Chapter 4
Evidence-Based Review of Current Botulinum Toxin Treatment Indications in Medicine

Dhanya Vijayakumar and Joseph Jankovic

Abstract Botulinum neurotoxin (BoNT) has been increasingly used not only as a cosmetic drug but, more importantly, it has emerged as the most versatile therapeutic, utilized in virtually all sub-specialties of medicine. In neurology, there is Level A (effective) evidence for the use of certain serotypes of BoNT in cervical dystonia, chronic migraines, upper- and lower-limb spasticity and Level B (probably effective) evidence in blepharospasm. These levels of recommendation, however, must be interpreted cautiously as they are based only on published randomized, controlled studies and are limited to particular products. United States Food and Drug Administration (US-FDA) approved BoNT for these and other indications, such as focal axillary hyperhidrosis and sialorrhea, but there are a growing number of conditions for which BoNT is used off-label. In addition to focal dystonia, BoNT is also increasingly used to treat tremor and other movement disorders and a variety of neuropathic pain disorders including trigeminal neuralgia, post-herpetic neuralgia, and diabetic neuropathy. In urology, there are several randomized controlled trials supporting the benefits of BoNT in overactive bladder and interstitial cystitis. In gastroenterology, BoNT is used to treat anal fissures and achalasia. Thus, BoNT is the most widely used therapeutic molecule.

Keywords Botulinum toxin · Dystonia · Blepharospasm · Tremor · Spasticity · Pain · Bladder

D. Vijayakumar (✉)
The University of South Carolina School of Medicine Greenville, Prisma Health Upstate, Neuroscience Associates/Department of Internal Medicine, Greenville, SC, USA
e-mail: dhanya.vijayakumar@prismahealth.org

J. Jankovic
Baylor College of Medicine, Baylor St. Luke's Medical Center at the McNair Campus, Houston, TX, USA
e-mail: josephj@bcm.edu

B. Jabbari (ed.), *Botulinum Toxin Treatment in Surgery, Dentistry, and Veterinary Medicine*, https://doi.org/10.1007/978-3-030-50691-9_4

Introduction

Botulinum neurotoxin (BoNT) is an exotoxin produced by *Clostridium botulinum* and is the most potent biological toxin [105]. Although the various BoNT products contain only 0.44–5 ng/vial, the estimated lethal dose is 0.09–0.15 μg when BoNT is injected intravenously and 70 μg when ingested; 39.2 g sufficient to eradicate humankind [33]. In addition to the well-defined seven BoNT serotypes (BoNT/A-G), a new mosaic toxin type termed BoNT/HA (also known as BoNT FA or H) was reported [103, 263]. All BoNTs act by inhibiting acetylcholine release at the nerve terminals of striatal and smooth muscles, and exocrine glands, but they also act on other neurotransmitters including adenosine triphosphate, substance P, and calcitonin gene-related peptide and may downregulate sensory receptors, such as transient receptor potential cation channel subfamily V member 1 (TRPV1). The latter mechanism is important in the analgesic's effects of BoNT.

BoNT acts as a zinc proteinase by cleaving neuronal vesicle-associated proteins, collectively called the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex, thereby preventing the docking and fusion of the vesicles with the presynaptic membrane and thus preventing the release (exocytosis) of acetylcholine into the nerve terminal [142]. Various BoNT serotypes work differently and the sites of cleavage of SNARE complex vary between serotypes. BoNT serotype A, C, and E cleave SNAP-25 (synaptosome-associated protein of 25 kd) while serotypes B, D, F, and G cleave synaptobrevin, also known as VAMP (vesicle-associated membrane protein) [263]. Due to this cleavage, acetylcholine is unable to leave the nerve terminal to initiate contraction in the postsynaptic muscle, resulting in chemodenervation [103]. Of the eight serotypes, only BoNT types A and B are approved for clinical use in the United States. There are three formulations of BoNT type A used in clinical practice in the United States, namely, onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), and incobotulinumtoxinA (Xeomin®). BoNT-type B classified as rimabotulinumtoxinB (Myobloc®) is the other neurotoxin available for clinical use in the United States.

In 1977, Dr. Allen Scott first injected BoNT in a patient with strabismus. In October 1981, Dr. Joseph Jankovic first injected a patient with blepharospasm with BoNT, and this was followed by a double-blind controlled study of BoNT in cranial-cervical dystonia including cervical dystonia (CD) and blepharospasm. In 1989, onabotulinumtoxinA (Botox) was the first BoNT product approved by the US Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm, and cranial nerve VII disorders including hemifacial spasms [105]. Since then, it has been widely adopted for several additional indications in neurology, urology, dermatology, gastroenterology, and pain management/neuro-rehabilitation. BoNT is most frequently used for the treatment of various conditions that involve abnormal, excessive, inappropriate exaggerated muscle contraction, and pain, but its use is expanding to many new and different indications [105].

The duration of benefits from BoNT injections last for about 3–4 months, after which there is a loss of inhibitory effect, likely due to sprouting of new terminals,

and eventual loss of effect at the original nerve terminal [193]. Side effects from BoNT vary depending on the area injected and adjacent non-target muscles or glands to which the toxin could spread, resulting in undesired effects such as ptosis, dry eyes with eyelid injections, dysphagia, especially following anterior neck injections, neck weakness, particularly with posterior neck injections, facial asymmetry with injections for hemifacial spasm or facial dystonia, and weakness in the hands with forearm injections for hand dystonia or tremor. In addition to local side effects, about 14% of treatment visits are associated with transient flu-like symptoms [13, 77]. BoNT should be avoided in patients with neuromuscular disorders and motor neuron disease and pregnant or lactating women, although there is no evidence of teratogenicity associated with BoNT therapy [25]. Although EMG, ultrasound, and kinematic guidance can be used for localization, no muscle targeting technique has yet proven to be superior [159, 215, 268].

Neurology

Tremor

The role of BoNT has been studied in different tremor conditions with good success, but BoNT is not yet FDA approved for these tremor indications and its use is off label. Several studies have provided evidence of beneficial effects of BoNT in the treatment of various tremors [148–150, 159].

(a) Dystonic tremor
Dystonic head and neck tremors could be present in patients with CD, voice tremor in spasmodic dysphonia, and dystonic hand tremors in patients with focal dystonia of the upper extremity such as organic writer's cramp, musician's dystonia, and other task-specific tremors. Primary dystonia patients are more likely to have tremor than patients with secondary dystonia including tardive dystonia [169]. Hand tremor has been reported in patients with dystonia affecting other parts of their body and reported the prevalence of postural or kinetic tremor in these patients to range from 14% to 86% [169].

In a retrospective chart review on 91 patients with medically refractory hand tremor treated with botulinum toxin, 31 patients had dystonic tremor. The majority of patients noted a benefit with BoNT injections in the forearm flexor muscles [159]. Other studies have confirmed the efficacy of BoNT in the treatment of essential (ET) and dystonic tremors [104, 148, 159].

(b) Task-specific tremor
Primary writing tremor (PWT) is a type of task-specific movement disorder where tremor occurs predominantly or exclusively while writing. This shares features with ET and dystonia [219, 246]. The lack of adequate response to typical medications used to treat ET like primidone and propranolol, presence of mirror movements

typically seen in patients with dystonia, makes this more closely related to dystonia than to ET. PWT causes significant inconvenience to patients in occupations that demand a great deal of writing or enjoy writing as a hobby. Several studies have examined the effects of BoNT on PWT. There are two case series and a case report, which showed beneficial effects of BoNT in this condition [11, 172, 219]. In one of the case series, four out of five patients noted a significant and sustained improvement in tremor during the course of BoNT treatment. In this study, 10–12 units of BoNT/A was injected into flexor carpi radialis, extensor carpi radialis and ulnaris, abductor pollicis longus and extensor digitorum communis [172]. In a case report of a 64-year-old man, retired postal worker, 12.5 units of BoNT type A was injected into flexor carpi radialis under EMG guidance. This resulted in a 75% improvement in the symptoms that sustained for 3 months [219].

(c) Essential tremor

BoNT has been studied in patients with ET resulting in hand tremor, voice tremor, and head tremor. There is a paucity of large trials looking at the efficacy of BoNT for tremors, but BoNT has been used for selected patients who are refractory to medications prior to consideration of more invasive strategies like deep brain stimulation (DBS). The mechanism of BoNT is thought to be from the relaxation of involved muscle groups, or due to altered peripheral or central mechanisms [131].

For ET involving the hands, there were small studies looking at injection of flexor and extensor muscles. These were limited due to side effects of hand weakness noted particularly with extensor muscle injections [109]. In one open label study which enrolled 26 tremor patients of whom 14 had ET, there was significant improvement in the tremor and disability scores of ET patients [234]. Five of the fourteen patients reported moderate-to-marked subjective improvement in functional abilities after BoNT. However, the average reduction in tremor amplitude was less than 25% and the degree of tremor amplitude reduction correlated with patients' subjective impression about tremor benefit [234]. There are a few other open label trials evaluating the efficacy of BoNT in ET hand tremor which have shown significant improvement in tremor subjectively [167, 185, 204] and some using objective tremor [203, 204].

In 1996, Jankovic et al. reported the first randomized double-blind placebo-controlled study to evaluate the effect of BoNT injections in patients with ET hand tremor. Twenty-five patients with moderate–to-severe hand tremor were injected with BoNT, and there was significant improvement in tremor noted on tremor severity rating scales and on accelerometry measurements. Fifty units of BoNT was injected into wrist flexors and extensors with repeat injections in 4 weeks. There was mild and transient weakness of finger and wrist extensors attributed to injections of the extensor carpi radialis and ulnaris muscles [110]. Subsequently, another randomized placebo-controlled study was done involving 133 patients who were injected in the flexors and extensors in two parallel groups of low- and high-dose injections. There was significant improvement in postural tremor in both groups, but there was more weakness in the group injected with higher dose BoNT. There were no major changes in measures of motor tasks and functional disability, possi-

bly due to weakness that resulted after the injections [27]. In a retrospective chart review done in patients with medically refractory tremor, of 53 patients with ET affecting their hands who received BoNT injections, the majority noted improvement in their tremor [159]. As a result of troublesome weakness-associated extensor muscle injections, many investigators tend to avoid injecting these muscles in patients with ET-related hand tremor, but the selection of the muscles and dosage must be individualized [114]. Another randomized double-blind placebo-controlled crossover trial evaluated the efficacy of BoNT in 33 ET patients with hand tremor, with injections customized to individual patients' tremor quality. Between 80 and 120 U of incobotulinumtoxinA was injected between 8 and 14 muscles in the hand and forearm of individual patients. There was significant improvement in Fahn Tolosa Marin tremor rating scales at 4 and 8 weeks. There was no significant hand weakness, but mild weakness was observed in 50% of patients receiving BoNT injections [150].

In ET patients with voice tremor, a minority of patients experience tremor benefit from BoNT injections into the vocal cords. Breathiness of voice is a common side effect seen with BoNT injection into the vocal cord. In a study which included 34 patients, 16 noted improvement in their voice tremor after BoNT injections into thyroarytenoid muscle [222]. In another study, EMG-guided injections were performed depending on the type of tremor, with thyroarytenoid injections performed for horizontal tremor, and strap muscle injections for vertical laryngeal tremor. For mixed tremor type, injections were performed based on the tremor type that was dominant/more severe. If both vertical and horizontal tremors were equally severe, strap muscles were injected first with thyroartytenoid injection done 2 weeks later. Starting doses of 1 unit was injected into the thyroarytenoid muscle with higher doses less than 10 units used for strap muscles and other adjacent neck muscles injected in this study. All 16 patients who received injections in this series had tremor benefit from BoNT; hoarseness was the only side effect observed, mostly following injections to the thyroarytenoid muscle [93]. Another small open label crossover study looked into BoNT injection into vocalis muscle either unilaterally or bilaterally. This was a small study in 10 patients with essential voice tremor, with EMG guided injections of 15 units into the left vocalis (unilaterally) with cross over to the bilateral vocalis injection arm (2.5 units into each vocalis) of the study after 16 or 18 weeks or vice versa. Only 3 of the 10 patients had objective reduction in voice tremor with bilateral injections and 2 of 9 patients who received unilateral injection. Breathiness and reduced vocal effort were seen, but 8 of the 10 patients chose to get re-injected at the end of the study [255]. In 15 patients with ET resulting in voice tremor, BoNT was injected into thyroarytenoid or into the cricothyroid or thyrohoid muscles; there was significant improvement in voice tremor based on subjective evaluation and also based on perceptual evaluation of recorded speech samples [97]. There is a small study by Ludlow et al. in 1989, another study by Brin et al. in 1992 and a case report by Warrick et al. in 2000, all of which showed efficacy of BoNT in the treatment of voice tremor. A prospective randomized trial over 6 weeks involving 13 ET patients with voice tremor showed that there was improvement in voice tremor in all patients over the observed period with dysphagia and

breathiness being the most common side effects [3]. Based on these studies, an evidence-based review suggested level 1 recommendation for the use of BoNT in ET affecting the voice [179].

About 30–40% of ET patients with head tremor do not respond well to medications. There was one small double-blind placebo-controlled trial by Pahwa et al. in 1995 assessing BoNT in 10 patients with head tremor. In this study, 40 units were injected into bilateral sternocleidomastoid muscles and 60 units into bilateral splenius capiti muscles, with subsequent crossover into the placebo group. There was over mild-to-moderate improvement in 50% of the patients compared to 10% improvement noted in the placebo group [168]. Transient, non-disabling, neck weakness is the most common side effect observed with this pattern of injection. Several patients with essential tremor also have concomitant CD and dystonic tremor affecting their head. BoNT appears to work better for dystonic head tremors than for ET associated head tremor [130].

In a study involving 43 patients of which 13 had head tremor due to ET without dystonic component, and the remaining had head tremor secondary to CD, BoNT was injected into neck muscles with dosing individualized based on neck position and visible and palpable tremor oscillation. A mean dose of 400 units of abobotulinumtoxinA was split between the two splenius capiti muscles in patients with ET head tremor. There was significant improvement in tremor, based on accelerometry analysis in both groups of patients with head tremor from ET and from CD [259]. In a study involving 51 patients with disabling tremor, 8 of whom had ET related head tremor, there was significant improvement in tremor with BoNT injections [109].

(d) Parkinson-associated rest tremor

The rest tremor in Parkinson's disease (PD) tends to be responsive to levodopa, but in some patients there is insufficient tremor control or side effects with medication titration which limits tremor control. In these patients, BoNT could be used for better tremor control with muscle selection individualized based on the nature of the tremor depending on the predominant movement (flexion-extension, pronation supination or ulnar-radial deviation type), and the predominant joint involved (finger tremor, wrist tremor or elbow tremor) [160].

In a randomized double-blind placebo-controlled cross-over study, 30 patients received BoNT injections into the hand and forearm muscles. Patients were injected customized to their tremor rather than a standard protocol. Between 2.5 and 20 units of BoNT/A was injected in different muscles, including lumbricals, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, pronator, biceps, triceps, extensor carpi radialis, extensor carpi ulnaris, extensor digitorum, flexor pollicis brevis, flexor digitorum profundus, abductor pollicis brevis, brachioradialis, supinator, and opponens pollicis. There was a significant improvement in the tremor on tremor severity scale and improvement in patients' impression of change and an improved ability to do activities at home, without much weakness as side effect [149].

In an open label study, 28 patients were injected with BoNT for PD tremor using kinematic measures to personalize muscle selection for injection. There was

significant decrease in Unified Parkinson's Disease Rating Scale (UPDRS) rest tremor scores and Fahn-Tolosa-Marin tremor severity scores. Ten patients experienced mild weakness which did not affect activities of daily living [187, 203]. In another 3-month open label study in 7 patients with PD-related upper-limb tremor, with kinematic assessment of tremor done pre and post injections, there was significant improvement in kinematic assessments of static and functional tasks at 2 and 3 months. There was also significant improvement in the UPDRS tremor scores and spiral drawings [186]. In another open label study in 26 patients, 12 of whom had PD; there was over 50% reduction in tremor in 2 patients and moderate-to-marked subjective improvement in functional benefit in 5 patients after BoNT injections. However, the average tremor reduction was less than 25% by quantitative measures [234]. In a prospective study in 187 patients with tremor, 15 patients with tremor due to Parkinson's disease, BoNT injections were done under EMG guidance with booster injections given if needed for optimum tremor control. In this study, there was an average BoNT efficacy of 35.7% for PD tremor. There was marked subjective improvement in tremor along with significant reduction in tremor amplitude of over 50% in 2 of 15 patients with PD tremor [185].

(e) Jaw tremor

Jaw tremor could be seen as part of the tremor spectrum in patients with ET, dystonic tremor, PD, task specific tremor and also in other neurologic conditions such as hereditary geniospasm. Patients with jaw tremor as part of ET typically have more widespread severe tremor and a long history of having ET. There is some thought that jaw tremor may be a marker of subsequent development of PD in these patients [132]. Jaw tremor is more common in PD than in ET patients, with prevalence in ET estimated to be between 7.5% and 18% [96]. Jaw tremor could also be a dystonic tremor in the setting of dystonia. In patients with bothersome jaw tremor, refractory to medical therapy, BoNT should be considered as a therapeutic option.

In a case report about a woman with position specific jaw tremor, likely dystonic in nature, where there was improvement in tremor after BoNT injections [228]. In a case series of 7 patients with jaw tremor in the setting of dystonia, one patient had BoNT injection for jaw tremor and noted improvement in the tremor. Others in this series did not receive injection and received oral medications with inadequate benefit [206].

In a pilot study involving three patients with jaw tremor due to PD, who were injected with onabotulinumtoxinA, there was significant improvement in jaw tremor in all 3 patients at 4 and 9 weeks post injection. Between 30 and 100 units of abobotulinumtoxinA was injected in the masseter bilaterally with mentalis muscle included in one of the patients. There were no side effects including no dry mouth [207].

(f) Holmes tremor

Holmes tremor, also called rubral, mesencephalic, or thalamic tremor, is a slow (2–5 Hz tremor), high-amplitude tremor, present at rest, worse with action. This often occurs after lesions affecting the thalamus, brainstem, or cerebellum. Usual

etiology of the lesion includes vascular lesions, demyelinating disorders, head trauma, AV malformations, or neoplasms [63, 188].

A case report of a 29-year-old male patient with Holmes tremor after pontine hemorrhage describes marked improvement in tremor after BoNT injection. BoNT was injected into the 2nd, 3rd, 4th flexor digitorum superficialis and 40 units in the extensor pollicis longus using ultrasound guidance. There was sustained improvement at the 4- and 9-week follow-up. There was some improvement noted in the activities of daily living [4].

(g) Cerebellar tremor

Lesions in the deep cerebellar nuclei (dentate, globose, or emboliform) or in the brachium conjunctivum (superior cerebellar peduncle), which contains fibers crossing over to the contralateral ventrolateral thalamus, could result in a cerebellar intention tremor. These deep cerebellar lesions cause intension tremor on the ipsilateral extremity. This is often an irregular 3–5 Hz tremor, affecting proximal more than distal muscle groups [63].

A retrospective analysis about the effect of BoNT on cerebellar tremor in 14 patients before and 1 month after injections, showed that there was improvement in tremor after BoNT injection into the agonist muscles alone. Antagonist muscles were avoided to prevent limb weakness. However, in this study, in addition to patients with cerebellar tremor from stroke, multiple sclerosis, and spinocerebellar ataxia, some ET patients were also included [243].

A small pilot study looked at the effect of BoNT in five patients with cerebellar tremor from multiple sclerosis and found no significant improvement in tremor with BoNT injection, but there was a trend toward improvement on some of the tremor ratings. Two of these five patients were injected again 2 months from first injection. There was worsening of pre-existing weakness that limited the use of BoNT in these patients [41].

(h) Palatal myoclonus (tremor)

Palatal myoclonus or tremor could either be primary/essential palatal myoclonus or secondary due to lesions in the Guillian-Mollaret triangle or the dentato-rubro-olivary network. Essential palatal myoclonus is due to repetitive contraction of the tensor veli palatini muscle, innervated by the trigeminal nerve, which results in rhythmic opening of the eustachian tube. Secondary palatal myoclonus is due to contraction of the levator veli palatini and results in repetitive palatal elevation [12]. This ear clicking and palatal myoclonus could be bothersome and distracting to patients.

There are several case reports which show efficacy of BoNT in palatal myoclonus [45, 49, 129, 214, 252]. BoNT is injected trans-palatal into the aponeurosis of the tensor veli palatini muscle.

In a case series of five patients with palatal myoclonus who received BoNT injections, four reported complete resolution of symptoms. One patient reported transient dysphagia and weak voice. BoNT was injected into the soft palate at the posteromedial aspect of maxillary tuberosity, where tensor veli palitini and levator veli palitini insert. Starting doses between 5 and 15 units of abobotulinumtoxinA were used in this study [178].

Other Parkinsonian Disorders

There are many symptoms experienced by patients with PD that may be amenable to BoNT therapy including blepharospasm, anterocollis, camptocormia, foot dystonia, hand and jaw tremor, sialorrhea, seborrhea, overactive bladder, and constipation [32, 104, 106, 111]. In addition to utilizing BoNT in the treatment of PD-related symptoms, there is emerging research on the role of BoNT in the central nervous system that may have relevance to the treatment of neurodegenerative disorders such as PD. For example BoNT/B when injected in the brains of animal models has been shown to block the transynaptic transmission of alpha-synuclein [164].

Freezing of gait (FoG)

There have been several studies suggesting the use of BoNT in FoG, but the results have been inconsistent [271]. This initially came about after a patient who received BoNT for off dystonia in the foot reported improvement in FoG [82, 84]. This was studied further in a pilot study of ten PD patients with FoG where three patients reported marked improvement in FoG, while two had no benefit, and one patient who was injected in a blinded manner had no improvement with saline injections and marked improvement after BoNT injection in calf muscles. Between 100 and 300 units of onabotulinumtoxinA was injected into the lateral and medial heads of gastrocnemius and into the soleus in this study. One or both legs were injected [83]. In another study involving 20 patients with PD of whom 10 had FoG, there was improvement in FoG after BoNT injection into the tensor fascia latae. Eight of the ten patients had significant improvement in FoG scores [240]. However, in a prospective double-blind placebo-controlled trial testing this concept further in 11 patients, 6 patients received 150 units of onabotulinumtoxinA injections and 5 received saline injections into the calves of both legs. There was no significant improvement in FoG in either group with leg weakness and falls, resulting in early termination of the study [92].

In a study involving 14 PD patients with FoG, 9 were injected with 5000 units of rimabotulinumtoxinB into the gastrocnemius-soleus complex of the predominantly affected leg. Five patients received placebo. There was marked improvement in symptoms in one patient, minimal improvement in two patients, unchanged symptoms in nine patients, and two patients with minimal worsening of symptoms. No significant differences in UPDRS scores between treatment and placebo groups were found [69].

Levodopa-induced Dyskinesia

Levodopa-induced dyskinesia (LID) occurs in over 90% of patients treated with levodopa for over 15 years, although the prevalence varies from study to study. Peak dose dyskinesia is the most common form of LID, followed by wearing off dystonia, both of which could benefit from BoNT injections as a treatment option [244]. In a randomized double-blind crossover study of 12 patients with medication refractory levodopa-induced cervical dyskinesia, 200 units of BoNT was injected in the neck muscles (bilateral sternocleidomastoid, splenius capitis, trapezius). Of these 12 patients, 8 were randomized and only 4 completed the study

before it was voluntarily terminated due to safety concerns, predominantly due to excessive neck weakness. There was a trend towards reduced On time with LID in the BoNT group compared to baseline, and reduced dyskinesia on self-reported dyskinesia and pain related to dyskinesia [65]. There are other studies demonstrating the utility of BoNT in the treatment of various forms of LID [106].

Axial Dystonia (anterocollis, camptocormia, Pisa syndrome)
See section "Dystonia"

Constipation: see section "Gastroenterology"

Hyperhidrosis: see section "Autonomic Disorders"

Dystonia

Dystonia is a movement disorder characterized by sustained or intermittent muscle contraction, resulting in abnormal repetitive movements, posture or both [5]. Dystonic movements are often patterned, initiated, or worsened with voluntary action and associated with overflow activation of involved muscles. Dystonia can be classified based on several factors including the age of onset, body distribution, temporal pattern, and also based on associated symptoms as part of a systemic condition. Dystonia could also be classified based on etiology. Based on body distribution, dystonia could be classified as focal, segmental, hemidystonia, multifocal, and generalized dystonia [5]. BoNT has become the mainstay treatment for focal and segmental dystonia. Muscle selection and adequate dosing are also important factors to determine efficacy, as in other dystonic conditions. BoNT has been noted to be an effective and safe treatment option for long term use [116].

(a) Blepharospasm and apraxia of eyelid opening
Blepharospasm is a type of focal cranial dystonia resulting in repetitive involuntary forceful eyelid closure, often associated with dystonia of other adjacent areas like neck, jaw, and facial muscles. Since BoNT was approved by the FDA in 1989, for the treatment of blepharospasm, this has become the mainstay of treatment for this form of focal dystonia [245]. Based on 2016 Practice Guidelines from the American Academy of Neurology [217], onabotulinumtoxinA and incobotulinumtoxinA have level B evidence (probably effective) and abobotulinumtoxinA has level C evidence (possibly effective) for use in the treatment of blepharospasm. OnabotulinumtoxinA and incobotulinumtoxinA are FDA approved in the United States for the treatment of blepharospasm; abobotulinumtoxinA is approved for the treatment of blepharospasm in Europe.

A randomized, double-blind, placebo-controlled multicenter trial evaluated the safety and efficacy of incobotulinumtoxinA in 109 patients in a 2:1 ratio for treatment to placebo, and found a significant difference in the Jankovic Rating Scale (JRS) in favor of the BoNT group [107]. There was also clinically relevant improvement in symptoms and in functional impairment assessed using the

Blepharospasm Disability Index (BSDI) and patient and physicians' global assessments. Ptosis and dry eyes were the few noted adverse effects.

There have been randomized, double-blind studies and split face studies (injecting different BoNT products to either side of the face) comparing different BoNT products which did not find significant difference between these toxins for use in blepharospasm [217]. A randomized double-blind trial compared incobotulinumtoxinA (Xeomin®) to onabotulinumtoxinA (Botox®) in patients with blepharospasm. Both BoNT products reduced scores on JRS, BSDI, and Patient Global Assessment (PGA) scales with no significant difference between the two products but with a tendency toward greater improvement with onabotulinumtoxinA [249]. Similarly, there are studies comparing incobotulinumtoxinA (Xeomin®) to onabotulinumtoxinA (Botox®) [192] and abobotulinumtoxinA (Dysport®) to onabotulinumtoxin A (Botox®) [162] with no significant difference in benefits seen between the two products.

Studies evaluating the long-term use of BoNT in patients with blepharospasm noted that the benefits persist for several decades of treatment [40, 217, 237]. A study in 128 patients who were receiving abobotulinumtoxinA or onabotulinumtoxinA had maintained benefit at 15 years [18, 189].

Frowning as a result of frontal dystonia, in the absence of blepharospasm, could also be treated using BoNT. A case series on two patients who had facial frowning reported an improvement in symptoms after BoNT injections. Corrugator and nasalis were the main muscles injected in these patients with improvement in facial frowning [99]. We have also used BoNT in the treatment of levodopa-induced dyskinesia, manifested by repetitive frontalis contractions [106].

Apraxia of eyelid opening

Apraxia of eyelid opening refers to the inability to open the eyelid in the absence of paralysis, sensory loss, or other disorders affecting language or alertness. This is often seen co-existing in patients with blepharospasm, Parkinson's disease, atypical parkinsonian syndromes, especially in progressive supranuclear palsy (PSP). The mechanism of "apraxia of eyelid opening" is not well understood, but it is probably not a true apraxia and more likely related to a dystonia phenomenon, inhibition of levator palpebrae, or other mechanisms [61].

Smaller studies have shown improvement in apraxia of eyelid opening after BoNT injections, especially if associated with blepharospasm. Injection of the pretarsal portion of the orbicularis oculi seems to be critical to help with apraxia of eyelid opening [102]. There have been several case reports on the benefit of BoNT in apraxia of eyelid opening [68, 126, 180].

One study noted benefits of BoNT in 32 patients with apraxia of lid opening, of which 3 patients had primary apraxia of eyelid opening, 20 with associated blepharospasm, 7 with PSP, and 2 with dystonic parkinsonian syndrome. Injections to the junction of preseptal and pretarsal portion of palpebral orbicularis oculi yielded best results. 83% of patients had improvement in symptoms after BoNT injections on a rating scale administered pre-and post-BoNT injections [119].

Another study looked into the effect of BoNT in 10 patients with apraxia of eyelid opening, where 8 of 10 had improvement in eyelid opening after BoNT injections. Between 20 and 30 units were used per eye injected at two sites at the junction of orbital and preseptal orbicularis oculi, compared to 10–20 units injected at one site at the middle of the upper lid close to the eyelash line. Injection of BoNT close to the pretarsal portion of orbicularis oculi resulted in improvement whereas injections to the preseptal and orbital portions did not yield the same benefit [53].

Ten patients with apraxia of eyelid opening associated with blepharospasm had BoNT injections and the lid opening parameters were compared to normal eyelid opening parameters obtained from 12 healthy control subjects. There was improvement in all lid opening measurements after BoNT injections [73].

(b) Cervical dystonia

Cervical dystonia (CD) is the most common isolated focal dystonia affecting the muscles of the neck and shoulders. BoNT is the first line treatment of CD. There are several good-quality studies that show the benefit of BoNT in CD. The 2008 American Academy of Neurology (AAN) evidence-based review identified 7 Class I studies showing the effect of BoNT in CD [215]. These have been listed and described briefly in Table 4.1.

The 2016 AAN Practice Guideline Update reviewed the evidence and listed level A (effective) evidence for the use of abobotulinumtoxinA and rimabotulinumtoxinB in patients with CD and level B (probably effective) evidence for the use of onabotulinumtoxinA and incobotulinumtoxinA in CD. These are based on 15 randomized double-blind clinical trials, listed in Table 4.1. All the formulations are approved for use in CD in the US [217].

Although anterocollis is often excluded from clinical trials of CD, some patients benefit from BoNT injections into the anterior scalene muscles, sternocleidomastoid muscles, and submental complex [106].

(c) Camptocormia

Camptocormia refers to an abnormal forward flexion in the thoracolumbar region, of more than 45°, apparent while standing or walking, but resolves in supine position. This is seen in PD patients with longer disease duration and severity, estimated to have prevalence between 3% and 17% in PD patients [59, 256].

In a case series studying 16 patients with camptocormia from different etiology, 9 patients were injected with BoNT for camptocormia. Between 300 and 600 units of onabotulinumtoxinA was injected in the rectus abdominus muscle. Of these 9 patients, 4 had marked improvement in symptoms lasting for about 3 months [10].

An open label study in 10 patients with camptocormia looked into the effect of ultrasound-guided injection of 100–300 units of incobotulinumtoxinA injected into either the rectus abdominus muscle or iliopsoas muscle based on whether the flexion was at the hip or lower trunk. There was no significant improvement in posture with these injections [72].

A case series of 4 patients with camptocormia, due to PD in 3 patients and one patient with MSA-P, evaluated changes in camptocormia after injecting 500–1500 units of abobotulinumtoxin A to bilateral iliopsoas using ultrasound

Table 4.1 Evidence-based review of the use of BoNT

Indication	Study	Results	BoNT injection pattern	Comments
Neurology:				
Essential tremor	Jankovic et al. [110]: Randomized double-blind placebo-controlled study in 25 patients with hand tremor	Significant improvement in tremor severity rating scale in BoNT-injected patients compared to placebo	50 units of Botox into wrist flexors and extensors of dominant limb Additional 100 units in 4 weeks for non-responders	Some degree of finger weakness in all patients
	Brin et al. [27]: Randomized placebo-controlled study involving 133 patients	Significant hand tremor improvement in the low-and high-dose BoNT groups compared to placebo	Low-dose group: 15 units into flexor carpi radialis and ulnaris; 10 units into extensor carpi radialis and ulnaris High-dose group: 30 units into flexors and 20 units into extensors	More weakness in the high-dose group (30% in low-dose and 70% in high-dose group)
	Pahwa et al. [168]: Double-blind placebo-controlled crossover study assessing head tremor in 10 patients	50% had moderate to marked improvement compared to 10% in placebo group in blinded raters' tremor scales 50% patients had moderate to marked subjective improvement compared to 30% in placebo group	40 units of Botox in each sternocleidomastoid and 60 units in splenius capiti	No statistical difference between the groups based on accelerometry
	Wissel et al. [259]: Study involving 14 patients with ET head tremor without dystonia and 29 with head tremor due to CD	Subjective improvement in 100% of ET patients and in 90% of CD patients Significant improvement in head tremor based on accelerometry analysis and clinical evaluation	Mean doses of 400 units of Dysport divided between bilateral splenius capiti muscles in ET patients Mean dose of 500 units in CD patients with muscle selection based on neck position	Local pain, neck weakness and dysphagia were side effects

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Hertegård et al. [97]: Study in 15 patients with ET voice tremor	Significant subjective and perceptual improvement in voice tremor	Between 0.6 and 7.5 units of BoNT injected into thyroarytenoid muscle or in some patients, into the cricothyroid or thyrohyoid muscle under EMG guidance	Acoustic evaluations showed that during sustained vowel phonation, there was a significant decrease in fundamental frequency variation after BoNT injection compared to pre-injection.
Cervical dystonia (CD)	Greene et al. [91]: Double-blind placebo-controlled parallel design study in 55 patients with CD	61% patients injected with BoNT improved statistically in severity of torticollis, pain, disability and degree of head turning In an open-label extension of the study with higher doses of BoNT, 74% patients had improvement	Between 30 and 250 units were injected in total (mean dose of 118 units) Between 15 and 55 units were injected to individual muscles including trapezius, SCM, and splenius capitis	
	Poewe et al. [184]: Randomized prospective multicenter double-blind placebo-controlled trial in 75 patients with CD who received abobotulinumtoxinA (Dysport®)	79% patients reported subjective improvement Postural head deviation rated using modified Tsui scale was significant at week 4 in the 500 and 1000 units Dysport® group compared to placebo	A total dose of 250, 500 or 1000 units of Dysport® was divided between one splenius capitis and contralateral sternocleidomastoid muscle	39% with dysphagia in the 1000 units Dysport® group, but 10% of patients in the placebo group also had dysphagia Neck weakness was present in 56% patients in the 1000 units group, which was significantly more than in the placebo group

	Brans et al. [23]: Prospective randomized double-blind trial in 64 patients comparing abobotulinumtoxinA (Dysport®) to oral trihexyphenidyl with 32 patients in each group. BoNT or placebo injections at entry to the study and repeated in 8 weeks	Significant improvement in disability score on Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS-Disability), Tsui scale and General Health Perception subscale in favor of BoNT	Mean dose of Dysport® was 292 units in the first session (week 0) and 262 units in the second session (week 8) Mean dose of trihexyphenidyl was 16.25 mg	Adverse effects were significantly less in the BoNT group compared to trihexyphenidyl group
	Lew et al. [127]: Randomized multicenter, double-blind, placebo-controlled 4-arm parallel group study in 122 patients with cervical dystonia who received botulinum toxin type B at 2500, 5000, or 10,000 units vs placebo	Significant improvement in TWSTRS – Total, Severity, Disability, and Pain scores at week 4 The proportion of patients that responded increased with increased doses of BoNT	Four arms included botulinum toxin type B at 2500, 5000, or 10,000 units vs placebo	Noted a dose response to AE (dry mouth and dysphagia) with higher doses causing more AE
	Brashear et al. [24]: Randomized multicenter, double-blind, placebo-controlled trial in 109 patients with three groups, including placebo, 5000 and 10,000 units of BoNT-B	Improvement in pain, disability and severity of CD on TWSTRS in BoNT B compared to placebo with most improvement noted in the 10,000 units group	5000 or 10,000 units of BoNT B compared to placebo injected into 2–4 muscles including levator, scalene, splenius capitis, SCM, semispinalis capitis, or trapezius	AE were mild
	Brin et al. [26]: Double-blind placebo-controlled trial of BoNT-B in 77 BoNT-A-resistant patients (38 placebo, 39 active)	Improvement in severity, disability, and pain scores on TWSTRS in the BoNT-B-treated group	Placebo vs 10,000 units of BoNT B into 2–4 involved muscles	Dry mouth and dysphagia were AE seen
	Truong et al. [236]: Multicenter double-blind placebo-controlled trial of abobotulinumtoxinA (Dysport®) in 80 patients	Significant improvement in symptoms quantified by reduction in TWSTRS total score in the Dysport® group 38% patients showed positive response in the Dysport® group	500 units of Dysport® vs placebo	Mean duration of benefit was 18.5 weeks

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Odergren et al. [163]: Double-blind, randomized, parallel group study in 73 patients to compare dose equivalence between onabotulinumtoxinA (Botox®) and abobotulinumtoxinA (Dysport®) with 38 patients in Dysport® group and 35 in Botox® group	Substantial improvement in Tsui score in both groups by week 2 Similar response in terms of efficacy and duration of response	Mean dose of 477 units of Dysport® and 152 units of Botox® into clinically determined muscles	In patients with rotational CD, patients treated with Botox® or Dysport® in 3 times the dose of Botox® had successful treatment of symptoms
	Comella et al. [43]: Multicenter, randomized double-blind parallel arm study in 139 patients randomized to BoNT-A or BoNT-B toxin	Improved TWSTRS score in both groups	Maximum dose received in the BoNT-A group was 250 units and in BoNT-B group was 10,000 units into muscles clinically determined by physician	The dose ration used was 1 U of BoNT-A to at least 40 units of BoNT-B
	Tintner et al. [233]: Randomized double-blind trial in 20 patients who were randomized to receive BoNT-A or BoNT-B (11 patients BoNT-A and 9 patients BoNT-B)	Improved TWSTRS severity, pain, and disability score in BoNT A and B compared to baseline scores pre-injection No significant difference in efficacy between BoNT-A and BoNT-B	BoNT-A (Botox®) dose: 227 ± 83 BoNT-B (Myobloc®) dose: 12,083 ± 5899	Less saliva production and increased constipation in BoNT-B group compared to BoNT-A group No other difference in autonomic function between the BoNT-A and BoNT-B groups
	Pappert et al. [173]: Randomized, double-blind, parallel group study in 111 patients (55 BoNT-A and 56 BoNT-B) comparing BoNT-A to BoNT-B	Improvement in TWSTRS Score in BoNT-A and BoNT-B groups with similar duration of benefit	BoNT-A 150 units BoNT-B 10,000 units injected into 2–4 neck or shoulder muscles clinically determined by a blinded physician	Mild dry mouth was more common with BoNT B than with BoNT A No difference in moderate to severe dry mouth

	Comella et al. [44]: Prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial of incobotulinumtoxinA (Xeomin®) in 233 patients (219 completed the study)	Significantly improved TWSTRS score compared to placebo at 120 U and 240 U	Xeomin®: 120 units or 240 units vs placebo	Dysphagia, neck pain, and mild neck weakness were AE noted; slightly more AE at 240 U dose compared to 120 U
	Charles et al. [35]: Double-blind, prospective, randomized, placebo-controlled trial in 170 patients (82 placebo and 88 BoNT-A) who received onabotulinumtoxinA or placebo in a 10-week study period (period 2). This was preceded by a 10-week open label study (period 1) in 214 patients, of whom 170 were randomized in period 2 of the study	Significant improvement in Cervical Dystonia Severity Scale and Physician Global assessment scale at 6 weeks	OnabotulinumtoxinA Period 1 (open label): Mean dose was 241 units (between 95 and 360 U) Period 2 (blinded placebo-controlled): Mean dose 236 units (95–360 units)	Rhinitis and dysphagia were significantly more in the BoNTA group compared to placebo Large number of drop outs: 37 of 170 due to lack of efficacy Two patients seroconverted from neutralizing Ab negative to positive status during the study but remained clinically responsive to BoNT
	Evidente et al. [66]: Randomized, double-blind, placebo-controlled multicenter trial of incobotulinumtoxinA (Xeomin®) in 214 patients injected with 120 or 240 U injected at a flexible interval of ≥6 weeks over a treatment period of 48 weeks followed by 20 weeks observation period; Of these, 169 patients completed the study	Both 120 U and 240 U doses resulted in significant improvement in TWSTRS total score, severity, disability, and pain scores	IncobotulinumtoxinA 120 U or 240 U vs placebo	Dysphagia was the most common AE (23.4% in 240 U group and 12.6% in the 120 U group)

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Yun et al. [267]: Randomized, double-blind, multicenter, parallel group crossover study in 103 patients, 94 completed the study. Patients received Botox® or Dysport® and were followed for 16 weeks followed by 4 week washout period before crossover to the other group	No statistical difference between Botox® and Dysport® at a conversion ratio 2.5:1 based on TWSTRS, Clinical Global Impression, and Patient Global Impression Mean changes in Tsui score tended to favor Botox®, but was not statistically significant	Botox® 200 units Dysport® 500 units Dysport®: Botox® ratio 2.5:1	No significant difference in AE between the groups
	Rystedt et al. [199]: Double-blind, randomized crossover study in 46 patients who received Botox® in 2 different doses and Dysport® using conversion ratios of 1:3 and 1:1.7	No significant difference between Botox® and Dysport® at 1:1.7 conversion ratio Median TWSTRS score was 1.96 points higher for Botox® at 1:3 ratio (not statistically significant). There was a statistically significant shorter duration of benefit for Botox® at 12 weeks when this 1:3 low dose was used	Botox®: Dysport® ratio 1: 3 and 1:1.7	When using 1:3 dose, patient assessments showed suboptimal benefit from Botox® Dose conversion of Botox®: Dysport® may be lower than 1:3
	Poewe et al. [183]: Randomized, double-blind, multicenter, placebo-controlled trial in 369 patients who were randomized to receive abobotulinumtoxinA dry formulation, and solution compared to placebo	AbobotulinumtoxinA 500 units in dry and solution formulation were superior to placebo based on TWSTRS score	AbobotulinumtoxinA 500 units in dry formulation and in solution formulation	Dysphagia and injection-site pain were similar between dry freeze dried formulation and solution formulation
	Yi et al. [264]: Randomized double-blind, placebo-controlled crossover study in 16 patients with CD secondary to dyskinetic cerebral palsy	Significant improvement in TWSTRS score in BoNT-A group compared to placebo (saline) at week 4	Median dose of BoNT-A: 145 U Mean dose: 139.7 U	There was improvement in pain and disability subscores Dysphagia was transient and improved within 2 weeks

	Lew et al. [128]: Multicenter, randomized double-blind placebo-controlled trial of abobotulinumtoxinA (Dysport®) at 500 units/2 ml dilution compared to placebo in 134 patients of which 129 completed the study (84 patients Dysport® and 45 placebo)	Significant improvement in TWSTRS score in BoNT group compared to placeo	500 U of Dysport® in toxin naïve patients Between 250 and 500 units of Dysport® at a conversion ratio of 2.5:1 to their previous Botox® dose	Dysphagia, neck pain, neck weakness, headaches were AE
Parkinson's disease hand rest tremor	Mittal et al. [149]: Randomized double-blind placebo-controlled crossover study in 30 patients with hand rest tremor	Significant improvement in tremor based on tremor rating scales and subjective patient impression	Between 2.5 and 20 units per muscle of incobotulinumtoxinA was injected in the forearm and hand muscles individualized based on tremor Between 85 and 110 units of incobotulinumtoxinA in a single patient	
PD freezing of gait	Gurevich et al. [92]: Double-blind placebo-controlled trial involving 11 PD patients with FoG, 6 of whom received BoNT and 5 received saline	Significant improvement in FoG after BoNT injection	OnabotulinumtoxinA between 100 and 300 units injected divided between the gastrocnemius and soleus of one or both legs	
	Fernandez et al. [69]: Randomized, double-blind, placebo-controlled trial in 14 PD patients with FoG who received BoNT ($n = 9$) or placebo ($n = 5$)	No significant difference between BoNT group and placebo	RimabotulinumtoxinB 5000 U to the gastrocnemius-soleus complex of predominantly affected leg involved in FoG	
Camptocormia	Case series only available			
Pisa syndrome	Tassorelli et al. [229]: Double-blind, randomized placebo-controlled trial of 26 patients, 13 who received BoNT injections and 13 received saline injections	Significant improvement in posture, pain, and range of motion in patients who received BoNT injection	50–200 units of incobotulinumtoxinA injected with EMG guidance into either iliopsoas, rectus abdominis, or thoracic or lumbar paravertebral muscles	

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Artusi et al. [9]: Open label pilot study of 15 patients, 13 of whom completed follow-up assessments	11 of 13 patients had over 40% improvement in trunk posture, while all had improvement in pain and discomfort	Between 50 and 75 units of onabotulinumtoxinA injected in paraspinal muscles using US and EMG guidance Between 25 and 50 units injected in the non-paraspinal muscles	No significant adverse events or complications
Levodopa-induced dyskinesia	Espay et al. [65]: Randomized double-blind placebo-controlled crossover study of 12 patients, of whom 8 were randomized	Study prematurely terminated due to safety concerns Only 4 patients completed the study There was a trend towards improved ON time without dyskinesia Reduction in self-reported dyskinesia	200 units of onabotulinumtoxinA injected in the neck muscles (25 units in each sternocleidomastoid, 50 units in each splenius capiti, 25 units in each trapezius)	Excessive neck weakness and dysphagia were noted, which led to termination of the study
Dystonic tremor	Data is from retrospective studies			
Sialorrhea	Mancini et al. [136]: Double-blind placebo-controlled trial to evaluate the effect of Dysport® on drooling in 20 patients with parkinsonism	Average secretion of saliva was significantly lower in the BoNT group compared to placebo	450 units of Dysport® into the parotid and submandibular glands under ultrasound guidance	No side effects in either group
	Ondo et al. [165]: Randomized, double-blind, placebo-controlled parallel group study in 16 PD patients	Significant improvement in the BoNT group in Visual Analog Scale, global impression of change, Drooling Rating Scale, Drooling Severity and Frequency Scale	BoNT-B 1000 units into each parotid and 250 U into submandibular gland vs pH matched placebo	AE was mild and included dry mouth
	Lagalla et al. [123]: Double-blind placebo-controlled trial in 32 patients, 16 of whom received BoNT	Significant improvement in drooling, ADLs, and decreased saliva weight	50 units of onabotulinumtoxinA injected in each parotid gland	

	Lagalla et al. [124]: Randomized, double-blind, placebo-controlled trial in 36 PD patients with drooling	Significant improvement in all measures of sialorrhea a month after BoNT injection	BoNT-B 4000 units vs placebo	Benefits lasted 19.2 weeks ±6.3 weeks
	Stone and O'Leary [221]: Systematic review	2 of 5 studies included in this review showed benefit of BoNT in sialorrhea, but all included studies were small studies		Not high-powered studies included
	Chinnapongse et al. [37]: Multicenter, randomized, double-blind placebo-controlled trial in 54 patients who received BoNT-B at 1500 U, 2500 U, 3500 units compared to placebo	Significant improvement in the Drooling Frequency and Severity Scale in a dose-related manner at week 4	BoNT-B at 1500 U, 2500 U, 3500 units	Dry mouth was more common in the BoNT group compared to placebo
	Narayanaswami et al. [154]: Randomized, double-blind placebo-controlled crossover study in 9 patients injected with incobotulinumtoxinA into parotid (20 units) and submandibular glands (30 units)	No significant change in saliva weight one month post injection	IncobotulinumtoxinA 20 units into parotid and 30 units into submandibular glands bilaterally	Doses used could have resulted in this outcome
Hyperhidrosis	Naumann and Lowe [156]: multicenter, randomized, double-blind, placebo-controlled, parallel group study in 307 patients with axillary hyperhidrosis	At 4 weeks, 94% of patients in BoNT group had responded, which was significantly better than the placebo group	Botox® 50 U per axilla or placebo	
	Heckmann et al. [95]: Multicenter, randomized double-blind placebo-controlled trial in 145 patients with axillary hyperhidrosis who received BoNT or placebo. Placebo group received 100 U of BoNT two weeks later.	Mean sweat production dropped significantly	Dysport® 200 U Placebo group received 100 U two weeks later	

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Schnider et al. [208]: Randomized, double-blind, placebo-controlled trial in 11 patients with palmar hyperhidrosis who received BoNT in one palm with placebo in the other	Mean sweat production dropped significantly (26–31%) between weeks 4 and 13	Dysport® 120 U per palm with placebo in contralateral palm	
	Lowe et al. [133]: Randomized double-blind placebo-controlled trial in 19 patients with palmar hyperhidrosis who received BoNT in one palm and placebo in the other	Significant reduction in palmar hyperhidrosis	OnabotulinumtoxinA 100 U in one palm and placebo in the other	No decrease in grip strength
Palatal myoclonus	Mostly case reports and case series available	No double-blind placebo-controlled studies available		
Oromandibular dystonia (OMD)	Tan and Jankovic [226]: Prospective study in 162 patients, majority with primary oromandibular dystonia, with jaw closing dystonia being the most common type	67.9% patients reported definite functional improvement after BoNT injections Mean duration of response: 16.4 weeks	Between 25 and 100 units in masseter muscle (Mean dose 54.2 units) Between 10 and 200 units in submental complex (mean dose 28.6)	Complication rate was low. Dysarthria and dysphagia were some of the reported AE
	Most studies for OMD are case series or observational studies			
Cerebellar tremor	Data is mostly from retrospective and pilot studies			
Tics	Marras et al. [141]: Randomized double-blind placebo-controlled crossover study of onabotulinumtoxinA in 20 patients with tics, 18 of whom completed the study	There was improved tic frequency and urge leading up to the tic Patients, however, did not notice an improvement in their tics	Doses were individualized to patients based on the type of tic	Disability burden of the targeted tic should be taken into account when deciding about BoNT injections
	Other studies for this condition are smaller open label trials			

Blepharospasm	Jankovic and Orman [108]: Double-blind, placebo-controlled, prospective, crossover study in 12 patients	All patients had improvement in blepharospasm	25 units of onabotulinumtoxinA/eye and if ineffective 50 units/eye	Blurred vision, tearing, ptosis, ecchymosis were some noted adverse effects
	Girlanda et al. [85]: Compared BoNT injection in one eye with saline injection in the other in 6 patients	Bilateral improvement in blepharospasm symptoms with unilateral BoNT injection	20 units of onabotulinumtoxinA/eye	Small cohort
	Nüssgens and Roggenkämper [162]: Double-blind study in 212 patients with blepharospasm who received either onabotulinumtoxin A or abobotulinumtoxin A at separate visits with the comparison of benefit	Similar benefits with similar duration of action for both formulation of BoNT (about 8 weeks)	Botox® average dose: 45 units Dysport® average dose: 182 units	The bioequivalence of onaB: aboB (Botox®: Dysport®) was found to be 1:4 in this study
	Roggenkämper et al. [192]: Randomized, double-blind, prospective, parallel study in 300 patients comparing Botox® to Xeomin®	There was improvement in symptoms in both groups quantified using JRS No significant difference in safety and efficacy of Botox® compared to Xeomin®	≤35 units/eye or 70 units total Botox® average dose: 40.8 units Xeomin® average dose: 39.6 units	Larger cohort
	Truong et al. [235]: Large multicenter, randomized, placebo-controlled trial evaluating the safety and efficacy of abobotulinumtoxinA (Dysport®) compared to placebo in 120 patients	Reduced frequency and intensity of spasms and improvement in functional ability Best balance between safety and efficacy was seen at 80 U of Dysport®/eye	abobotulinumtoxinA doses of 40 U, 80 U and 120 U	Blurred vision and ptosis were observed with higher doses There were a high number of withdrawals (35 patients) but this was more in the placebo group due to lack of benefit

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Wabbels et al. [249]: Randomized, double-blind, parallel group study comparing incobotulinumtoxinA (Xeomin®) to onabotulinumtoxinA (Botox®) in 65 patients	Improved symptoms with both products, quantified using JRS, BSDI and PGA No significant difference in benefits with Xeomin® and Botox®	Doses individualized to patients (≥20 U/eye)	Trend toward greater improvement with Botox® than Xeomin®
	Jankovic et al. [107]: Randomized, double-blind placebo-controlled multicenter trial in 109 patients with blepharospasm	Significant improvement in the severity of blepharospasm assessed by JRS and in functional impairment, assessed by blepharospasm disability index (BSDI), and patient and physician evaluation of global effect	IncobotulinumtoxinA dosing was individual specific, not to exceed 50 units per eye	Ptosis and dry eyes were some noted adverse effects
	Truong et al. [237]: Open label extension of Jankovic et al. [107] study of Xeomin® in 102 patients for 69 weeks	Significant improvement in JRS, BSDI	Xeomin® individually dosed	Ptosis and dry eyes were most common AE noted
	Saad and Gourdeau [200]: Randomized, double-blind, prospective split face study in 48 patients	Similar improvement between Xeomin® and Botox® using JRS and BSDI to quantify improvement	Average 20 units/eye of Xeomin® or Botox®	
Apraxia of eyelid opening	Forget et al. [73]: Pilot study in 10 patients with apraxia of eyelid opening associated with blepharospasm	Improved lid opening measures post BoNT injection and reduction in functional impairment	4–5 units of Botox® in the orbicularis oculi with 3 injections in the pretarsal portion (medial and lateral upper lid and lateral lower lid) and 4th injection in the external canthus	

Synkinesis	Borodic et al. [21]: Randomized double-blind placebo-controlled trial in 30 patients with chronic facial palsy, 15 of whom received onabotulinumtoxinA injections to the side with synkinesis compared to 15 patients who received placebo	There was reduction in the synkinesis based on videotape and blinded physician examination and improved quality of life, vision, and social interaction Improved vertical palpebral fissure distance, synkinesis physician grading scale in the BoNT group compared to placebo	BoNT was quantified using Schantz-Kautter method of "LD 50" determination. 2.5 LD 50 units per 0.1 cc was injected to four injection points in the periocular areas avoiding the medial lower lid and mid upper lid to avoid side effects	Increased incidence of exposure keratitis in the BoNT group compared to placebo group
	do Nascimento Remigio et al. [57]: Randomized comparative study analyzing the effects of onabotulinumtoxinA and abobotulinumtoxinA in 55 patients with chronic facial nerve palsy; 25 patients received onabotulinumtoxinA and 30 patients received abobotulinumtoxinA	Both toxins improved facial symmetry	A dose conversion ratio of 1:3 was used for onabotulinumtoxinA to abobotulinumtoxinA BoNT was injected to the non-paralyzed side of the face	
	Monini et al. [152]: Randomized placebo-controlled trial in 20 patients with synkinesis after recovery from facial palsy; 10 patients received BoNT followed by neuromuscular retraining therapy (NMRT) compared to 10 patients who received NMRT alone	Significant improvement in synkinesis in BoNT group compared to placebo group that received NMRT only	Between 10 and 40 units were injected	
Hemifacial spasm	Yoshimura et al. [265]: Prospective blinded, placebo-controlled crossover study in 11 patients	Subjective improvement in 79% and objective improvement in 84% patients	3 different graded doses between 2.5 and 10 U	Facial weakness was seen in 97% after injection Ptosis, diplopia, and facial bruising were other adverse effects

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Sampaio et al. [205]: Randomized, single-blind, parallel group study in 49 patients with HFS, 22 received Botox® and 27 received Dysport®	Similar improvement with Botox® and Dysport®	17.5 units of Botox® 70 units of Dysport®	Single-blinded study (investigator was not blinded)
	Park et al. [175]: started as a placebo-controlled study, and then later switched to an open trial, in 101 patients	98.6% had significant improvement in symptoms	Mean dose of Botox® used in a patient with HFS: 13.5 units 71% of patients with HFS received between 7.5 and 20 units	Dry eye, facial weakness and ptosis were the adverse
Pain:				
Trigeminal neuralgia	Zhang et al. [270]: Randomized double-blind placebo-controlled trial in 84 patients with trigeminal neuralgia	Significantly better response rate with BoNT compared to placebo Response rate was 70.4% for the 25 U group, 86.2% for 75 U group, and 32.1% for placebo group	BoNT/A 25 U and 75 U vs placebo intradermal or submucosal Injection was submucosal if pain involved oral mucosa	
	Wu et al. [260]: Randomized double-blind placebo-controlled trial in 40 patients	Significant improvement in pain intensity and pain attacks and more response rate in BoNT group Response rate in BoNT group was 68.18% and 15% in placebo group	Intradermal and/or submucosal injection of 75 U of BoNT/A in the dermatome of pain symptoms; submucosal injections done if pain was in the oral mucosa	
	Zúñiga et al. [272]: Randomized double-blind placebo-controlled trial in 36 patients	Significant improvement in Visual Analog Scale (VAS) at 3 months in the BoNT group	BoNT/A 50 U subcutaneous injection in the involved distribution Additional 10 U BoNT A vs placebo intramuscular injection in the ipsilateral masseter if pain involved was in the third branch of trigeminal nerve	

Post-herpetic neuralgia	Xiao et al. [261]: Randomized double-blind placebo-controlled trial in 60 patients who received BoNT, lidocaine, or placebo	Significant decrease in pain scores at day 7 and month 3 in the BoNT group compared to lidocaine and placebo Percent of patients on opiods was least post treatment in the BoNT group	BoNT/A less than 200 U in the involved dermatome	VAS scores improved in all three groups post treatment compared to pre
	Apalla et al. [8]: Randomized double-blind placebo-controlled parallel group study in 30 patients	Significant improvement in VAS pain scores in BoNT group compared to placebo	BoNT/A 5 U per site in a chessboard pattern	
Diabetic neuropathy	Ghasemi et al. [78]: Randomized double-blind placebo-controlled trial in 40 patients with diabetic neuropathy, 20 patients BoNT and 20 patients placebo	Reduction in neuropathic pain scores compared to placebo	BoNT/A 100 U distributed between 12 sites at 8–10 U per site on the dorsum of the foot	
	Yuan et al. [266]: Randomized double-blind placebo-controlled crossover trial in 18 patients	Significant reduction in VAS pain score in the BoNT group 44.4% patients had reduction in VAS scores in BoNT group with no similar effect in the placebo group	50 U per foot intradermal injections of BoNT/A with 4 U per site	There was transient improvement in sleep quality in the BoNT group
Neuro-rehabilitation:				
Upper-limb spasticity	There are smaller DB PC trials earlier than 2009, that are not included in this table			
	Kaňovský et al. [115]: Multicenter, double-blind, randomized-controlled trial in 148 patients with upper-limb spasticity post stroke	Statistically improved tone and disability in BoNT group	Xeomin® dose ≤400 units Median dose: 320 U	

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Simpson et al. [216]: Multicenter, randomized, double-blind, placebo-controlled, parallel group study in 60 patients with upper-limb spasticity post stroke or from traumatic brain injury with 3 arms, BoNT injection group, Tizanidine, and placebo	BoNT reduced tone more than tizanidine	OnabotulinumtoxinA 50 units each to flexor carpi radialis and ulnaris Remaining muscles were injected with doses at the discretion of the physician; Max dose 500 U	Higher incidence of AE in Tizanidine group
	McCrory et al. [143]: Multicenter, randomized, double-blind, placebo-controlled trial in 96 patients with upper-limb spasticity, who were treated with BoNT compared to placebo	BoNT group had significant reduction in spasticity However, quality of life, mood, disability, and caregiver burden did not differ between the groups	AbobotulinumtoxinA 750–1000 U initial Repeat 500–1000 U in 12 weeks	
	Turner-Stokes et al. [238]: Secondary analysis of McCrory et al. [143] study	Significant treatment effect	Dysport® 500–1000 U	
	Kaji et al. [112]: Multicenter, randomized, double-blind, placebo-controlled trial in 109 patients with post-stroke upper-limb spasticity who were randomized to get a low- or high-dose BoNT compared to placebo	Significant improvement in spasticity in the higher dose BoNT group	BoNT-A Low-dose group: 120–150 U High-dose group: 200–240 U	
	Cousins et al. [47]: Randomized double-blind placebo-controlled trial in 30 patients with upper-limb spasticity post stroke, 21 of whom completed the study. Half or quarter of the standard doses were used in the active arms of the study	No benefit for active treatment compared to control On subgroup analysis, both treatment groups had improvement in functional gain compared to placebo	OnabotulinumtoxinA Half or quarter of the standard doses of BoNT vs placebo Standard doses identified in this study: 100 units for biceps brachii, 60 units for brachialis, 50 U brachioradialis, 50 units flexor digitorum superficialis, 50 units flexor digitorum profundus	No serious AE Inadequate dosing likely resulted in the observed result

	Shaw et al. [211]: Multicenter, randomized trial in 333 patients with upper-limb spasticity with one group who received BoNT-A and therapy; the second group received therapy only	Significant improvement in tone in the BoNT group at 1 month and improved arm strength at 3 months; No significant differences between the groups in arm function at 1 month	Dysport® Median dose 200–300 U	
	Hesse et al. [98]: Single-blind, randomized pilot study in 18 patients with upper extremity spasticity with group A receiving BoNT-A injection into wrist and finger flexors compared to group B receiving no injection followed by aggressive rehab in both groups	Significant improvement in finger flexor stiffness in BoNT-injected group compared to the other group, and improved disability scores	IncobotulinumtoxinA 150 units into superficial and deep finger flexors (100 units) using ultrasound guidance and wrist flexors (50 units)	No significant AE
	Rosales et al. [195]: Multicenter, randomized, placebo-controlled trial in 163 patients with upper-limb spasticity injected with BoNT or placebo (80 patient received BoNT and 83 received placebo)	Significant improvement in Modified Ashworth Scale (MAS) scores in BoNT group The Functional Motor Assessment Scale did not show significant differences between the groups	Dysport® 500 U to wrist and elbow mover muscles	
	Lam et al. [125]: Randomized, double-blind placebo-controlled trial in 55 patients with upper-limb spasticity who received BoNT injections or saline as placebo	Significant improvement in Carer Burden Scale in BoNT group, MAS scores and passive range of motion at the joints	Dysport Max dose 100 U Doses individualized to patient needs	

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Marciniak et al. [140]: Randomized double-blind placebo-controlled trial in 21 post-stroke patients with shoulder spasticity that received BoNT injections vs placebo	BoNT and placebo groups had no difference in pain scores at 4 weeks Significant improvement in hygiene score on Disability Assessment Scale in the BoNT group	OnabotulinumtoxinA 140–200 U into pectoralis major with or without injections to teres major	
	Gracies et al. [88]: Randomized double-blind placebo-controlled trial in 24 hemiparetic patients who received two different doses of BoNT-B	Both BoNT groups improvement elbow function compared to placebo Higher dose of BoNT-B improved patient perceived stiffness, pain and functioning	RimabotulinumtoxinB 10,000 U (2500 U into elbow flexors) Or 15,000 U (5000 U into elbow flexors)	No AE
	Ward et al. [254]: Prospective double-blind study in 273 patients with focal post-stroke spasticity, followed by open-label extension in 225 patients. Patients randomized to BoNT or placebo along with standard of care treatment	No significant changes in principal active functional goal achievement between the BoNT group and placebo Significant improvement in passive function in BoNT group compared to placebo	OnabotulinumtoxinA max dose 800 U	No major AE
	Gracies et al. [89]: Multicenter, double-blind, randomized, placebo-controlled trial in 243 patients with upper-limb spasticity from stroke or brain injury	Mean changes in MAS was significant in both the BoNT groups compared to placebo Change in PGA scores were significant in BoNT groups compared to placebo	AbobotulinumtoxinA 500 U, 1000 U vs placebo injected into the most hypertonic muscle among elbow, wrist, and finger flexors (primary target muscles) and at least 2 other muscle groups	No serious treatment-related AE; mild muscle weakness was the AE

	Elovic et al. [64]: Randomized, placebo-controlled trial randomized to 2:1 ratio of incobotulinumtoxinA: placebo in 259 patients with post-stroke spasticity	Significant improvement in upper-limb spasticity and associated disability BoNT resulted in larger improvement in Ashworth Scale compared to placebo	IncobotulinumtoxinA 400 U in a fixed dose pattern Flexed elbow 200 U Flexed wrist 150 U Clenched fist 100 U	Mild/moderate AE reported in BoNT group, dry mouth being the most common
	Rosales et al. [194]: Randomized, double-blind, placebo-controlled trial in 163 patients with upper-limb spasticity	BoNT significantly improved MAS scores; BoNT group had sustained improvement in upper-limb spasticity when combined with rehabilitation	AbobotulinumtoxinA 500 units (200 units to biceps brachii, 100 units to brachioradialis, 100 U flexor carpi radialis and 100 U flexor carpi ulnaris) Vs placebo	No significant AE
Lower-limb spasticity	Richardson et al. [191]: Prospective, randomized, double-blind, placebo-controlled parallel group study in 52 patients with hypertonia in upper and lower extremity injected with BoNT or placebo	Significant improvement in Ashworth Scale, passive range of motion, Rivermead scores for lower limb and subjective rating of problem severity in the BoNT group compared to placebo	OnabotulinumtoxinA injected with EMG guidance into clinically determined muscles in the upper or lower extremity	Pain at injection site for 4 patients
	Hyman et al. [101]: Prospective, randomized, double-blind, placebo-controlled dose ranging study in 74 patients	Primary efficacy variable (passive hip abduction and distance between the knees) improved for BoNT and placebo group Improvement in distance between the knees was significantly better in the 1500 U Dysport group Muscle tone improved in the BoNT groups only	Dysport® 500 U, 1000 U and 1500 U	Twice as much AE in the higher BoNT dose than lower doses with muscle weakness being a common AE

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Pittock et al. [182]: Randomized, double-blind, placebo-controlled trial of three doses of Dysport® in 234 patients with spastic equinovarus deformity post stroke	Small but significant improvement in calf spasticity, limb pain and reduction in the use of walking aids in the BoNT group 2 min walking distance and stepping rate improved significantly in all groups including placebo without significant differences between groups	Dysport® 500 U, 1000 U and 1500 U	
	Verplancke et al. [242]: Prospective, randomized double-blind, placebo-controlled trial in 35 patients with lower-limb spasticity	Significant improvement in MAS scores in BoNT group and significant improvement in Glasgow Outcome Scale (GOS)	OnabotulinumtoxinA 200 units per leg (100 units to gastrocnemius and 100 units soleus) Vs saline placebo	Flu-like illness in one patient in the BoNT group 3 deaths (none in the BoNT group; unrelated to treatment intervention) and 4 were withdrawn from the study
	Gusev et al. [94]: Multinational, randomized, double-blind, placebo-controlled trial in 55 patients who received BoNT or placebo injections into adductor muscle of each leg	Significant pain reduction in BoNT groups Trend in favor of BoNT for other endpoints without statistical significance	Dysport® 500–750 U into adductor muscles of each leg with dose adjustment based on spasticity severity, patient size, and prior BoNT exposure	

	Kaji et al. [113]: Multicenter, randomized, double-blind, placebo-controlled parallel group study in 120 post-stroke patients with lower-limb spasticity randomized to receive BoNT or placebo injections	Significant improvement in spasticity in BoNT group Significant change in MAS in BoNT group compared to placebo	OnabotulinumtoxinA 300 U to ankle plantar flexors or invertors	
	Maanum et al. [134]: Single center, randomized, double-blind, placebo-controlled trial in 66 patients with spastic cerebral palsy where patients received BoNT or placebo injections	No significant differences between groups in primary outcome sagittal kinematics of knee, ankle and hip; and health-related quality of life Improvement in self-reported muscle stiffness/spasticity in BoNT group	OnabotulinumtoxinA with EMG guidance into clinically determined muscles Semimembranosus, semitendinosus, biceps femoris, flexor digitorum brevis, flexor digitorum longus were muscles injected	
	Dunne et al. [60]: Randomized, double-blind placebo-controlled trial in 85 patients with lower-limb spasticity, followed by open label extension	No difference between BoNT groups with different doses No difference in hypertonia between groups Significant improvement in spasm frequency, pain reduction, active dorsiflexion, and gait quality in BoNT group compared to placebo	OnabotulinumtoxinA 200 U or 300 U	No significant difference in AE between groups

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Fietzek et al. [71]: Single-center, double-blind, randomized, placebo-controlled trial in 52 patients with lower-limb spasticity, followed by open label extension of the study	BoNT group with lower MAS compared to placebo During open label extension, there was a further decline in muscle tone in patients previously in the placebo group. Overall patients that received BoNT in the first cycle had lower MAS scores	OnabotulinumtoxinA 230 units (60 units medial gastrocnemius, 30 U later gastrocnemius, 70 units soleus and 70 U tibialis posterior) 230 U: Unilateral 460 U: Bilateral injections Vs saline as placebo	No major AE
	Tao et al. [227]: Randomized, double-blind, placebo-controlled trial in 23 patients with lower-limb spasticity	Significant improvement in gait analysis measures in BoNT treated group	OnabotulinumtoxinA 200 units (100 units in medial and lateral gastrocnemius, 50 units soleus and 50 units tibialis posterior) vs saline placebo	No major AE
	Ding et al. [55]: Randomized blinded study in 80 post-stroke patients with one group who received BoNT and another group who received BoNT and stimulation by a spasmodic muscle therapeutic instrument. The stimulation is thought to improve muscle spasms.	Muscle tension reduced significantly in both groups after BoNT injection. MAS reduced significantly in both groups after BoNT injection. Motor function of lower extremities improved after BoNT + use of therapeutic instrument	OnabotulinumtoxinA 350 U injected with 50–100 U per muscle under ultrasound guidance	
	Gracies et al. [90]: Multicenter, randomized, double-blind placebo-controlled trial in 381 patients with chronic hemiparesis who received one lower-limb injection with BoNT or placebo. This was followed by an open extension study	After a single BoNT injection, there were improved MAS scores and muscle tone. After repeat BoNT injections in the open label phase, there was improved walking speed	Dysport® 1000 U, 1500 U or placebo	

	Gracies et al. [90]: Post hoc analysis of Gracies et al. [90] study comparing upper and lower extremity BoNT to lower extremity only BoNT injections in 127 patients	Simultaneous upper and lower extremity BoNT injections does not hamper walking speed improvement compared to BoNT injections in the lower limbs only	AbobotulinumtoxinA 1000 U, 1500 U in lower extremities for cycle 1 and 3 Optional upper extremity injection with 500 U and lower extremity 1000 units from cycle 3 onward	
	Kerzoncuf et al. [118]: Multicenter, prospective, randomized, double-blind, placebo-controlled study in 40 post-stroke patients with lower-limb spasticity where 19 patients received BoNT and 21 placebo (physiologic serum)	Spasticity decreased significantly in the BoNT group During dual task, there was a significant improvement in sway area in the BoNT group	OnabotulinumtoxinA up to 300 units Mean dose 227 U Main muscles injected were gastrocnemius and soleus	Treating lower-limb spasticity with BoNT also improved postural sway/ balance
	Baricich et al. [16]: Randomized, single blind pilot study in 30 patients where one group was given electrical stimulation to antagonistic muscles after BoNT injection of flexor muscles for patients with spastic equinus foot	Significant reduction in muscle tone and ankle range of motion in both groups No significant difference between the groups receiving only BoNT vs BoNT + electrical stimulation	OnabotulinumtoxinA: Between 50 and 120 U for each muscle under ultrasound guidance Gastrocnemius and soleus were the muscles injected	
Urology:				
Overactive bladder (OAB)	Sahai et al. [201]: Randomized, double-blind, placebo-controlled trial in 34 patients with OAB who received BoNT injections ($n = 16$) or placebo ($n = 18$)	Significant increase in maximum cystometric capacity (MCC) at weeks 4 and 12 in BoNT group compared to placebo. Significant improvement in quality of life	BoNT-A 200 U or placebo	Extension study showed that BoNT benefits lasted at least 24 weeks

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Dmochowski et al. [56]: Double-blind, randomized, placebo-controlled trial of BoNT in 313 patients with OAB who received intradetrusor injections of BoNT or placebo	Improved durable efficacy for all BoNT group over 100 U for primary and secondary measures including urinary incontinence free patients. Doses greater than 150 U contributed minimal additional or clinically relevant improvement in symptoms	OnabotulinumtoxinA 50 U, 100 U, 150 U, 200 U or 300 U or placebo	There was a significant increase in UTI and urinary retention in the BoNT group compared to placebo
	Rovner et al. [196]: Randomized, double-blind, placebo-controlled trial in 313 patients with OAB and urinary urge incontinence with or without detrusor overactivity, who received intradetrusor injections of BoNT (269 patients) vs placebo (44 patients)	Changes in MCC with BoNT >100 U was superior to placebo at week 12 Dose-dependent increase in MCC was seen for 150 U, 200 U, and 300 U	OnabotulinumtoxinA 50 U, 100 U, 150 U, 200 U, and 300 U	Doses >100 U were commonly associated with post-void residual urine volumes >200 ml
	Cruz et al. [48]: Multicenter, randomized, double-blind, placebo-controlled trial in 275 patients with urinary incontinence due to neurogenic detrusor overactivity secondary to multiple sclerosis or spinal cord injury, who received BoNT injections 200 U (92 patients), 300 U (91 patients), or placebo (92 patients)	BoNT 200 U and 300 U significantly reduced urinary incontinence at week 6 compared to placebo	OnabotulinumtoxinA 200 U, 300 U, or placebo intradetrusor injections at 30 sites	Urinary tract infections (UTI) and urinary retention were AE seen

	Tincello et al. [232]: Multicenter, randomized, double-blind, placebo-controlled trial in 240 patients with OAB, 122 received BoNT, and 118 placebo	Median voiding frequency was lower in BoNT group compared to placebo. Continence was more common in BoNT group compared to placebo	OnabotulinumtoxinA 200 U or placebo	UTI and voiding difficulty requiring self-catheterization was more common in the BoNT group
	Denys et al. [54]: Prospective, randomized, double-blind, placebo-controlled trial in 99 patients with idiopathic overactive bladder who received BoNT injections at three different doses or placebo	3 months after BoNT injection, there was >50% improvement in 65% patients who received 100 U and in 56% who received 150 U; >75% improvement in 40% patients of both 100 U and 150 U groups	Onabotulinumtoxin A 50 U, 100 U or 150 U	100 U showed reasonable efficacy with less risk of high post-void residual
	Chapple et al. [34]: Multicenter, randomized, double-blind, placebo-controlled trial in 548 patients, 277 of whom received BoNT and 271 placebo	BoNT significantly decreased urinary incontinence episodes per day at week 12. All other OAB symptoms were reduced in the BoNT group compared to placebo	OnabotulinumtoxinA 100 U injected at 20 sites intradetrusor	
	Chuang et al. [38]: Prospective, randomized, double-blind, two center study in 62 patients, 31 of whom received a single intravesical application of liposomal-BoNT and 31 patients received placebo	Statistically significant improvement in micturition frequency per 3 days Reduced urgency severity scores in BoNT group compared to placebo	Catheter intravesical installation of 200 U of liposomal onabotulinumtoxinA	Lipo-BoNT installation was not associated with increased urinary retention

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Nitti et al. [161]: Randomized, multicenter, placebo-controlled trial in 557 patients, 280 patients received BoNT injections, 277 received placebo	At 12 weeks, there was a 3–4 fold decrease in mean frequency of urinary incontinence in the BoNT group compared to placebo. BoNT group had significant improvement in all OAB symptoms and multiple measures of quality of life compared to placebo	OnabotulinumtoxinA 100 U into the detrusor muscle	
	de Sá Dantas Bezerra et al. [51]: Prospective randomized, single-blinded study in 21 female patients with overactive bladder, who received intravesical injections with two different doses of BoNT	Maximum cistometric capacity increased in both BoNT groups without significant difference between the groups. Patients were better or much better in 70% patients who received 300 U and in 88.9% who received 500 U at 12 weeks	AbobotulinumtoxinA 300 or 500 U Injected into 30 sites, avoiding the trigone	
	Schurch et al. [209]: Randomized, double-blind, placebo-controlled trial in 23 patients with neurogenic detrusor overactivity, who received BoNT 200 U or 300 U vs placebo	Significant decrease in urinary frequency; with no significant difference between 200 U and 300 U groups	OnabotulinumtoxinA 200 U or 300 U	No significant AE
	Ghei et al. [79]: Randomized, double-blind, placebo-controlled crossover study in 20 patients with neurogenic and non-neurogenic detrusor overactivity	Significant differences in the urinary frequency, changes in voided volume, and episodes of incontinence in the BoNT group compared to placebo	Myobloc® 5000 U or placebo through cystoscope	4 patients with urinary retention

Interstitial cystitis (IC)/ painful bladder syndrome (PBS)	Kuo and Chancellor [120]: Prospective, randomized, placebo-controlled trial in 67 patients with IC/PBS who received BoNT injections at 200 U (n = 15), 100 U (n = 29) followed by hydrodistention (HD), or placebo (n = 23) followed by HD	IC symptoms score reduced in all three groups Pain reduction visual analogue scale, functional bladder capacity, and cystometric bladder capacity increased significantly in BoNT+HD group compared to HD only at 3 months	OnabotulinumtoxinA 100 U or 200 U	
	El-Bahnasy et al. [62]: Randomized controlled trial in 36 patients with IC who either received intravesical bacillus Calmette-Guerin (BCG) (n = 16) or BoNT (n = 16)	Global IC survey improved in 71% in BCG group and in 92% in the BoNT group. BoNT group had statistically significant improvement in all parameters including nocturia, pelvic pain, urgency, and dysuria compared to BCG group	BoNT-A 300 U	
	Taha et al. [225]: Randomized controlled trial in 28 women with IC/ PBS who were randomized to BoNT (n = 14) or Pentosan polysulfate sodium (PPS) (n = 14)	BoNT group had significant improvement over placebo in all parameters compared including global PBS/IC survey, decrease in daily void, urgency, nocturia, pelvic pain, and dysuria	Cystoscopic intravesical injection of BoNT-A 300 U in 30 points including trigone	
	Gottsch et al. [87]: Randomized, double-blind, placebo-controlled trial in 20 women with IC/PBS who received BoNT (n = 9) or placebo (n = 11)	No improvement in female modified Chronic Prostatitis Symptom Index or other symptom indices between BoNT and placebo groups	BoNT-A 50 U injected peri-urethrally	

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Kasyan and Pushkar [117]: Randomized controlled trial in 32 women with IC/PBS who were randomized to BoNT ($n = 15$) or placebo who got standard hydrodistention ($n = 17$)	BoNT-A had similar efficacy to hydrodistention in IC	BoNT-A 100 U injected into the trigone of the bladder using a flexible needle through a cystoscope	
	Manning et al. [137]: Double-blind, randomized, placebo-controlled trial in 50 women, randomized to receive HD, HD + saline or abobotulinumtoxinA	BoNT was not associated with significant increase in total O-Leary Sant questionnaire (OLS) score	AbobotulinumtoxinA 500 U intravesical	12 patients had UTI treated during the follow-up period, which confounded the results
	Kuo et al. [121]: Multicenter, randomized, placebo-controlled, double-blind study in 60 IC/PBS patients randomized in a 2:1 ratio of HD + BoNT ($n = 40$): saline ($n = 20$)	Significant reduction in pain in the BoNT group compared to placebo cystometric bladder capacity increased in the BoNT group	BoNT-A 100 U	AE did not differ significantly between groups
	Chuang and Kuo [39]: Randomized, two-center, double-blind, placebo-controlled trial in patients with IC/PBS who received intravesical liposomal botulinum toxin ($n = 31$), BoNT injection ($n = 28$) or placebo ($n = 31$)	Improved pain scores and OLS score in all 3 groups No difference in improvement between the groups	Intravesical liposomal botulinum toxin OnabotulinumtoxinA 200 U	No significant AE
	Pinto et al. [181]: Single-center, randomized, double-blind, placebo-controlled pilot trial in 19 women with IC/PBS who received trigonal injections of BoNT ($n = 10$) or placebo ($n = 9$)	Significant pain reduction in BoNT group compared to placebo at week 12 Significant improvement in OLS score and quality of life in BoNT group compared to placebo	OnabotulinumtoxinA 100 U injected in trigone at 10 sites	
Detrusor sphincter dyssynergia	Gallien et al. [76]: Randomized, double-blind, placebo-controlled trial in 86 patients with MS	No difference in post-voiding residual urine volume (PRUV)	OnabotulinumtoxinA 100 U as single transperineal injection into the sphincter	

	de Sèze et al. [52]: Randomized, double-blind, placebo-controlled trial in 13 patients with urinary retention from detrusor sphincter dyssynergia, who received transperineal injections of BoNT or lidocaine	Significant mean decrease of PRUV in the BoNT group	OnabotulinumtoxinA 100 U as single transperineal injection into the sphincter Or lidocaine	
Otolaryngology:				
Laryngeal dystonia	Data is based on observational studies and retrospective chart reviews			
Spasmodic dysphonia	Data is based on observational studies and retrospective chart reviews			
Gastroenterology:				
Achalasia	Mikaeli et al. [146]: Prospective, randomized, single-blinded, placebo-controlled trial in 40 patients with achalasia who were randomized to receive BoNT ($n = 20$) or pneumatic dilatation ($n = 20$)	12-month remission rate was significantly higher for pneumatic dilatation group than patients receiving single injection of BoNT	Dysport® 200 U	Efficacy of a single pneumatic dilatation is similar to two BoNT injections
	Bansal et al. [14]: Randomized, double-blind study in 34 patients with achalasia randomized to receive BoNT ($n = 16$) or Witzel balloon dilatation ($n = 18$)	Initial therapy with Witzel procedure is associated with better long-term outcome than a single BoNT injection	Botox® 80 U into lower esophageal sphincter (LES)	Due to risk of perforation with Witzel, BoNT remains a possible alternative
	Mikaeli et al. [145]: Randomized controlled trial in 54 patients with achalasia randomized to receive BoNT one month before pneumatic dilatation ($n = 27$) or pneumatic dilatation alone ($n = 27$)	One-year remission rate was 77% in BoNT group compared to 62% in pneumatic dilatation group Injection of BoNT before dilatation does not significant enhance the efficacy of pneumatic dilatation	Dysport® 400 U in LES	

(continued)

Table 4.1 (continued)

Indication	Study	Results	BoNT injection pattern	Comments
	Zaninotto et al. [269]: Randomized controlled trial in patients with achalasia randomized to receive BoNT ($n = 40$) or laparoscopic myotomy ($n = 40$)	After 6 months, results were comparable between the groups	Botox® 100 U injected in the LES; Patients with a good response received a second round of injection	
	Zaninotto et al. [269]: Randomized trial in 37 patients with achalasia who were randomized to receive laparoscopic myotomy ($n = 20$) or two injections of BoNT one month apart ($n = 17$)	Probability of being asymptomatic 2 years later was 34% for BoNT and 90% for myotomy No significant difference in cost effectiveness between these two groups over 2 years	Two injections of Botox® 100 U injected one month apart	
Anal fissure	Brisinda et al. [29]: Randomized, placebo-controlled trial in 50 patients injected with BoNT or nitroglycerin application twice daily	96% patients in the BoNT group had healing of anal fissure at 2 months compared to 60% in the placebo group, which was statistically significant	OnabotulinumtoxinA 20 U 9 patients in the nitroglycerin group crossed over to the BoNT group due to lack of benefit; 1 patient in BoNT group crossed over to nitroglycerin group due to lack of benefit	
	De Nardi et al. [50]: Randomized controlled trial in 30 patients who received either BoNT ($n = 15$) or 0.2% glycerine trinitrate (GTN) ointment three times daily at the anal margin	12 patients in GTN group and 11 patients in BoNT group had relief in symptoms at one month visit; no significant difference between the groups	OnabotulinumtoxinA 20 U into the internal anal sphincter on each side of anterior midline	No incontinence in either group
	Brisinda et al. [28]: Randomized controlled trial in 100 patients, who were randomized to receive BoNT (30 U Botox® or 90 U Dysport®) or 0.2% nitroglycerin ointment	92% patients (46 of 50 patients) in BoNT group and 70% patients in nitroglycerin group (35 of 50 patients) had healed anal fissures at 2 months. 12 patients from nitroglycerin group and 4 from BoNT group crossed over to the other group due to inadequate benefit	30 U Botox® or 90 U Dysport® injected into internal anal sphincter	Mild incontinence and flatus in BoNT group that lasted 3 weeks Mild headache in nitroglycerin group

	Festen et al. [70]: Randomized blinded trial in 108 patients with anal fissure, randomized to get BoNT injection and placebo ointment or placebo injection and isosorbide dinitrate (ISDN) ointment	14 of 37 patients in BoNT group and 21 of 36 patients in ISDN group had healing of anal fissure after 4 months; BoNT not found to have an advantage over ISDN	OnabotulinumtoxinA 10 U to each side of anterior midline in the internal anal sphincter (20 units total)	
	Berkel et al. [19]: Multicenter randomized clinical trial in 60 patients with anal fissure who received either BoNT or ISDN ointment	Significant improvement in healing of anal fissure in BoNT group over ISDN group at 9 weeks (18 of 27 patients in Dysport group and 11 of 33 patients in ISDN group had healing of anal fissure)	Dysport® 60 U 30 U on each side of the anterior midline of the internal anal sphincter	Recurrence rate in both groups is high; 28% of Dysport group and 50% in ISDN group had recurrence of fissure in a year
	Abd Elhady et al. [2]: Randomized controlled parallel group study in 160 patients with chronic anal fissure who were divided into 4 treatment groups (n = 40 each group), including treatment by lateral internal sphincterotomy, local diltiazem ointment, local GNT ointment, and BoNT injections into internal anal sphincter	Mean time to healing was not statistically different between the groups. Mean time to pain relief was significantly lower in the BoNT group compared to diltiazem and local GNT group. Mean time to pain relief was lower in the BoNT group compared to sphicterotomy group but the difference was not statistically significant. Most patients refused to continue medical therapy and were referred for lateral sphincterotomy	OnabotulinumtoxinA 20 U to each side (40 U total) of anterior midline of the internal anal sphincter	Recurrence rate after BoNT was 52.5% while recurrence rate in sphincterotomy group was 10%
Gastroparesis	Data is from case series			
Constipation	Data is from open label trials			

guidance. There was subtle improvement in two patients, worsening of posture in one, and marked worsening in one patient. At the highest doses, all patients complained of mild hip weakness [247].

Another study in two patients where 300 units of BoNT was injected in the rectus abdominis with CT guidance showed no improvement in symptoms after BoNT injection [42].

A case report of a single patient with camptocormia, who had insufficient benefit in trunk posture and pain after rectus abdominis injection, was injected with 200 units of onabotulinumtoxinA in the external oblique on one side and rectus abdominis on the other side. This led to an improvement in trunk posture and improvement in pain. This patient had a partial resection of rectus abdominis on one side for breast cancer reconstruction surgery [257]. This was based on the observation in a previous study where injection of lidocaine into external oblique muscles in patients with camptocormia resulted in an improvement in posture and pain in 8 of 12 patients [75].

(d) Pisa syndrome

Pisa syndrome refers to the marked lateral flexion of the trunk, of more than 10°, improves with lying down, and with passive manipulation. This is estimated to have a prevalence of about 8% in PD patients with longer disease duration [59], and in patients with atypical parkinsonian syndromes.

In a randomized placebo-controlled trial involving 26 patients, 13 patients received BoNT injections while the remaining 13 received saline injections for camptocormia. Between 50 and 200 units of incobotulinumtoxinA was injected using EMG guidance into iliopsoas, rectus abdominis, thoracic, or lumbar paravertebral muscles. There was significant improvement in trunk posture in the patients injected with BoNT and also in pain and range of motion [229].

In an open label pilot study of the effect of BoNT in Pisa syndrome, 13 of 15 patients initially enrolled completed follow-up assessments, and of these, 11 patients had at least 40% improvement in posture, and all patients had improvement in pain/discomfort. Between 50 and 75 units of onabotulinumtoxinA was injected into the paraspinal muscles under ultrasound or EMG guidance, and between 25 and 50 units injected in the non-paraspinal muscles with pathologic hyperactivity on EMG [9].

Hemifacial Spasm (HFS)

HFS is characterized by unilateral, involuntary clonic contraction of muscles innervated by the seventh cranial nerve. This is often due to an aberrant vascular loop compressing the exiting nerve root [262]. Secondary HFS could occur when seventh cranial nerve is damaged due to tumor, infection, Bell's palsy, or demyelinating causes. HFS is primary in 79% patients and secondary in 21% [116].

There is level C (possibly effective) recommendation for the use of BoNT in HFS. The evidence for the use of BoNT is not optimal but the initial open label

studies showed significant degree of benefit and this has discouraged larger controlled studies for this condition [215]. However, BoNT has become the mainstay first-line treatment for HFS and both primary and secondary HFS respond well to BoNT injection [116]. Pretarsal injections have been noted to be more beneficial to help the eyelid spasms in HFS than preseptal injections [31].

An open trial studied the effects of BoNT in 101 patients with HFS. Of 144 treatments, 98.6% had significant improvement in symptoms. This study initially started as a double-blind study with 8 patients randomized to receive BoNT and 4 patients in the placebo arm received saline injections. Due to the benefits noted with BoNT, the remaining patients were studied in an open trial and all patients treated with BoNT received benefit after the first injection for HFS. Patients with suboptimal benefit received repeat injections 7–10 days after the first round of BoNT [175]. This practice is generally discouraged due to concern for immunoresistance with injections repeated less than 3 weeks apart [17]. Dry eye, facial weakness, and ptosis were the adverse effects noted.

A prospective, placebo-controlled blinded study in 11 patients with HFS showed subjective improvement in 79% and objective improvement in 84% after BoNT injections [265].

In a single-blinded randomized parallel group study comparing two BoNT products, onabotulinumtoxinA (Botox®) and abobotulinumtoxinA (Dysport®) were studied in 49 patients with HFS. Similar improvement was noted with the two BoNT products with a slightly higher number of patients needing booster injections with Dysport® than with Botox®. A conversion ratio of 4:1 was used for Dysport®: Botox® to estimate an equivalent potency [205]. In a study of BoNT in blepharospasm and HFS, 28 patients with HFS had improvement in symptoms with the injection of BoNT to pretarsal orbicularis oculi [31]. In a retrospective chart, review of 32 patients injected with BoNT for blepharospasm and HFS, 11 patients had HFS. There was improvement in symptoms with BoNT injections, and these persisted with repeat treatments over the course of 10 years. A slightly higher dose was needed for similar benefits over time [1].

Synkinesis

Aberrant regeneration of the facial nerve after facial nerve injury or paralysis from a variety of etiologies could result in abnormal movement of facial muscles called synkinesis. The involved muscles could include eyelid and upper or lower facial muscles. BoNT can treat these abnormal movements to restore facial symmetry in these patients.

A double-blind multicenter placebo-controlled trial evaluated the use of BoNT in 30 patients with synkinesis and an additional 6 patients in an open label pilot study design. Etiology of facial paralysis for patients in this study included chronic Bell's palsy in 20 patients, post-acoustic neuroma surgery in 4 patients, Ramsey-Hunt syndrome in 4 patients and one patient after mastoiditis and another after

meningioma resection. BoNT/A injected to the synkinetic side suppressed the degree of abnormal movements associated with different facial movements in both study designs. In the double-blind placebo-controlled study, 15 patients received BoNT injections and were compared to 15 patients who received placebo. In this study, there was reduction in the synkinetic movements based on videotape and blinded physician examination and improvement in quality of life, vision, social interaction, and self-perception of facial asymmetry [21].

Another study compared onabotulinumtoxinA to abobotulinumtoxinA in facial synkinesis by injecting BoNT to the non-paralyzed side of the face using a dose conversion ratio of 1:3, which is the most commonly used conversion ratio. After randomization, 25 patients received onabotulinumtoxinA and 30 patients received abobotulinumtoxinA with doses individualized to the patients. Both toxins showed an improvement in facial asymmetry after injections using subjective and objective assessments. Facial symmetry was assessed subjectively by independent evaluation by two plastic surgeons on a four-point scale, and objective evaluation included Clinical Score for Facial Palsy and Facial Disability index [57].

A randomized placebo-controlled trial in 20 patients with facial palsy followed by synkinesis evaluated the effects of BoNT in these patients. Ten were randomized to receive BoNT followed by neuromuscular retraining therapy (NMRT), which is an exercise program to improve synkinesis, compared to 10 patients who received NMRT alone. There was significant improvement in synkinesis in the BoNT group compared to placebo [46, 152].

Another randomized single-blind three-arm comparison clinical trial compared three different BoNT types, onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA, in 28 patients with facial synkinesis. Of these, 6 patients were enrolled multiple times. Of a total of 38 treatment visits, 15 were onabotulinumtoxinA, 13 abobotulinumtoxinA, and 10 incobotulinumtoxinA injection visits. There was no significant difference in SAQ score improvement between the three toxin groups, implying similar efficacy of these toxins for facial synkinesis up to 4 weeks. At 4 weeks, incobotulinumtoxinA had less effect on SAQ scores compared to onabotulinumtoxinA, probably due to shorter duration of action. Higher doses may be needed to allow for longer duration of benefit when using incobotulinumtoxinA for facial synkinesis [231].

In addition to these randomized clinical trials, there are multiple other open label studies showing benefits of BoNT in synkinesis.

A prospective cohort study in 23 patients who received BoNT injections for facial synkinesis showed improvement in synkinesis after injections. Some of these patients got injections to the buccinator muscle, which is thought to be a symptomatic muscle in synkinesis. Although all patients who received BoNT injections had improved synkinesis, patients who received injections to the buccinator had greater improvement in post-injection scores and greater difference between the pre- and post-injection scores on the Synkinesis Assessment Questionnaire (SAQ). Buccinator injections were performed, using EMG guidance, below the dentate line in the buccal mucosa anterior to the level of Stenson's duct [176].

Another prospective cohort study in 99 patients with facial synkinesis who received BoNT injections showed that there was significant improvement in synkinesis after BoNT injections. Bell's palsy and facial paralysis after resection of vestibular schwannoma were the main etiology preceding facial synkinesis in these patients. A group of 6 muscles including corrugator, orbicularis oculi superioris, orbicularis oculi inferioris, risorius, mentalis, and platysma were injected in these patients. SAQ was used to assess symptoms pre and post injections. Higher doses of BoNT injections resulted in increased improvement in SAQ scores [212].

In a cohort of 51 patients who received BoNT injections, SAQ was administered pre and post injections. There was significant improvement in SAQ scores and improvement in scores for every question on the SAQ post onabotulinumtoxinA injection compared to the pre scores [158].

Orofacial and Oromandibular Dystonia

Orofacial/oromandibular dystonia (OMD) refers to dystonic contraction of the facial muscles along with pharyngeal, laryngeal, and masticatory muscles [116]. This could accompany dystonia in the neck as part of cranial cervical dystonia. There are numerous case reports and case series describing the benefit of BoNT in OMD, but there is paucity of well-designed, placebo-controlled trials [144, 151]. Jaw closing dystonia with or without bruxism tends to be more responsive to BoNT than jaw opening dystonia [218, 226]. In a double-blind, placebo-controlled trial of 23 patients with sleep bruxism treated with BoNT/A injections into masseter and temporalis (60 and 40 units each, respectively) or placebo, the clinical global impression and the visual analog scale favored the BoNT/A group [166].

A prospective, longitudinal, observational case series evaluated 30 patients with focal facial dystonia pre and post BoNT injections using Abnormal Involuntary Movement Scale (AIMS). BoNT doses between 3 and 100 units were used (mean dose 27.4 units). There was improvement in the AIMS score and the percentage of improvement depended on the dose injected, the area affected, and the etiology. However, among patients with facial dystonia, this study included 11 patients with HFS and 7 patients with facial paralysis, all inappropriately listed under the facial dystonia class [197].

In a large prospective open label study looking at the safety and efficacy of BoNT in OMD, 162 patients with OMD had Botox® injections in either the masseter or the submental complex or both muscle groups. Jaw closing dystonia was the most common type in this study and the majority had primary/idiopathic dystonia. 110 of the 162 patients had a global improvement of ≥ 3 on a scale where 4 means complete resolution/marked improvement of symptoms [226].

A cross-sectional survey of 23 patients, 5 with OMD, showed that patients with OMD had benefits noted on the Glasgow Benefit Inventory (GBI). This questionnaire evaluates quality of life after otolaryngologic interventions, in this case, BoNT for spasmodic dysphonia and OMD. The benefit was less than what was noted in

patients with spasmodic dysphonia (SD), but there was not a significant difference between the groups. All patients with SD and OMD noticed benefits after BoNT injections [20].

Another similar study in 12 patients with jaw opening OMD, using GBI scores pre and post BoNT injections showed a significant improvement in quality of life after BoNT injections. Doses of 40 units or more were injected into the lateral pterygoid muscles bilaterally with an additional midline injection of 10 units into the submental complex for patients with suboptimal benefit despite dose increase to the lateral pterygoid muscles. There was significant reduction in the GBI scores after BoNT injections. There were no major adverse effects [36].

Neuro-rehabilitation: Spasticity

BoNT has level A evidence of efficacy in patients with upper- and lower-limb spasticity [105]. There are several reports which show a significant reduction in post-stroke spasticity in patients receiving BoNT. There is also improved pain with reduced spasticity in these patients. However, a meta-analysis of six studies reported no significant improvement in functional status or change in disability after BoNT injections. However, there was a trend toward reduced spasticity-related pain [194]. The AAN Practice Update in 2016 and a meta-analysis by Sun et al. in 2019 lists several randomized placebo-controlled trials which show the efficacy and safety of BoNT in patients with upper- and lower-limb spasticity [217, 223]. Some of these studies, along with a brief description, are listed in Table 4.1. BoNT injections in patients with spasticity should occur in conjunction with aggressive neurorehabilitation for improved functional status and reduced disability in this patient population.

Tics

There are not many studies providing good-quality evidence for this indication, but BoNT injections continue to be a strategy that is considered when tics are at danger of causing secondary complications or if there are isolated simple tics affecting one body segment which is not responding well to medications [131, 230]. For example, with whiplash tics, which are forceful and repetitive, there is a risk of cervical myelopathy and cord injury if left untreated or inadequately treated. With forceful repetitive eye blinking tics, there could be functional blindness, which could limit driving or potentially result in harmful situations. BoNT injections into the vocal cords have been found to be very effective in the treatment of troublesome phonic tics, including coprolalia [122]. There are reports on the efficacy of BoNT in reducing tic frequency and severity, and this is also thought to reduce the premonitory urge associated with both motor and phonic tics. A small randomized double-blind

placebo-controlled cross-over study involving 18 patients with tics, noted a significant improvement in tic frequency and the urge leading up to the tic. However, this study interestingly noted that the patients did not appreciate any improvement in their tics. This discrepancy between the lack of adequate benefit noted by the patients and significant tic reduction observed by the examiner was thought to be due to presence of other tics in muscle groups that were not injected [141].

A Cochrane review which looked into the utility of BoNT for the treatment of motor and phonic tics was able to only find one study that met their selection criteria [170]. This is the study mentioned above by Marras et al. in 2001. The overall beneficial effect of BoNT was deemed to be uncertain by the Cochrane review [170].

There are other small open label studies where there has been improved patient-reported tic control after BoNT injection. In an open label study of BoNT in 35 patients with tics, 29 patients reported an improvement in tics after BoNT injections, and 21 of 25 patients with a premonitory urge noted an improvement in this urge after BoNT injections [122].

Autonomic Disorders

(a) Sialorrhea

Sialorrhea may accompany several neurological disorders including PD, atypical parkinsonian conditions, amyotrophic lateral sclerosis (ALS), and cerebral palsy. Sialorrhea results in social embarrassment for the patient and family members and in addition could result in tissue breakdown where saliva pools in the neck or result in fungal infections from drooling and constant moisture. BoNT works by inhibiting acetylcholine release at the parasympathetic ganglion, thereby reducing saliva secretion [100]. In these patients, drooling is often thought to be due to decreased swallowing more than due to overproduction of saliva [157].

There are several randomized controlled trials showing efficacy of BoNT in sialorrhea [123, 179, 221]. Injections are typically done in the parotid gland and submandibular glands, with benefits lasting between 3 and 6 months, with injections repeated for benefit maintenance. Both BoNT type A and B could be used for injections with benefit in sialorrhea [214].

Over 50% patients with ALS have problems with sialorrhea and trouble handling the secretions. Trouble swallowing saliva due to bulbar involvement contributes to this symptom. About 20% patients have sialorrhea despite the use of anticholinergics or have side effects limiting the use of oral medications. A systematic review of five small studies in 28 patients showed positive benefit of BoNT on sialorrhea in this patient population [221]. This review included 5 small studies, two of which showed reduction in sialorrhea after BoNT-A injection [80, 258], one study showed no change in the number of tissue papers used and no subjective effect on sialorrhea [210], another showed some improvement based on QoL questions in 5 patients [138], and the last included study showed 30% reduction in daily tissue use and improvement in drooling impact score in over half the patients with bulbar ALS [241].

Between 40% and 80% patients with PD have sialorrhea. BoNT is thought to probably be safe and effective for treating drooling in patients with PD [157]. Oropharyngeal dysphagia due to bradykinesia is thought to cause sialorrhea. A double-blind placebo-controlled trial of the use of BoNT in sialorrhea in 32 PD patients showed that there was significant improvement in sialorrhea when assessed a month after injecting 50 units of BoNT in each parotid when compared to placebo [123]. Another double-blind study involving 20 parkinsonian patients, 14 with PD and 6 with multiple system atrophy (MSA), showed significant improvement in sialorrhea starting a week after injecting 145 units of BoNT in bilateral parotid glands and 80 units in each submandibular gland [136]. Another double-blind placebo-controlled trial in 54 patients also showed improved salivation after BoNT injection [37]. A list of double-blind placebo-controlled trials evaluating the use of BoNT in patients with sialorrhea has been listed in Table 4.1.

BoNT has been studied for sialorrhea from other etiology as well. In pediatric population with neurologic impairment, Dohar, J retrospectively looked at the effect of BoNT for sialorrhea in a long-term study which showed persistent benefit of BoNT over time in 112 children over the study period of 9 years [58].

(b) Hyperhidrosis

Sweating abnormalities could be seen in patients with PD with prevalence as high as 60%. Injection of BoNT is thought to work by inhibiting acetylcholine at the parasympathetic nerve terminals [250]. The use of BoNT in these patients is based on studies done on patients with essential hyperhidrosis.

Primary focal hyperhidrosis is a disorder of excessive sweating which could be localized to the axilla, palms, soles, or forehead. Based on the 2008 AAN review, BoNT is established to be safe and effective in axillary hyperhidrosis and is probably safe and effective for use in patients with palmar hyperhidrosis [157]. A list of randomized controlled trials that led to these recommendations is briefly described in Table 4.1.

Otolaryngology

BoNT is the preferred treatment for laryngeal dystonia/spasmodic dysphonia (SD), a form of focal dystonia affecting the larynx and vocal cords resulting in a strained effortful voice or irregular, interrupted speech during spasms of vocal cords [198]. There are three main different subtypes are adductor SD, abductor SD, and mixed SD. Abductor SD is characterized by a breathy voice and breaks in speech due to inappropriate glottal opening during speech. The posterior cricoarytenoid muscles are the main muscles involved in abductor SD. In Adductor SD, there is a strained quality to the voice and speech interruptions due to excessive glottal closure [213]. Injection of BoNT into thyroarytenoid muscle improves the symptoms of adductor spasmodic dysphonia [153]. In a survey of 70 physicians who inject patients with SD, where they collectively injected over 4000 patients with SD over the prior year.

In this survey, the physicians self-reported that the majority used EMG to inject the thyroarytenoid or throarytenoid-lateral cricoarytenoid muscle complex or for adductor SD via transcricothyroid membrane approach. A substantial majority (87%) preferred to start with bilateral injections. For abductor SD, 92% targeted the posterior cricoarytenoid muscle alone, 31 physicians (51%) preferred the anterior transcricoid injection approach, and 67% used EMG guidance for the injections [213].

A prospective, observational study in 30 patients with laryngeal dystonia (LD), with or without accompanying jaw dystonia, evaluated the effect of BoNT in patients with LD using oromandibular dystonia questionnaire-25 (OMDQ-25). This study noted a significant reduction in the OMDQ-25 scores after BoNT injections at 4 and 8 weeks post injection. No major adverse effects were observed. A consistent, measurable improvement in quality of life was noted after BoNT injections in LD patients with the injection of genioglossus and other muscles in the oromandibular region [155].

A cross-sectional survey of 23 patients, 18 with SD and 5 with OMD, showed that patients with SD had significant benefit in symptoms noted after BoNT injections when quantified on the Glasgow Benefit Inventory. The benefit was higher in the SD group than patients with OMD [20].

The dose of BoNT required for adductor spasmodic dysphonia typically tends to reduce over time. A retrospective chart review in the charts of 44 patients who were on BoNT treatment for adductor Spasmodic Dysphonia showed that over time, patients received less BoNT doses over a course of 10 years with maintained benefit [22]. Similar results were noted by another study where the BoNT doses required reduced over time when patients were observed for a 20-year period. Unilateral or bilateral thyroarytenoid muscles were injected in these patients [153].

A retrospective study of 8 patients with adductor SD as part of Meige syndrome, who received BoNT injections under EMG guidance had clinically relevant improvement noted after injections [177].

A retrospective chart review in 32 patients with adductor spasmodic dysphonia, who received EMG-guided intracordal BoNT injections, were performed. Doses of BoNT injected ranged from 2.74 U to 3.85 U, with mean dose of 3.64 U. There was significant improvement in voice quality after 1 month and this stabilized after 3 months [139].

Urology

Overactive bladder affects 12–17% of the general population at some point in life, of which about a third experience urge incontinence [161]. BoNT chemodenervation is the third-line treatment for overactive bladder (OAB) in patients that have refractory symptoms despite behavioral and pharmacologic treatment [224].

Mechanism of action for the benefit is thought to be secondary to blockage of synaptic release of acetylcholine, resulting in paralysis of detrusor muscle, and

relaxation and improvement in symptoms of overactive bladder. There is, however, increasing evidence that BoNT has effects on afferent nerve terminals as well. There is now high-quality evidence for the efficacious use of BoNT in detrusor overactivity. Effects from BoNT last about 8–11 months before injections have to be repeated [171]. Urinary retention is a possible adverse effect, and patients may need to self-catheterize for urinary retention, if this happens.

In an open label study in 20 PD patients with overactive bladder, 100 units of onabotulinumtoxinA was injected into submucosal intradetrusor. This resulted in improved bladder symptoms at 1 and 3 months, and 50% decreased incontinence episodes over 6 months. 57% had moderate to marked improvement [7].

In another open label study of onabotulinumtoxinA in 24 PD patients with OAB, 100 units of onabotulinumtoxinA was injected into bladder wall and trigone. In this study, 79.2% patients had improved symptoms of OAB at 4 weeks, and 29.1% had resolution of urge incontinence [248].

A large randomized placebo-controlled clinical trial in 557 patients with OAB, 280 of who received BoNT injections for urge incontinence refractory to anticholinergic medications, about 65% of BoNT-treated patients had improvement in symptoms. The rate of urinary retention in these patients was 5.4% [161].

In a prospective randomized single-blinded trial in 21 female patients with OAB who had failed first-line and second-line therapies, abobotulinumtoxinA was injected at two doses of 300 U and 500 U. Intravesical injections were done at 30 sites, avoiding the trigone. At 12 weeks, there was significant improvement in 91% patients in both groups. Patients were better or much better in 70% patients who received 300 U and in 88.9% patients who received 500 U BoNT injections at 12 weeks; and in 50% who received 300 U and in 100% at 500 U at 24 weeks. Intravesical injections of 500 U improved quality of life and symptoms for longer periods of time than 300 U [51].

There are several other trials which demonstrated the benefits of BoNT for overactive bladder, some of which are listed in Table 4.1.

BoNT has also been used to treat interstitial cystitis (IC)/bladder painful syndrome. Several randomized controlled trials (RCT) have evaluated the efficacy of BoNT in IC, some of which have been described briefly in Table 4.1.

Gastroenterology

(a) Esophageal motility disorders

BoNT has been used for the treatment of spastic esophageal motility disorders and achalasia. BoNT provides short-term symptom relief in patients who are considered high risk for more invasive surgical treatment options like myotomy or esophageal dilatation [239]. BoNT is considered less efficacious than the surgical alternatives [190] but could be considered in high-risk surgical candidates. About 70–90% of patients notice improvement in symptoms within a month of injection; but over half requires repeat injections within 6–24 months [239].

There are several randomized controlled trials that evaluated the benefits of BoNT in achalasia. A meta-analysis that evaluated this deemed that there were better remission rate and reduced relapse rate in patients that received pneumatic dilatation when compared to BoNT injections [253]. Several of these RCTs are included in Table 4.1.

In patients with nonachalasia spastic dysmotility disorders, BoNT may improve dysphagia symptoms, based on small retrospective studies [220].

(b) Anal fissure

Anal fissure is a linear ulceration in the anal canal, affecting especially young adults, resulting in pain and bleeding after defecation. Chronic anal fissure is a fissure that persists after 4–12 weeks of treatment. BoNT injection into the internal anal sphincter or intersphincteric groove is a minimally invasive procedure that results in symptom release, often for 3 months. Flatus (18%) and fecal incontinence (5% of patients) are possible side effects with less of a risk of fecal incontinence when compared to the other surgical interventions including lateral internal sphincterotomy (LIS), which is first-line surgery for medically refractory anal fissure [15]. Three meta-analysis showed that LIS is superior to BoNT for anal fissure, but there is less of a risk of fecal incontinence with BoNT injections compared to LIS [15]. In a retrospective observational study of 128 patients treated with BoNT over 5 years, 46.6% of patients had complete response, 23.9% had partial response, and 29.5% were refractory. Complete response was defined by symptomatic improvement along with anal fissure healing, while partial response including symptomatic improvement without fissure healing and refractory patients had neither symptomatic improvement or fissure resolution [15]. Reported dosages of BoNT vary between 20 and 100 units injected into the internal anal sphincter, under the anal fissure, on both sides of the fissure, or circumferential injections, with no one method deemed superior to another [15, 86, 251].

A meta-analysis identified six randomized controlled trials evaluating the effect of BoNT in chronic anal fissure which showed that BoNT has fewer side effects than topical nitrates, but there is no difference in fissure healing or recurrence [202]. These studies are briefly described in Table 4.1.

(c) Internal anal sphincter achalasia

Internal anal sphincter achalasia is a condition similar to Hirschsprung disease but with ganglion cells preserved. BoNT has been studied in this condition. A meta-analysis that looked at 16 prospective and retrospective studies deemed posterior myectomy to be a more efficacious procedure than interspincteric BoNT in patients with internal anal sphincter achalasia [74].

(d) Constipation

There are a few open label studies looking into the utility of BoNT for constipation [111]. In an open label involving 10 patients, onabotulinum toxin A was injected into the puborectalis muscle; there was reduced rectal tone while straining [6]. In another study involving 18 patients, where 100 units of onabotulinum toxin A was injected at two sites on the puborectalis muscle, there was subjective symptomatic

improvement in 10 patients at 2 months and in 8 patients at 1 month post injection. There was also a significant reduction in the straining pressure [30].

(e) Gastroparesis

Pyloric sphincter dysfunction could result in delayed gastric emptying and lead to idiopathic and diabetic gastroparesis; and relaxation of this using BoNT has been postulated to improve gastroparesis. There are some case reports and case series on the use of BoNT for gastroparesis.

In a case series of two patients with PD who had gastroparesis diagnosed by gastroenterologist via gastric emptying study (GES), both received 100 U of BoNT into the pyloric sphincter via endoscopy and was followed for 4–8 weeks. The first patient had complete resolution of abdominal discomfort and nausea at 5 weeks and a repeat GES was "within normal limits." The second patient had complete resolution of nausea and abdominal discomfort after 2 months from injection and repeat GES was normal [81].

In another case series of ten patients with idiopathic gastroparesis not responding to medications, 80–100 U of BoNT was injected into the pyloric sphincter. There was significant improvement in mean solid gastric retention 4 weeks after injections and significant improvement in symptoms as well after BoNT injections [147].

In a case series of six patients with diabetic gastroparesis and an abnormal solid phase gastric emptying study, injection of 100 U of BoNT into the pyloric sphincter improved symptoms. There was mean improvement of 55% in subjective symptoms by 2 weeks, with improvement maintained at 6 weeks [67].

Pain Medicine

BoNT has been found to have an effect on many peripheral and central mechanisms of pain and has been studied in multiple conditions associated with pain [142]. At the peripheral nerve endings, BoNT inhibits the secretion of pain modulators like substance P, calcitonin gene–related peptide (CGRP), glutamate from nerve endings, and dorsal root ganglion; reduces local inflammation at the nerve endings; and is also thought to potentially have a regenerative effect on injured nerves [142, 174]. Currently, chronic migraine is the only FDA-approved pain condition for which BoNT is approved. BoNT is also approved for use in spasticity and could help relieve spasticity-related pain. BoNT has also been observed to reduce pain associated with dystonia. BoNT has been studied in painful temporomandibular disorders in several RCTs, but the level of evidence was low and insufficient to support the use of BoNT for this condition. However, BoNT was well tolerated without significant increase in adverse effects [135]. BoNT is being studied for use in neuropathic pain conditions and considered effective in the treatment of conditions including post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, and intractable neuropathic pain [174]. There are smaller

studies showing a beneficial role of BoNT in occipital neuralgia, carpal tunnel syndrome, phantom limb pain, and some randomized controlled trials showing a beneficial role of BoNT in spinal cord injury–related neuropathic pain and central post-stroke pain [174]. The possible role for BoNT in pain management is being increasingly recognized and studied. Evidence for a few of these indications is briefly discussed below. Other pain conditions will be discussed in further detail in a separate chapter.

(a) Trigeminal neuralgia

A randomized double-blind placebo-controlled trial in 84 patients who received submucosal and intradermal injections of BoNT/A at two doses of 25 U and 75 U showed that patients had reduced pain, with patient reports of being "much improved" or "very much improved." The response rate was 70.4% for the 25 U group and 86.2% for 75 U group, significantly higher than the placebo group at 32.1% [270].

In another randomized double-blind placebo-controlled trial in 42 patients who received intradermal and/or submucosal injections of BoNT/A compared to placebo, there was significant improvement in pain intensity and pain attacks at week 1. There were significantly more responders in the BoNT injection group (68.18%) than in placebo group (15%) [260].

Another randomized double-blind placebo-controlled trial in 36 patients compared patients who received placebo to patients who received subcutaneous injections of BoNT in the affected area, along with an additional intramuscular injection of 10 U BoNT or placebo in the ipsilateral masseter of patients with involvement of the third branch of the trigeminal nerve. Three months after injection, there was significant improvement in the visual analog scale (VAS) of pain in the BoNT group when compared to placebo [272].

(b) Post-herpetic neuralgia

In a randomized double-blind placebo-controlled trial in 60 patients who received BoNT, lidocaine, or placebo in the affected dermatome. Doses less than 200 U of BoNT/A were used based on individualized patient dosing. There was significant decrease in pain scores at week 1 and at 3 months compared to the lidocaine and placebo groups [261].

In another randomized double-blind placebo-controlled parallel group trial in 30 patients who received BoNT vs placebo, 13 patients had over 50% reduction in VAS score [8].

(c) Diabetic neuropathy

In a randomized double-blind placebo-controlled trial in 40 patients, 20 of whom received intradermal injections on the dorsum of the foot (total of 12 sites with 8–10 u per site), there was a reduction in neuropathic pain score compared to placebo [78].

In another randomized double-blind placebo-controlled crossover trial in 18 patients who received intradermal injections (4 U per site, 50 U per foot) of BoNT vs placebo, 44.4% had a reduction in VAS scores within 3 months with no similar response in the placebo group [266].

References

1. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. Clin Exp Ophthalmol. 2014;42:254–61. https://doi.org/10.1111/ceo.12165.
2. Abd Elhady HM, Othman IH, Hablus MA, et al. Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. S Afr J Surg. 2009;47:112–4.
3. Adler CH, Bansberg SF, Hentz JG, et al. Botulinum toxin type A for treating voice tremor. Arch Neurol. 2004;61:1416–20. https://doi.org/10.1001/archneur.61.9.1416.
4. Ahn S-Y, Kim D-A, Park Y-O, Shin J-H. Effect of ultrasonography-guided botulinum toxin type A injection in holmes' tremor secondary to pontine hemorrhage: case report. Ann Rehabil Med. 2014;38:694–7. https://doi.org/10.5535/arm.2014.38.5.694.
5. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28:863–73. https://doi.org/10.1002/mds.25475.
6. Albanese A, Brisinda G, Bentivoglio AR, Maria G. Treatment of outlet obstruction constipation in Parkinson's disease with botulinum neurotoxin A. Am J Gastroenterol. 2003;98:1439–40. https://doi.org/10.1111/j.1572-0241.2003.07514.x.
7. Anderson RU, Orenberg EK, Glowe P. OnabotulinumtoxinA office treatment for neurogenic bladder incontinence in Parkinson's disease. Urology. 2014;83:22–7. https://doi.org/10.1016/j.urology.2013.09.017.
8. Apalla Z, Sotiriou E, Lallas A, et al. Botulinum toxin A in postherpetic neuralgia. Clin J Pain. 2013;29:857–64. https://doi.org/10.1097/AJP.0b013e31827a72d2.
9. Artusi CA, Bortolani S, Merola A, et al. Botulinum toxin for Pisa syndrome: an MRI-, ultrasound- and electromyography-guided pilot study. Parkinsonism Relat Disord. 2019;62:231–5. https://doi.org/10.1016/j.parkreldis.2018.11.003.
10. Azher SN, Jankovic J. Camptocormia: pathogenesis, classification, and response to therapy. Neurology. 2005;65:355–9. https://doi.org/10.1212/01.wnl.0000171857.09079.9f.
11. Bain PG, Findley LJ, Britton TC, et al. Primary writing tremor. Brain. 1995;118:1461–72. https://doi.org/10.1093/brain/118.6.1461.
12. Baizabal-Carvallo JF, Cardoso F, Jankovic J. Myorhythmia: phenomenology, etiology, and treatment. Mov Disord. 2015;30:171–9. https://doi.org/10.1002/mds.26093.
13. Baizabal-Carvallo JF, Jankovic J, Feld J. Flu-like symptoms and associated immunological response following therapy with botulinum toxins. Neurotox Res. 2013;24:298–306. https://doi.org/10.1007/s12640-013-9400-9.
14. Bansal R, Nostrant TT, Scheiman JM, et al. Intrasphincteric botulinum toxin versus pneumatic balloon dilation for treatment of primary achalasia. J Clin Gastroenterol. 2003;36:209–14. https://doi.org/10.1097/00004836-200303000-00005.
15. Barbeiro S, Atalaia-Martins C, Marcos P, et al. Long-term outcomes of botulinum toxin in the treatment of chronic anal fissure: 5 years of follow-up. United European Gastroenterol J. 2017;5:293–7. https://doi.org/10.1177/2050640616656708.
16. Baricich A, Picelli A, Carda S, et al. Electrical stimulation of antagonist muscles after botulinum toxin type A for post-stroke spastic equinus foot. A randomized single-blind pilot study. Ann Phys Rehabil Med. 2019;62:214–9. https://doi.org/10.1016/j.rehab.2019.06.002.
17. Bellows S, Jankovic J. Immunogenicity associated with botulinum toxin treatment. Toxins (Basel). 2019;11:491. https://doi.org/10.3390/toxins11090491.
18. Bentivoglio AR, Fasano A, Ialongo T, et al. Fifteen-year experience in treating blepharospasm with Botox or Dysport: same toxin, two drugs. Neurotox Res. 2009;15:224–31. https://doi.org/10.1007/s12640-009-9023-3.
19. Berkel AEM, Rosman C, Koop R, et al. Isosorbide dinitrate ointment vs botulinum toxin A (Dysport) as the primary treatment for chronic anal fissure: a randomized multicentre study. Color Dis. 2014;16:O360–6. https://doi.org/10.1111/codi.12615.

20. Bhattacharyya N, Tarsy D. Impact on quality of life of botulinum toxin treatments for spasmodic dysphonia and oromandibular dystonia. Arch Otolaryngol Head Neck Surg. 2001;127:389–92. https://doi.org/10.1001/archotol.127.4.389.
21. Borodic G, Bartley M, Slattery W, et al. Botulinum toxin for aberrant facial nerve regeneration: double-blind, placebo-controlled trial using subjective endpoints. Plast Reconstr Surg. 2005;116:36–43. https://doi.org/10.1097/01.PRS.0000169689.27829.C4.
22. Bradley JP, Barrow EM, Hapner ER, et al. Botulinum toxin-A dosing trends for adductor spasmodic dysphonia at a single institution over 10 years. J Voice. 2017;31:363–5. https://doi.org/10.1016/j.jvoice.2016.09.022.
23. Brans JW, Lindeboom R, Snoek JW, et al. Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. Neurology. 1996;46:1066–72. https://doi.org/10.1212/wnl.46.4.1066.
24. Brashear A, Lew MF, Dykstra DD, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology. 1999;53:1439–46. https://doi.org/10.1212/wnl.53.7.1439.
25. Brin MF, Kirby RS, Slavotinek A, et al. Pregnancy outcomes following exposure to onabotulinumtoxinA. Pharmacoepidemiol Drug Saf. 2016;25:179–87. https://doi.org/10.1002/pds.3920.
26. Brin MF, Lew MF, Adler CH, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology. 1999;53:1431–8. https://doi.org/10.1212/wnl.53.7.1431.
27. Brin MF, Lyons KE, Doucette J, et al. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. Neurology. 2001;56:1523–8. https://doi.org/10.1212/wnl.56.11.1523.
28. Brisinda G, Cadeddu F, Brandara F, et al. Randomized clinical trial comparing botulinum toxin injections with 0·2 per cent nitroglycerin ointment for chronic anal fissure. Br J Surg. 2007;94:162–7. https://doi.org/10.1002/bjs.5514.
29. Brisinda G, Maria G, Bentivoglio AR, et al. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. N Engl J Med. 1999;341:65–9. https://doi.org/10.1056/NEJM199907083410201.
30. Cadeddu F, Bentivoglio AR, Brandara F, et al. Outlet type constipation in Parkinson's disease: results of botulinum toxin treatment. Aliment Pharmacol Ther. 2005;22:997–1003. https://doi.org/10.1111/j.1365-2036.2005.02669.x.
31. Cakmur R, Ozturk V, Uzunel F, et al. Comparison of preseptal and pretarsal injections of botulinum toxin in the treatment of blepharospasm and hemifacial spasm. J Neurol. 2002;249:64–8. https://doi.org/10.1007/pl00007849.
32. Cardoso F. Botulinum toxin in parkinsonism: the when, how, and which for botulinum toxin injections. Toxicon. 2018;147:107–10. https://doi.org/10.1016/j.toxicon.2017.08.018.
33. Cenciarelli O, Riley PW, Baka A. Biosecurity threat posed by botulinum toxin. Toxins (Basel). 2019;11:681. https://doi.org/10.3390/toxins11120681.
34. Chapple C, Sievert K-D, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013;64:249–56. https://doi.org/10.1016/j.eururo.2013.04.001.
35. Charles D, Brashear A, Hauser RA, et al. Efficacy, tolerability, and immunogenicity of OnabotulinumtoxinA in a randomized, double-blind, placebo-controlled trial for cervical dystonia. Clin Neuropharmacol. 2012;35:208–14. https://doi.org/10.1097/WNF.0b013e31826538c7.
36. Charous SJ, Cornelia CL, Fan W. Jaw-opening dystonia: quality of life after botulinum toxin injections. Ear Nose Throat J. 2011;90:E9–E12. https://doi.org/10.1177/014556131109000210.
37. Chinnapongse R, Gullo K, Nemeth P, et al. Safety and efficacy of botulinum toxin type B for treatment of sialorrhea in Parkinson's disease: a prospective double-blind trial. Mov Disord. 2012;27:219–26. https://doi.org/10.1002/mds.23929.

38. Chuang Y-C, Kaufmann JH, Chancellor DD, et al. Bladder instillation of liposome encapsulated onabotulinumtoxina improves overactive bladder symptoms: a prospective, multicenter, double-blind, randomized trial. J Urol. 2014;192:1743–9. https://doi.org/10.1016/j.juro.2014.07.008.
39. Chuang Y-C, Kuo H-C. A prospective, multicenter, double-blind, randomized trial of bladder instillation of liposome formulation OnabotulinumtoxinA for interstitial cystitis/bladder pain syndrome. J Urol. 2017;198:376–82. https://doi.org/10.1016/j.juro.2017.02.021.
40. Cillino S, Raimondi G, Guépratte N, et al. Long-term efficacy of botulinum toxin A for treatment of blepharospasm, hemifacial spasm, and spastic entropion: a multicentre study using two drug-dose escalation indexes. Eye (Lond). 2010;24:600–7. https://doi.org/10.1038/eye.2009.192.
41. Clarke CE. Botulinum toxin type A in cerebellar tremor caused by multiple sclerosis. Eur J Neurol. 1997;4:68–71. https://doi.org/10.1111/j.1468-1331.1997.tb00301.x.
42. Colosimo C, Salvatori FM. Injection of the iliopsoas muscle with botulinum toxin in camptocormia. Mov Disord. 2009;24:316–7. https://doi.org/10.1002/mds.22249.
43. Comella CL, Jankovic J, Shannon KM, et al. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. Neurology. 2005;65:1423–9. https://doi.org/10.1212/01.wnl.0000183055.81056.5c.
44. Comella CL, Jankovic J, Truong DD, et al. Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia. J Neurol Sci. 2011;308:103–9. https://doi.org/10.1016/j.jns.2011.05.041.
45. Conill Tobías N, de Paula Vernetta C, García Callejo FJ, Marco Algarra J. Mioclonía palatal como causa de acúfeno objetivo. Uso de toxina botulínica: a propósito de un caso. Acta Otorrinolaringol Esp. 2012;63:391–2. https://doi.org/10.1016/j.otorri.2011.02.004.
46. Cooper L, Lui M, Nduka C. Botulinum toxin treatment for facial palsy: a systematic review. J Plast Reconstr Aesthet Surg. 2017;70:833–41. https://doi.org/10.1016/j.bjps.2017.01.009.
47. Cousins E, Ward A, Roffe C, et al. Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size. Clin Rehabil. 2010;24:501–13. https://doi.org/10.1177/0269215509358945.
48. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of OnabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011;60:742–50. https://doi.org/10.1016/j.eururo.2011.07.002.
49. Dang J, Carol Liu Y-C. Treatment of objective tinnitus with transpalatal Botox® injection in a pediatric patient with middle ear myoclonus: a case report. Int J Pediatr Otorhinolaryngol. 2019;116:22–4. https://doi.org/10.1016/j.ijporl.2018.09.024.
50. De Nardi P, Ortolano E, Radaelli G, Staudacher C. Comparison of glycerine trinitrate and botulinum toxin-a for the treatment of chronic anal fissure: long-term results. Dis Colon Rectum. 2006;49:427–32. https://doi.org/10.1007/s10350-005-0287-2.
51. de Sá Dantas Bezerra D, de Toledo LGM, da Silva Carramão S, et al. A prospective randomized clinical trial comparing two doses of AbobotulinumtoxinA for idiopathic overactive bladder. Neurourol Urodyn. 2018;38:nau.23884. https://doi.org/10.1002/nau.23884.
52. de Sèze M, Petit H, Gallien P, et al. Botulinum a toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol. 2002;42:56–62. https://doi.org/10.1016/S0302-2838(02)00209-9.
53. Defazio G, Livrea P, Lamberti P, et al. Isolated so-called apraxia of eyelid opening: report of 10 cases and a review of the literature. Eur Neurol. 1998;39:204–10. https://doi.org/10.1159/000007935.
54. Denys P, Le Normand L, Ghout I, et al. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. Eur Urol. 2012;61:520–9. https://doi.org/10.1016/j.eururo.2011.10.028.

55. Ding X, Huang L, Wang Q, et al. Clinical study of botulinum toxin A injection combined with spasmodic muscle therapeutic instrument on lower limb spasticity in patients with stroke. Exp Ther Med. 2017;13:3319–26. https://doi.org/10.3892/etm.2017.4376.
56. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol. 2010;184:2416–22. https://doi.org/10.1016/j.juro.2010.08.021.
57. do Nascimento Remigio AF, Salles AG, de Faria JCM, Ferreira MC. Comparison of the efficacy of OnabotulinumtoxinA and AbobotulinumtoxinA at the 1. Plast Reconstr Surg. 2015;135:239–49. https://doi.org/10.1097/PRS.0000000000000800.
58. Dohar JE. Sialorrhea & aspiration control – a minimally invasive strategy uncomplicated by anticholinergic drug tolerance or tachyphylaxis. Int J Pediatr Otorhinolaryngol. 2019;116:97–101. https://doi.org/10.1016/j.ijporl.2018.10.035.
59. Doherty KM, van de Warrenburg BP, Peralta MC, et al. Postural deformities in Parkinson's disease. Lancet Neurol. 2011;10:538–49. https://doi.org/10.1016/S1474-4422(11)70067-9.
60. Dunne JW, Gracies J-M, Hayes M, et al. A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. Clin Rehabil. 2012;26:787–97. https://doi.org/10.1177/0269215511432016.
61. Dutton JJ, Fowler AM. Botulinum toxin in ophthalmology. Surv Ophthalmol. 2007;52:13–31.
62. El-Bahnasy AE, Farahat YA, El-Bendary M, et al. A randomized controlled trail of bacillus Calmette-Guerin and botulinum toxin-A for the treatment of refractory interstitial cystitis. UroToday Int J. 2008;02. https://doi.org/10.3834/uij.1944-5784.2008.12.06.
63. Elble RJ. Tremor: clinical features, pathophysiology, and treatment. Neurol Clin N Am. 2009;27:679–95. https://doi.org/10.1016/j.ncl.2009.04.003.
64. Elovic EP, Munin MC, Kaňovský P, et al. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. Muscle Nerve. 2016;53:415–21. https://doi.org/10.1002/mus.24776.
65. Espay AJ, Vaughan JE, Shukla R, et al. Botulinum toxin type A for Levodopa-induced cervical dyskinesias in Parkinson's disease: unfavorable risk-benefit ratio. Mov Disord. 2011;26:913–4. https://doi.org/10.1002/mds.23522.
66. Evidente VGH, Fernandez HH, LeDoux MS, et al. A randomized, double-blind study of repeated incobotulinumtoxinA (Xeomin®) in cervical dystonia. J Neural Transm. 2013;120:1699–707. https://doi.org/10.1007/s00702-013-1048-3.
67. Ezzeddine D, Jit R, Katz N, et al. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc. 2002;55:920–3. https://doi.org/10.1067/mge.2002.124739.
68. Fernández E, Latasiewicz M, Pelegrin L, et al. Botulinum toxin for treating unilateral apraxia of eyelid opening in a patient with congenital myotonia. Arq Bras Oftalmol. 2017;80:330–1. https://doi.org/10.5935/0004-2749.20170081.
69. Fernandez HH, Lannon MC, Trieschmann ME, Friedman JH. Botulinum toxin type B for gait freezing in Parkinson's disease. Med Sci Monit. 2004;10:CR282–4.
70. Festen S, Gisbertz SS, van Schaagen F, Gerhards MF. Blinded randomized clinical trial of botulinum toxin versus isosorbide dinitrate ointment for treatment of anal fissure. Br J Surg. 2009;96:1393–9. https://doi.org/10.1002/bjs.6747.
71. Fietzek UM, Kossmehl P, Schelosky L, et al. Early botulinum toxin treatment for spastic pes equinovarus--a randomized double-blind placebo-controlled study. Eur J Neurol. 2014;21:1089–95. https://doi.org/10.1111/ene.12381.
72. Fietzek UM, Schroeteler FE, Ceballos-Baumann AO. Goal attainment after treatment of parkinsonian camptocormia with botulinum toxin. Mov Disord. 2009;24:2027–8. https://doi.org/10.1002/mds.22676.
73. Forget R, Tozlovanu V, Iancu A, Boghen D. Botulinum toxin improves lid opening delays in blepharospasm-associated apraxia of lid opening. Neurology. 2002;58:1843–6. https://doi.org/10.1212/wnl.58.12.1843.

74. Friedmacher F, Puri P. Comparison of posterior internal anal sphincter myectomy and intrasphincteric botulinum toxin injection for treatment of internal anal sphincter achalasia: a meta-analysis. Pediatr Surg Int. 2012;28:765–71. https://doi.org/10.1007/s00383-012-3123-5.
75. Furusawa Y, Mukai Y, Kawazoe T, et al. Long-term effect of repeated lidocaine injections into the external oblique for upper camptocormia in Parkinson's disease. Parkinsonism Relat Disord. 2013;19:350–4. https://doi.org/10.1016/j.parkreldis.2012.09.008.
76. Gallien P, Reymann J-M, Amarenco G, et al. Placebo controlled, randomised, double blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. J Neurol Neurosurg Psychiatry. 2005;76:1670–6. https://doi.org/10.1136/jnnp.2004.045765.
77. George EB, Cotton AC, Shneyder N, Jinnah HA. A strategy for managing flu-like symptoms after botulinum toxin injections. J Neurol. 2018;265:1932–3. https://doi.org/10.1007/s00415-018-8934-4.
78. Ghasemi M, Ansari M, Basiri K, Shaigannejad V. The effects of intradermal botulinum toxin type A injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci. 2014;19:106–11.
79. Ghei M, Maraj BH, Miller R, et al. Effects of botulinum toxin B on refractory detrusor overactivity: a randomized, double-blind, placebo controlled, crossover trial. J Urol. 2005;174:1873–7; discussion 1877. https://doi.org/10.1097/01.ju.0000177477.83991.88.
80. Giess R, Naumann M, Werner E, et al. Injections of botulinum toxin A into the salivary glands improve sialorrhoea in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2000;69:121–3. https://doi.org/10.1136/jnnp.69.1.121.
81. Gil RA, Hwynn N, Fabian T, et al. Botulinum toxin type A for the treatment of gastroparesis in Parkinson's disease patients. Parkinsonism Relat Disord. 2011;17:285–7. https://doi.org/10.1016/j.parkreldis.2011.01.007.
82. Giladi N. Medical treatment of freezing of gait. Mov Disord. 2008;23:S482–8. https://doi.org/10.1002/mds.21914.
83. Giladi N, Gurevich T, Shabtai H, et al. The effect of botulinum toxin injections to the calf muscles on freezing of gait in parkinsonism: a pilot study. J Neurol. 2001;248:572–6.
84. Giladi N, Honigman S. Botulinum toxin injections to one leg alleviate freezing of gait in a patient with Parkinson's disease. Mov Disord. 1997;12:1085–6. https://doi.org/10.1002/mds.870120641.
85. Girlanda P, Quartarone A, Sinicropi S, et al. Unilateral injection of botulinum toxin in blepharospasm: single fiber electromyography and blink reflex study. Mov Disord. 1996;11:27–31. https://doi.org/10.1002/mds.870110107.
86. Glover PH, Tang S, Whatley JZ, et al. High-dose circumferential chemodenervation of the internal anal sphincter: a new treatment modality for uncomplicated chronic anal fissure: a retrospective cohort study (with video). Int J Surg. 2015;23:1–4. https://doi.org/10.1016/j.ijsu.2015.08.076.
87. Gottsch HP, Miller JL, Yang CC, Berger RE. A pilot study of botulinum toxin for interstitial cystitis/painful bladder syndrome. Neurourol Urodyn. 2011;30:93–6. https://doi.org/10.1002/nau.20946.
88. Gracies J-M, Bayle N, Goldberg S, Simpson DM. Botulinum toxin type B in the spastic arm: a randomized, double-blind, placebo-controlled, preliminary study. Arch Phys Med Rehabil. 2014;95:1303–11. https://doi.org/10.1016/j.apmr.2014.03.016.
89. Gracies J-M, Brashear A, Jech R, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. Lancet Neurol. 2015;14:992–1001. https://doi.org/10.1016/S1474-4422(15)00216-1.
90. Gracies J-M, Esquenazi A, Brashear A, et al. Efficacy and safety of abobotulinumtoxinA in spastic lower limb. Neurology. 2017;89:2245–53. https://doi.org/10.1212/WNL.0000000000004687.

91. Greene P, Kang U, Fahn S, et al. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. Neurology. 1990;40:1213. https://doi.org/10.1212/WNL.40.8.1213.
92. Gurevich T, Peretz C, Moore O, et al. The effect of injecting botulinum toxin type A into the calf muscles on freezing of gait in Parkinson's disease: a double blind placebo-controlled pilot study. Mov Disord. 2007;22:880–3. https://doi.org/10.1002/mds.21396.
93. Gurey LE, Sinclair CF, Blitzer A. A new paradigm for the management of essential vocal tremor with botulinum toxin. Laryngoscope. 2013;123:2497–501. https://doi.org/10.1002/lary.24073.
94. Gusev YI, Banach M, Simonow A, et al. Efficacy and safety of botulinum type A toxin in adductor spasticity due to multiple sclerosis. J Musculoskelet Pain. 2008;16:175–88. https://doi.org/10.1080/10582450802161952.
95. Heckmann M, Ceballos-Baumann AO, Plewig G, Hyperhidrosis Study Group. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med. 2001;344:488–93. https://doi.org/10.1056/NEJM200102153440704.
96. Hernandez NC, Louis ED. Jaw tremor resulting in broken teeth: on the essential tremor spectrum. Tremor Other Hyperkinet Mov (N Y). 2015;5:354. https://doi.org/10.7916/D8T15339.
97. Hertegård S, Granqvist S, Lindestad P-Å. Botulinum toxin injections for essential voice tremor. Ann Otol Rhinol Laryngol. 2000;109:204–9. https://doi.org/10.1177/000348940010900216.
98. Hesse S, Mach H, Fröhlich S, et al. An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial. Clin Rehabil. 2012;26:237–45. https://doi.org/10.1177/0269215511421355.
99. Hirota N, Hirota M, Mezaki T. Dystonic frowning without blepharospasm. Parkinsonism Relat Disord. 2008;14:579–80. https://doi.org/10.1016/j.parkreldis.2007.12.001.
100. Hosp C, Naumann M, Hamm H. Botulinum toxin treatment of autonomic disorders: focal hyperhidrosis and Sialorrhea. Semin Neurol. 2016;36:020–8. https://doi.org/10.1055/s-0035-1571214.
101. Hyman N, Barnes M, Bhakta B, et al. Botulinum toxin (Dysport(R)) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry. 2000;68:707–12. https://doi.org/10.1136/jnnp.68.6.707.
102. Inoue K, Rogers JD. Botulinum toxin injection into Riolan's muscle: somatosensory 'trick'. Eur Neurol. 2007;58:138–41. https://doi.org/10.1159/000104713.
103. Intiso D, Basciani M, Santamato A, et al. Botulinum toxin type A for the treatment of neuropathic pain in neuro-rehabilitation. Toxins (Basel). 2015;7:2454–80. https://doi.org/10.3390/toxins7072454.
104. Jankovic J. Disease-oriented approach to botulinum toxin use. Toxicon. 2009;54:614–23. https://doi.org/10.1016/j.toxicon.2008.11.013.
105. Jankovic J. Botulinum toxin: state of the art. Mov Disord. 2017;32:1131–8. https://doi.org/10.1002/mds.27072.
106. Jankovic J. An update on new and unique uses of botulinum toxin in movement disorders. Toxicon. 2018;147:84–8. https://doi.org/10.1016/j.toxicon.2017.09.003.
107. Jankovic J, Comella C, Hanschmann A, Grafe S. Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin) in the treatment of blepharospasm-a randomized trial. Mov Disord. 2011;26:1521–8. https://doi.org/10.1002/mds.23658.
108. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. Neurology. 1987;37:616–23.
109. Jankovic J, Schwartz K. Botulinum toxin treatment of tremors. Neurology. 1991;41:1185. https://doi.org/10.1212/WNL.41.8.1185.
110. Jankovic J, Schwartz K, Clemence W, et al. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord. 1996;11:250–6. https://doi.org/10.1002/mds.870110306.

111. Jocson A, Lew M. Use of botulinum toxin in Parkinson's disease. 2019. https://doi.org/10.1016/j.parkreldis.2018.12.002.
112. Kaji R, Osako Y, Suyama K, et al. Botulinum toxin type A in post-stroke upper limb spasticity. Curr Med Res Opin. 2010;26:1983–92. https://doi.org/10.1185/03007995.2010.497103.
113. Kaji R, Osako Y, Suyama K, et al. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. J Neurol. 2010;257:1330–7. https://doi.org/10.1007/s00415-010-5526-3.
114. Kamel JT, Cordivari C, Catania S. Treatment of upper limb tremor with botulinum toxin: an individualized approach. Mov Disord Clin Pract. 2019;6:652–5. https://doi.org/10.1002/mdc3.12832.
115. Kaňovský P, Slawek J, Denes Z, et al. Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity. Clin Neuropharmacol. 2009;32:259–65. https://doi.org/10.1097/WNF.0b013e3181b13308.
116. Karp BI, Alter K. Botulinum toxin treatment of blepharospasm, orofacial/oromandibular dystonia, and hemifacial spasm. Semin Neurol. 2016;36:84–91. https://doi.org/10.1055/s-0036-1571952.
117. Kasyan G, Pushkar D. Randomized controlled trial for efficacy of botulinum toxin type A in treatment of patients suffering bladder pain syndrome/interstitial cystitis with hunners' lesions preliminary results. J Urol. 2012;187. https://doi.org/10.1016/j.juro.2012.02.912.
118. Kerzoncuf M, Viton J-M, Pellas F, et al. People post-stroke' postural sway improved by botulinum toxin: a multicenter randomized double-blind controlled trial. Arch Phys Med Rehabil. 2019. https://doi.org/10.1016/j.apmr.2019.04.024.
119. Krack P, Marion MH. "Apraxia of lid opening," a focal eyelid dystonia: clinical study of 32 patients. Mov Disord. 1994;9:610–5. https://doi.org/10.1002/mds.870090605.
120. Kuo H-C, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009;104:657–61. https://doi.org/10.1111/j.1464-410X.2009.08495.x.
121. Kuo H-C, Jiang Y-H, Tsai Y-C, Kuo Y-C. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment – a prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. Neurourol Urodyn. 2016;35:609–14. https://doi.org/10.1002/nau.22760.
122. Kwak CH, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol. 2000;57:1190–3.
123. Lagalla G, Millevolte M, Capecci M, et al. Botulinum toxin type A for drooling in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord. 2006;21:704–7. https://doi.org/10.1002/mds.20793.
124. Lagalla G, Millevolte M, Capecci M, et al. Long-lasting benefits of botulinum toxin type B in Parkinson's disease-related drooling. J Neurol. 2009;256:563–7. https://doi.org/10.1007/s00415-009-0085-1.
125. Lam K, Lau KK, So KK, et al. Can botulinum toxin decrease carer burden in long term care residents with upper limb spasticity? A randomized controlled study. J Am Med Dir Assoc. 2012;13:477–84. https://doi.org/10.1016/j.jamda.2012.03.005.
126. Lepore V, Defazio G, Acquistapace D, et al. Botulinum a toxin for the so-called apraxia of lid opening. Mov Disord. 1995;10:525–6. https://doi.org/10.1002/mds.870100425.
127. Lew MF, Adornato BT, Duane DD, et al. Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. Neurology. 1997;49:701–7. https://doi.org/10.1212/WNL.49.3.701.
128. Lew MF, Brashear A, Dashtipour K, et al. A 500 U/2 mL dilution of abobotulinumtoxinA vs. placebo: randomized study in cervical dystonia. Int J Neurosci. 2018;128:619–26. https://doi.org/10.1080/00207454.2017.1406935.
129. Liu H-B, Fan J-P, Lin S-Z, et al. Botox transient treatment of tinnitus due to stapedius myoclonus: case report. Clin Neurol Neurosurg. 2011;113:57–8. https://doi.org/10.1016/j.clineuro.2010.07.022.

130. Lotia M, Jankovic J. New and emerging medical therapies in Parkinson's disease. Expert Opin Pharmacother. 2016;19:1–15.
131. Lotia M, Jankovic J. Botulinum toxin for the treatment of tremor and tics. Semin Neurol. 2016;36:054–63. https://doi.org/10.1055/s-0035-1571217.
132. Louis ED, Rios E, Applegate LM, et al. Jaw tremor: prevalence and clinical correlates in three essential tremor case samples. Mov Disord. 2006;21:1872–8. https://doi.org/10.1002/mds.21069.
133. Lowe NJ, Yamauchi PS, Lask GP, et al. Efficacy and safety of botulinum toxin type A in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. Dermatol Surg. 2002;28:822–7. https://doi.org/10.1046/j.1524-4725.2002.02039.x.
134. Maanum G, Jahnsen R, Stanghelle JK, et al. Effects of botulinum toxin A in ambulant adults with spastic cerebral palsy: a randomized double-blind placebo controlled-trial. J Rehabil Med. 2011;43:338–47. https://doi.org/10.2340/16501977-0672.
135. Machado D, Martimbianco ALC, Bussadori SK, et al. Botulinum toxin type A for painful temporomandibular disorders: systematic review and meta-analysis. J Pain. 2019. https://doi.org/10.1016/j.jpain.2019.08.011.
136. Mancini F, Zangaglia R, Cristina S, et al. Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Mov Disord. 2003;18:685–8. https://doi.org/10.1002/mds.10420.
137. Manning J, Dwyer P, Rosamilia A, et al. A multicentre, prospective, randomised, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2014;25:593–9. https://doi.org/10.1007/s00192-013-2267-8.
138. Manrique D. Application of botulinum toxin to reduce the saliva in patients with amyotrophic lateral sclerosis. Braz J Otorhinolaryngol. 2005;71:566–9. S0034-72992005000500004.
139. Marchese MR, D'Alatri L, Bentivoglio AR, Paludetti G. OnabotulinumtoxinA for adductor spasmodic dysphonia (ADSD): functional results and the role of dosage. Toxicon. 2018;155:38–42. https://doi.org/10.1016/j.toxicon.2018.10.006.
140. Marciniak CM, Harvey RL, Gagnon CM, et al. Does botulinum toxin type A decrease pain and lessen disability in hemiplegic survivors of stroke with shoulder pain and spasticity?: a randomized, double-blind, placebo-controlled trial. Am J Phys Med Rehabil. 2012;91:1007–19. https://doi.org/10.1097/PHM.0b013e31826ecb02.
141. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology. 2001;56:605–10. https://doi.org/10.1212/WNL.56.5.605.
142. Matak I, Bölcskei K, Bach-Rojecky L, Helyes Z. Mechanisms of botulinum toxin type A action on pain. Toxins (Basel). 2019;11:459. https://doi.org/10.3390/toxins11080459.
143. McCrory P, Turner-Stokes L, Baguley IJ, et al. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes. J Rehabil Med. 2009;41:536–44. https://doi.org/10.2340/16501977-0366.
144. Mendes RA, Upton LG. Management of dystonia of the lateral pterygoid muscle with botulinum toxin A. Br J Oral Maxillofac Surg. 2009;47:481–3. https://doi.org/10.1016/j.bjoms.2008.08.010.
145. Mikaeli J, Bishehsari F, Montazeri G, et al. Injection of botulinum toxin before pneumatic dilatation in achalasia treatment: a randomized-controlled trial. Aliment Pharmacol Ther. 2006;24:983–9. https://doi.org/10.1111/j.1365-2036.2006.03083.x.
146. Mikaeli J, Fazel A, Montazeri G, et al. Randomized controlled trial comparing botulinum toxin injection to pneumatic dilatation for the treatment of achalasia. Aliment Pharmacol Ther. 2001;15:1389–96. https://doi.org/10.1046/j.1365-2036.2001.01065.x.
147. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. Am J Gastroenterol. 2002;97:1653–60. https://doi.org/10.1111/j.1572-0241.2002.05823.x.

148. Mittal SO, Lenka A, Jankovic J. Botulinum toxin for the treatment of tremor. 2019. https://doi.org/10.1016/j.parkreldis.2019.01.023.
149. Mittal SO, Machado D, Richardson D, et al. Botulinum toxin in Parkinson disease tremor. Mayo Clin Proc. 2017;92:1359–67. https://doi.org/10.1016/j.mayocp.2017.06.010.
150. Mittal SO, Machado D, Richardson D, et al. Botulinum toxin in essential hand tremor – a randomized double-blind placebo-controlled study with customized injection approach. Parkinsonism Relat Disord. 2018;56:65–9. https://doi.org/10.1016/j.parkreldis.2018.06.019.
151. Møller E, Bakke M, Dalager T, Werdelin LM. Oromandibular dystonia involving the lateral pterygoid muscles: four cases with different complexity. Mov Disord. 2007;22:785–90. https://doi.org/10.1002/mds.21304.
152. Monini S, De Carlo A, Biagini M, et al. Combined protocol for treatment of secondary effects from facial nerve palsy. Acta Otolaryngol. 2011;131:882–6. https://doi.org/10.3109/00016489.2011.577447.
153. Namin AW, Christopher KM, Eisenbeis JF. Botulinum toxin dosing trends in spasmodic dysphonia over a 20-year period. J Voice. 2017;31:107–10. https://doi.org/10.1016/j.jvoice.2016.01.006.
154. Narayanaswami P, Geisbush T, Tarulli A, et al. Drooling in Parkinson's disease: a randomized controlled trial of incobotulinum toxin A and meta-analysis of botulinum toxins. Parkinsonism Relat Disord. 2016;30:73–7. https://doi.org/10.1016/j.parkreldis.2016.07.001.
155. Nastasi L, Mostile G, Nicoletti A, et al. Effect of botulinum toxin treatment on quality of life in patients with isolated lingual dystonia and oromandibular dystonia affecting the tongue. J Neurol. 2016;263:1702–8. https://doi.org/10.1007/s00415-016-8185-1.
156. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ. 2001;323:596–9. https://doi.org/10.1136/bmj.323.7313.596.
157. Naumann M, So Y, Argoff CE, et al. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70:1707–14. https://doi.org/10.1212/01.wnl.0000311390.87642.d8.
158. Neville C, Venables V, Aslet M, et al. An objective assessment of botulinum toxin type A injection in the treatment of post-facial palsy synkinesis and hyperkinesis using the synkinesis assessment questionnaire. J Plast Reconstr Aesthet Surg. 2017;70:1624–8. https://doi.org/10.1016/j.bjps.2017.05.048.
159. Niemann N, Jankovic J. Botulinum toxin for the treatment of hand tremor. Toxins (Basel). 2018;10:299. https://doi.org/10.3390/toxins10070299.
160. Niemann N, Jankovic J. Treatment of tardive dyskinesia: a general overview with focus on the vesicular monoamine transporter 2 inhibitors. Drugs. 2018;78:525–41. https://doi.org/10.1007/s40265-018-0874-x.
161. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2017;197:S216–23. https://doi.org/10.1016/j.juro.2016.10.109.
162. Nüssgens Z, Roggenkämper P. Comparison of two botulinum-toxin preparations in the treatment of essential blepharospasm. Graefes Arch Clin Exp Ophthalmol. 1997;235:197–9.
163. Odergren T, Hjaltason H, Kaakkola S, et al. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. J Neurol Neurosurg Psychiatry. 1998;64:6–12. https://doi.org/10.1136/jnnp.64.1.6.
164. Okuzumi A, Kurosawa M, Hatano T, et al. Rapid dissemination of alpha-synuclein seeds through neural circuits in an in-vivo prion-like seeding experiment. Acta Neuropathol Commun. 2018;6:96. https://doi.org/10.1186/s40478-018-0587-0.
165. Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology. 2004;62:37–40. https://doi.org/10.1212/01.wnl.0000101713.81253.4c.

166. Ondo WG, Simmons JH, Shahid MH, et al. Onabotulinum toxin-A injections for sleep bruxism. Neurology. 2018;90:e559–64. https://doi.org/10.1212/WNL.0000000000004951.
167. Pacchetti C, Mancini F, Bulgheroni M, et al. Botulinum toxin treatment for functional disability induced by essential tremor. Neurol Sci. 2000;21:349–53. https://doi.org/10.1007/s100720070049.
168. Pahwa R, Busenbark K, Swanson-Hyland EF, et al. Botulinum toxin treatment of essential head tremor. Neurology. 1995;45:822–4. https://doi.org/10.1212/WNL.45.4.822.
169. Pandey S, Sarma N. Tremor in dystonia. Parkinsonism Relat Disord. 2016;29:3–9. https://doi.org/10.1016/j.parkreldis.2016.03.024.
170. Pandey S, Srivanitchapoom P, Kirubakaran R, Berman BD. Botulinum toxin for motor and phonic tics in Tourette's syndrome. Cochrane Database Syst Rev. 2018;1:CD012285. https://doi.org/10.1002/14651858.CD012285.pub2.
171. Panicker J, DasGupta R, Amit B. Neurourology. In: Bradley's neurology in clinical practice. 7th ed. London: Elsevier; 2016.
172. Papapetropoulos S, Singer C. Treatment of primary writing tremor with botulinum toxin type A injections. Clin Neuropharmacol. 2006;29:364–7. https://doi.org/10.1097/01.WNF.0000236765.00785.9C.
173. Pappert EJ, Germanson T, Myobloc/Neurobloc European Cervical Dystonia Study Group. Botulinum toxin type B vs. type A in toxin-naïve patients with cervical dystonia: randomized, double-blind, noninferiority trial. Mov Disord. 2008;23:510–7. https://doi.org/10.1002/mds.21724.
174. Park J, Park H. Botulinum toxin for the treatment of neuropathic pain. Toxins (Basel). 2017;9:260. https://doi.org/10.3390/toxins9090260.
175. Park YC, Lim JK, Lee DK, Yi SD. Botulinum a toxin treatment of hemifacial spasm and blepharospasm. J Korean Med Sci. 1993;8:334–40. https://doi.org/10.3346/jkms.1993.8.5.334.
176. Patel PN, Owen SR, Norton CP, et al. Outcomes of buccinator treatment with botulinum toxin in facial synkinesis. JAMA Facial Plast Surg. 2018;20:196. https://doi.org/10.1001/jamafacial.2017.1385.
177. Pedrero-Escalas MF, García-López I, Santiago-Pérez S, et al. Experiencia clínica en pacientes con síndrome de Meige primario y disfonía espasmódica. Acta Otorrinolaringol Esp. 2019;70:1–5. https://doi.org/10.1016/j.otorri.2017.11.007.
178. Penney SE, Bruce IA, Saeed SR. Botulinum toxin is effective and safe for palatal tremor: a report of five cases and a review of the literature. J Neurol. 2006;253:857–60. https://doi.org/10.1007/s00415-006-0039-9.
179. Persaud R, Garas G, Silva S, et al. An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions. JRSM Short Rep. 2013;4:10. https://doi.org/10.1177/2042533312472115.
180. Piccione F, Mancini E, Tonin P, Bizzarini M. Botulinum toxin treatment of apraxia of eyelid opening in progressive supranuclear palsy: report of two cases. Arch Phys Med Rehabil. 1997;78:525–9. https://doi.org/10.1016/s0003-9993(97)90169-6.
181. Pinto RA, Costa D, Morgado A, et al. Intratrigonal OnabotulinumtoxinA improves bladder symptoms and quality of life in patients with bladder pain syndrome/interstitial cystitis: a pilot, single center, randomized, double-blind, placebo controlled trial. J Urol. 2018;199:998–1003. https://doi.org/10.1016/j.juro.2017.10.018.
182. Pittock SJ, Moore AP, Hardiman O, et al. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis. 2003;15:289–300. https://doi.org/10.1159/000069495.
183. Poewe W, Burbaud P, Castelnovo G, et al. Efficacy and safety of abobotulinumtoxinA liquid formulation in cervical dystonia: a randomized-controlled trial. Mov Disord. 2016;31:1649–57. https://doi.org/10.1002/mds.26760.
184. Poewe W, Deuschl G, Nebe A, et al. What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo controlled, dose ranging

study using Dysport. J Neurol Neurosurg Psychiatry. 1998;64:13–7. https://doi.org/10.1136/jnnp.64.1.13.
185. Pullman SL. Approach to the treatment of limb disorders with botulinum toxin A. Arch Neurol. 1996;53:617. https://doi.org/10.1001/archneur.1996.00550070055012.
186. Rahimi F, Bee C, Debicki D, et al. Effectiveness of BoNT A in Parkinson's disease upper limb tremor management. Can J Neurol Sci/J Can des Sci Neurol. 2013;40:663–9. https://doi.org/10.1017/S031716710001489X.
187. Rahimi F, Samotus O, Lee J, Jog M. Effective management of upper limb Parkinsonian tremor by IncobotulinumtoxinA injections using sensor-based biomechanical patterns. Tremor Other Hyperkinet Mov (N Y). 2015;5:348. https://doi.org/10.7916/D8BP0270.
188. Raina GB, Cersosimo MG, Folgar SS, et al. Holmes tremor: clinical description, lesion localization, and treatment in a series of 29 cases. Neurology. 2016;86:931–8. https://doi.org/10.1212/WNL.0000000000002440.
189. Ramirez-Castaneda J, Jankovic J. Long-term efficacy, safety, and side effect profile of botulinum toxin in dystonia: a 20-year follow-up. Toxicon. 2014;90:344–8. https://doi.org/10.1016/j.toxicon.2014.07.009.
190. Ramzan Z, Nassri AB. The role of botulinum toxin injection in the management of achalasia. Curr Opin Gastroenterol. 2013;29:468–73. https://doi.org/10.1097/MOG.0b013e328362292a.
191. Richardson D, Sheean G, Werring D, et al. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. J Neurol Neurosurg Psychiatry. 2000;69:499–506. https://doi.org/10.1136/jnnp.69.4.499.
192. Roggenkämper P, Jost WH, Bihari K, et al. Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm. 2006;113:303–12. https://doi.org/10.1007/s00702-005-0323-3.
193. Rogozhin AA, Pang KK, Bukharaeva E, et al. Recovery of mouse neuromuscular junctions from single and repeated injections of botulinum neurotoxin A. J Physiol. 2008;586:3163–82. https://doi.org/10.1113/jphysiol.2008.153569.
194. Rosales RL, Efendy F, Teleg ES, et al. Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: a meta-analysis. J Neurol Sci. 2016;371:6–14. https://doi.org/10.1016/j.jns.2016.10.005.
195. Rosales RL, Kong KH, Goh KJ, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2012;26:812–21. https://doi.org/10.1177/1545968311430824.
196. Rovner E, Kennelly M, Schulte-Baukloh H, et al. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxina in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourol Urodyn. 2011;30:556–62. https://doi.org/10.1002/nau.21021.
197. Ruiz-de-León-Hernández G, Díaz-Sánchez R-M, Torres-Lagares D, et al. Botulinum toxin A for patients with orofacial dystonia: prospective, observational, single-centre study. Int J Oral Maxillofac Surg. 2018;47:386–91. https://doi.org/10.1016/j.ijom.2017.11.006.
198. Rumbach A, Aiken P, Novakovic D. Outcome measurement in the treatment of spasmodic dysphonia: a systematic review of the literature. J Voice. 2018. https://doi.org/10.1016/j.jvoice.2018.03.011.
199. Rystedt A, Zetterberg L, Burman J, et al. A comparison of Botox 100 U/mL and Dysport 100 U/mL using dose conversion ratio 1. Clin Neuropharmacol. 2015;38:170–6. https://doi.org/10.1097/WNF.0000000000000101.
200. Saad J, Gourdeau A. A direct comparison of OnabotulinumtoxinA (Botox) and IncobotulinumtoxinA (Xeomin) in the treatment of benign essential blepharospasm. J Neuro-Ophthalmol. 2014;34:233–6. https://doi.org/10.1097/WNO.0000000000000110.
201. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. J Urol. 2007;177:2231–6. https://doi.org/10.1016/j.juro.2007.01.130.

202. Sahebally SM, Meshkat B, Walsh SR, Beddy D. Botulinum toxin injection *vs* topical nitrates for chronic anal fissure: an updated systematic review and meta-analysis of randomized controlled trials. Color Dis. 2018;20:6–15. https://doi.org/10.1111/codi.13969.
203. Samotus O, Lee J, Jog M. Long-term tremor therapy for Parkinson and essential tremor with sensor-guided botulinum toxin type A injections. PLoS One. 2017;12:e0178670. https://doi.org/10.1371/journal.pone.0178670.
204. Samotus O, Rahimi F, Lee J, Jog M. Functional ability improved in essential tremor by IncobotulinumtoxinA injections using kinematically determined biomechanical patterns – a new future. PLoS One. 2016;11:e0153739. https://doi.org/10.1371/journal.pone.0153739.
205. Sampaio C, Ferreira JJ, Simões F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A--Dysport and Botox--assuming a ratio of 4:1. Mov Disord. 1997;12:1013–8. https://doi.org/10.1002/mds.870120627.
206. Schneider SA, Bhatia KP. The entity of jaw tremor and dystonia. Mov Disord. 2007;22:1491–5. https://doi.org/10.1002/mds.21531.
207. Schneider SA, Edwards MJ, Cordivari C, et al. Botulinum toxin A may be efficacious as treatment for jaw tremor in Parkinson's disease. Mov Disord. 2006;21:1722–4. https://doi.org/10.1002/mds.21019.
208. Schnider P, Binder M, Auff E, et al. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Br J Dermatol. 1997;136:548–52.
209. Schurch B, de Sèze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005;174:196–200. https://doi.org/10.1097/01.ju.0000162035.73977.1c.
210. Scott K, Shannon R, Roche-Green A. Management of sialorrhea in amyotrophic lateral sclerosis #299. J Palliat Med. 2016;19:110–1. https://doi.org/10.1089/jpm.2015.0360.
211. Shaw LC, Price CIM, van Wijck FMJ, et al. Botulinum toxin for the upper limb after stroke (BoTULS) trial. Stroke. 2011;42:1371–9. https://doi.org/10.1161/STROKEAHA.110.582197.
212. Shinn JR, Nwabueze NN, Du L, et al. Treatment patterns and outcomes in botulinum therapy for patients with facial synkinesis. JAMA Facial Plast Surg. 2019;21:244. https://doi.org/10.1001/jamafacial.2018.1962.
213. Shoffel-Havakuk H, Rosow DE, Lava CX, et al. Common practices in botulinum toxin injection for spasmodic dysphonia treatment: a national survey. Laryngoscope. 2019;129:1650–6. https://doi.org/10.1002/lary.27696.
214. Shogan AN, Rogers DJ, Hartnick CJ, Kerschner JE. Use of botulinum toxin in pediatric otolaryngology and laryngology. 2014. https://doi.org/10.1016/j.ijporl.2014.06.026.
215. Simpson DM, Blitzer A, Brashear A, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70:1699–706. https://doi.org/10.1212/01.wnl.0000311389.26145.95.
216. Simpson DM, Gracies JM, Yablon SA, et al. Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatry. 2008;80:380–5. https://doi.org/10.1136/jnnp.2008.159657.
217. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86:1818–26. https://doi.org/10.1212/WNL.0000000000002560.
218. Singer C, Papapetropoulos S. A comparison of jaw-closing and jaw-opening idiopathic oromandibular dystonia. Parkinsonism Relat Disord. 2006;12:115–8. https://doi.org/10.1016/j.parkreldis.2005.07.007.

219. Singer C, Papapetropoulos S, Spielholz NI. Primary writing tremor: report of a case successfully treated with botulinum toxin A injections and discussion of underlying mechanism. Mov Disord. 2005;20:1387–8. https://doi.org/10.1002/mds.20590.
220. Sterling JL, Schey R, Malik Z. The role of botulinum toxin injections for esophageal motility disorders. Curr Treat Options Gastroenterol. 2018;16:528–40. https://doi.org/10.1007/s11938-018-0212-0.
221. Stone CA, O'Leary N. Systematic review of the effectiveness of botulinum toxin or radiotherapy for sialorrhea in patients with amyotrophic lateral sclerosis. J Pain Symptom Manag. 2009;37:246–58. https://doi.org/10.1016/j.jpainsymman.2008.02.006.
222. Sulica L, Louis ED. Clinical characteristics of essential voice tremor: a study of 34 cases. Laryngoscope. 2010;120:516–28. https://doi.org/10.1002/lary.20702.
223. Sun L-C, Chen R, Fu C, et al. Efficacy and safety of botulinum toxin type A for limb spasticity after stroke: a meta-analysis of randomized controlled trials. Biomed Res Int. 2019;2019:1–17. https://doi.org/10.1155/2019/8329306.
224. Syan R, Briggs MA, Olivas JC, et al. Transvaginal ultrasound guided trigone and bladder injection: a cadaveric feasibility study for a novel route of intradetrusor chemodenervation. Investig Clin Urol. 2019;60:40. https://doi.org/10.4111/icu.2019.60.1.40.
225. Taha RM, Farahat A, Bahnasy M, et al. A prospective randomized study of intravesical pentosan polysulfate and botulinum toxin-A for the treatment of painful bladder syndrome/interstitial cystitis. Eur Urol Suppl. 2010;2(9):213.
226. Tan E-K, Jankovic J. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. Neurology. 1999;53:2102. https://doi.org/10.1212/WNL.53.9.2102.
227. Tao W, Yan D, Li J-H, Shi Z-H. Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients. J Phys Ther Sci. 2015;27:759–62. https://doi.org/10.1589/jpts.27.759.
228. Tarsy D, Ro SI. Unusual position-sensitive jaw tremor responsive to botulinum toxin. Mov Disord. 2006;21:277–8. https://doi.org/10.1002/mds.20737.
229. Tassorelli C, De Icco R, Alfonsi E, et al. Botulinum toxin type A potentiates the effect of neuromotor rehabilitation of Pisa syndrome in Parkinson disease: a placebo controlled study. Parkinsonism Relat Disord. 2014;20:1140–4. https://doi.org/10.1016/j.parkreldis.2014.07.015.
230. Thenganatt MA, Jankovic J. Recent advances in understanding and managing Tourette syndrome. F1000Research. 2016;5:152. https://doi.org/10.12688/f1000research.7424.1.
231. Thomas AJ, Larson MO, Braden S, et al. Effect of 3 commercially available botulinum toxin neuromodulators on facial synkinesis. JAMA Facial Plast Surg. 2018;20:141. https://doi.org/10.1001/jamafacial.2017.1393.
232. Tincello DG, Kenyon S, Abrams KR, et al. Botulinum toxin A versus placebo for refractory detrusor overactivity in women: a randomised blinded placebo-controlled trial of 240 women (the RELAX study). Eur Urol. 2012;62:507–14. https://doi.org/10.1016/j.eururo.2011.12.056.
233. Tintner R, Gross R, Winzer UF, et al. Autonomic function after botulinum toxin type A or B: a double-blind, randomized trial. Neurology. 2005;65:765–7. https://doi.org/10.1212/01.wnl.0000174433.76707.8c.
234. Trosch RM, Pullman SL. Botulinum toxin A injections for the treatment of hand tremors. Mov Disord. 1994;9:601–9. https://doi.org/10.1002/mds.870090604.
235. Truong D, Comella C, Fernandez HH, et al. Efficacy and safety of purified botulinum toxin type A (Dysport®) for the treatment of benign essential blepharospasm: a randomized, placebo-controlled, phase II trial. Parkinsonism Relat Disord. 2008;14:407–14. https://doi.org/10.1016/j.parkreldis.2007.11.003.
236. Truong D, Duane DD, Jankovic J, et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord. 2005;20:783–91. https://doi.org/10.1002/mds.20403.

237. Truong DD, Gollomp SM, Jankovic J, et al. Sustained efficacy and safety of repeated incobotulinumtoxinA (Xeomin(®)) injections in blepharospasm. J Neural Transm. 2013;120:1345–53. https://doi.org/10.1007/s00702-013-0998-9.
238. Turner-Stokes L, Baguley I, De Graaff S, et al. Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: a secondary analysis from a double-blind placebo-controlled randomized clinical trial. J Rehabil Med. 2010;42:81–9. https://doi.org/10.2340/16501977-0474.
239. van Hoeij FB, Tack JF, Pandolfino JE, et al. Complications of botulinum toxin injections for treatment of esophageal motility disorders†. Dis Esophagus. 2016;30:1–5. https://doi.org/10.1111/dote.12491.
240. Vastik M, Hok P, Hlustik P, et al. Botulinum toxin treatment of freezing of gait in Parkinson's disease patients as reflected in functional magnetic resonance imaging of leg movement. Neuro Endocrinol Lett. 2016;37:147–53.
241. Verma A, Steele J. Botulinum toxin improves sialorrhea and quality of living in bulbar amyotrophic lateral sclerosis. Muscle Nerve. 2006;34:235–7. https://doi.org/10.1002/mus.20545.
242. Verplancke D, Snape S, Salisbury CF, et al. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury. Clin Rehabil. 2005;19:117–25. https://doi.org/10.1191/0269215505cr827oa.
243. Vielotte J. Effectiveness of intramuscular injections of botulinum toxin in the treatment of disabling cerebellar tremor of the hand. Ann Phys Rehabil Med. 2016;59:e142. https://doi.org/10.1016/J.REHAB.2016.07.319.
244. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 1: treatment of levodopa-induced dyskinesia. Drugs. 2016;76:759–77. https://doi.org/10.1007/s40265-016-0566-3.
245. Vijayakumar D, Jankovic J. Medical treatment of blepharospasm. Expert Rev Ophthalmol. 2018;13:233–43. https://doi.org/10.1080/17469899.2018.1503535.
246. Vives-Rodriguez A, Kim CY, Louis ED. Primary writing tremor. Tremor Other Hyperkinet Mov (N Y). 2018;8:586. https://doi.org/10.7916/D8T740ZZ.
247. von Coelln R, Raible A, Gasser T, Asmus F. Ultrasound-guided injection of the iliopsoas muscle with botulinum toxin in camptocormia. Mov Disord. 2008;23:889–92. https://doi.org/10.1002/mds.21967.
248. Vurture G, Peyronnet B, Feigin A, et al. Outcomes of intradetrusor onabotulinum toxin A injection in patients with Parkinson's disease. Neurourol Urodyn. 2018;37:2669–77. https://doi.org/10.1002/nau.23717.
249. Wabbels B, Reichel G, Fulford-Smith A, et al. Double-blind, randomised, parallel group pilot study comparing two botulinum toxin type A products for the treatment of blepharospasm. J Neural Transm. 2011;118:233–9. https://doi.org/10.1007/s00702-010-0529-x.
250. Wagle Shukla A, Malaty I. Botulinum toxin therapy for Parkinson's disease. Semin Neurol. 2017;37:193–204. https://doi.org/10.1055/s-0037-1602246.
251. Wald A, Bharucha AE, Cosman BC, Whitehead WE. ACG clinical guideline: management of benign anorectal disorders. Am J Gastroenterol. 2014;109:1141–57; (Quiz) 1058. https://doi.org/10.1038/ajg.2014.190.
252. Wan TK, Chen JT, Wang PC. EMG-guided salpingopharyngeus Botox injection for palatal myoclonus. B-ENT. 2013;9:67–9.
253. Wang L, Li Y-M, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. Dig Dis Sci. 2009;54:2303–11. https://doi.org/10.1007/s10620-008-0637-8.
254. Ward A, Wissel J, Borg J, et al. Functional goal achievement in post-stroke spasticity patients: the BOTOXÂ® Economic Spasticity Trial (BEST). J Rehabil Med. 2014;46:504–13. https://doi.org/10.2340/16501977-1817.
255. Warrick P, Dromey C, Irish JC, et al. Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor: a crossover design study of unilateral versus bilateral injection. Laryngoscope. 2000;110:1366–74. https://doi.org/10.1097/00005537-200008000-00028.

256. Wijemanne S, Jankovic J. Hand, foot, and spine deformities in parkinsonian disorders. J Neural Transm. 2019;126:253–64. https://doi.org/10.1007/s00702-019-01986-1.
257. Wijemanne S, Jimenez-Shahed J. Improvement in dystonic camptocormia following botulinum toxin injection to the external oblique muscle. Parkinsonism Relat Disord. 2014;20:1106–7. https://doi.org/10.1016/j.parkreldis.2014.06.002.
258. Winterholler MG, Erbguth FJ, Wolf S, Kat S. Botulinum toxin for the treatment of sialorrhoea in ALS: serious side effects of a transductal approach. J Neurol Neurosurg Psychiatry. 2001;70:417–8. https://doi.org/10.1136/jnnp.70.3.417.
259. Wissel J, Masuhr F, Schelosky L, et al. Quantitative assessment of botulinum toxin treatment in 43 patients with head tremor. Mov Disord. 1997;12:722–6. https://doi.org/10.1002/mds.870120516.
260. Wu C-J, Lian Y-J, Zheng Y-K, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32:443–50. https://doi.org/10.1177/0333102412441721.
261. Xiao L, Mackey S, Hui H, et al. Subcutaneous injection of botulinum toxin A is beneficial in postherpetic neuralgia. Pain Med. 2010;11:1827–33. https://doi.org/10.1111/j.1526-4637.2010.01003.x.
262. Yaltho TC, Jankovic J. The many faces of hemifacial spasm: differential diagnosis of unilateral facial spasms. Mov Disord. 2011;26:1582–92. https://doi.org/10.1002/mds.23692.
263. Yao G, Lam K, Perry K, et al. Crystal structure of the receptor-binding domain of botulinum neurotoxin type HA, also known as type FA or H. Toxins (Basel). 2017;9:93. https://doi.org/10.3390/toxins9030093.
264. Yi Y, Kim K, Yi Y, et al. Botulinum toxin type A injection for cervical dystonia in adults with dyskinetic cerebral palsy. Toxins (Basel). 2018;10:203. https://doi.org/10.3390/toxins10050203.
265. Yoshimura DM, Aminoff MJ, Tami TA, Scott AB. Treatment of hemifacial spasm with botulinum toxin. Muscle Nerve. 1992;15:1045–9. https://doi.org/10.1002/mus.880150909.
266. Yuan RY, Sheu JJ, Yu JM, et al. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology. 2009;72:1473–8. https://doi.org/10.1212/01.wnl.0000345968.05959.cf.
267. Yun JY, Kim JW, Kim H-T, et al. Dysport and Botox at a ratio of 2.5:1 units in cervical dystonia: a double-blind, randomized study. Mov Disord. 2015;30:206–13. https://doi.org/10.1002/mds.26085.
268. Zakin E, Simpson D. Botulinum toxin in management of limb tremor. Toxins (Basel). 2017;9:365. https://doi.org/10.3390/toxins9110365.
269. Zaninotto G, Annese V, Costantini M, et al. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. Ann Surg. 2004;239:364–70. https://doi.org/10.1097/01.sla.0000114217.52941.c5.
270. Zhang H, Lian Y, Ma Y, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J Headache Pain. 2014;15:65. https://doi.org/10.1186/1129-2377-15-65.
271. Zhang L-L, Canning SD, Wang X-P. Freezing of gait in Parkinsonism and its potential drug treatment. Curr Neuropharmacol. 2016;14:302–6.
272. Zúñiga C, Piedimonte F, Díaz S, Micheli F. Acute treatment of trigeminal neuralgia with onabotulinum toxin A. Clin Neuropharmacol. 2013;36:146–50. https://doi.org/10.1097/WNF.0b013e31829cb60e.