, indicating the need for further evaluation of disability outcomes in tic disorders. However, a recent open-label study on 30 patients treated with onabotulinumtoxinA (2.5 U in both vocal cords) for vocal tics reported that BoNT/A also ameliorates quality of life [209]. The only relevant side effect was hypophonia. The long-term outcome of BoNT in tic disorders is still unreported.

On the other hand, BoNT has been also used to control life-threatening tics, such as dystonic cervical tics that could cause compressive myelopathy or radiculopathy [210], [211].

## 3.9 Other Movement Disorders

### *3.9.1 Tardive Dyskinesias*

Drug-induced movement disorders are potentially persistent and disable abnormal involuntary movement disorders caused by exposure to dopamine receptor-blocking agents. The term "tardive" indicates iatrogenic origin related to antidopaminergic agents. The clinical features are quite variable, but most often these movement disorders present with stereotypic orolingual and facial dyskinesias that are very characteristic. There is some terminological uncertainty, as some authors use the term TDs to indicate any drug-induced movement disorder, while others mean uniquely the facial stereotyped hyperkinetic disorder and use the expression "tardive syndrome" as an umbrella term to encompass all drug-induced movement disorders. Tardive syndromes can present features of dystonia, tics, tremor, parkinsonism, akathisia, virtually the entire spectrum of movement disorders. In a minority of patients, TDs remit following withdrawal of the causative neuroleptic drug, but the hyperkinetic

disorder commonly persists. Anticholinergics are prescribed in association with neuroleptics to reduce the incidence of TDs, but they are ineffective in or may aggravate TDs once these are manifest. Tetrabenazine, a dopamine-depleting drug, has been reported to improve TDs, although remission or satisfactory control of symptoms is not achieved in all cases.

Focal tardive dystonia responds to BoNT treatment as well as primary dystonia [212]. In particular, tardive blepharospasm and cervical dystonia require the same BoNT doses used to treat the primary conditions [213]–[215].

Patients with bruxism grind, gnash or clench their teeth during sleep or emotional conditions. This condition is associated with masseter (and sometimes temporalis) muscle contracture that occurs also during sleep. When severe or untreated, it can be associated with headache, dysarthria, temporomandibular joint destruction and dental wear. Bruxism may be idiopathic or symptomatic to different neurological conditions, such as parkinsonism, Huntington's disease, tardive syndromes, CP, etc. The use of night guards and other dental appliances and procedures may be helpful, but no strategies are curative. BoNT/A has been reported to be effective with satisfactory clinical control regardless of the etiology [216]. However, there are no controlled studies on bruxism. The masseter muscles (and the temporalis, when involved) have been treated bilaterally, with wide-ranging doses, from 25 to 100 onabotulinumtoxinA U.

Some cases of myoclonus have been treated with BoNT. Tinnitus associated with palatal myoclonus has proven responsive to BoNT/A (4–10 onabotulinumtoxinA U or 30–60 abobotulinumtoxinA U) injected into the tensor veli palatini muscle (or alternatively into the levator veli palatini).

Also anecdotal reports indicate that akathisia can also be treated with BoNT injections {Shulman, 1996 10703/id}.

### *3.9.2 Comprehensive Approach to Motor Symptoms of Parkinsonian Patients*

While most of the motor symptoms, particularly the cardinal features of PD, such as tremor, bradykinesia, rigidity and gait difficulty, improve with dopaminergic drugs and other therapeutic options, including DBS, many troublesome symptoms do not respond to conventional treatments [217].

Motor symptoms amenable of treatment with BoNT include dystonia, contractures, tremor, painful rigidity and freezing of gait; non-motor symptoms include sialorrhea, seborrhea, hyperhidrosis, constipation, achalasia and overactive bladder [218].

Different forms of dystonia may complicate "on" as well as "off" periods in up to 60 % of PD patients, most often those with early onset [219], [220]. Off-period dystonia involves more frequently limbs and neck or facial muscles (mainly periocular) and can be painful, particularly in the foot [221].

Blepharospasm, apraxia of eyelid opening and oromandibular and cervical dystonia (observed not only in PD but also in other parkinsonisms, such as progressive supranuclear palsy) can be managed the same way as the corresponding forms of primary dystonia. Low starting doses of BoNT can be gradually increased until clinical benefit is achieved. BoNT may be also used to relieve pain associated to non-dystonic contractures of neck or other body regions.

Although BoNT is considered the first-line therapy in primary cervical dystonia, no class I studies proved BoNT effectiveness in cervical dystonia associated with PD. While patients with PD often have abnormal neck postures, there is some controversy whether this abnormality is due to cervical dystonia, rigidity, a combination of the two or some other mechanisms [219], [222].

Antecollis is the most common abnormal neck posture associated with parkinsonism, particularly PD and multiple system atrophy (MSA). Antecollis is difficult to treat with BoNT; moreover, the bilateral injection of sternocleidomastoid and scalenus muscles is often associated with dysphagia. The adverse effects can be avoided by a prudent approach, but treatment failures are common. The contraction of the submental muscle complex may contribute to antecollis and in some cases, an injection in this region, with or without concomitant treatment of the sternocleidomastoid and scalenus muscles, may improve the abnormal neck flexion. This approach, however, must be undertaken with great caution as dysphagia and aspiration pneumonia may complicate the treatment. By contrast, retrocollis associated to progressive supranuclear palsy can be safely and easily treated by injecting the posterior neck muscles [223].

Axial dystonia may manifest as cervical dystonia or an abnormal posture of the trunk causing scoliosis, kyphosis, camptocormia, Pisa syndrome or any combination of these. These axial features are a common cause of physical and social problems in patients with PD. BoNT has been used to treat axial postural abnormalities, including scoliosis, with uncertain results [224]–[226].

Camptocormia refers to a severe dynamic abnormal posture of the trunk with marked flexion of the thoracolumbar spine when standing and walking, almost resolved when lying in a supine position. It is associated with parkinsonian disorders such as PD or MSA [227]–[229]. The abnormal trunk flexion is often associated with EMG evidence of active contraction in the rectus abdominis. Despite the severe trunk flexion, patients with dystonic camptocormia can straighten their trunk when lying down or when raising their hands against a wall. The choice of which muscles to inject is crucial. Improvement was observed in 9 of 11 camptocormia patients who received BoNT treatment into the rectus abdominis muscle (300–600 onabotulinumtoxinA U) [228]. By contrast, ultrasound-guided injection into the iliopsoas muscles (500–1,500 abobotulinumtoxinA U on each side) was not effective in four patients with camptocormia [230].

The most common presentation of dystonia in PD is foot dystonia. Abnormal foot and hand postures may be seen in up to 10 % of untreated patients with advanced PD [231]. BoNT may be effective in correcting abnormal postures that did not yet progress to fixed contractures [232] and alleviating pain associated to peak-dose dyskinesia and end-of-dose dystonia [220]. EMG guidance may be required

in order to inject deep muscles, particularly in the legs. Patients with PD and other forms of parkinsonism (such as progressive supranuclear palsy, corticobasal degeneration, etc.) occasionally develop secondary fixed dystonia of the hand which may be relieved by local BoNT injections (particularly helpful to ease pain and improve hygiene) [233].

Freezing of gait is a disabling symptom, characterized by a sudden inability to initiate gait or continue walking, particularly when facing a narrow passage, turning around or under stressful situations [234], [235]. In most cases, freezing of gait is poorly responsive to dopaminergic medication. The possibility that freezing of gait is partly due to involuntary contractions in distal muscles of legs and feet has prompted clinical trials of BoNT in PD and other parkinsonian disorders. Although initial reports were encouraging [236], [237], further observations were not confirmatory [238], [239].

Hand tremor is one of the most recognizable features of PD; it frequently interferes with the ability to hold objects such as newspaper or a cup and can often be troublesome for patients. Levodopa and other anti-PD treatments are usually effective in improving this cardinal feature of PD, but other treatment such as DBS must be considered as well. Some studies have demonstrated that BoNT may be of benefit in PD-related tremor [185], [186].

## 3.10 Conclusion and Outlook

BoNTs act as focal muscle relaxants and have several indications in clinical practice, particularly for the symptomatic improvement of hyperkinetic disorders. Solid evidence has been collected for different forms of dystonia and of spasticity. However, some indications still need to be supported by controlled trials. Long-term observations have proven that BoNT/A brands are safe when used by experienced doctors; caution is required when high per kilo doses are injected, particularly in children. There is much less experience with BoNT/B than with BoNT/A brands and this gap needs to be bridged.

BoNTs are useful as solo treatments (e.g., for some focal dystonia forms) or in combination with physical treatments or other procedures. Consensus algorithms need to be developed for different indications and different combination strategies, in order to facilitate homogeneity of BoNT administration among different centers and distinct specialties.

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