Curr Neurol Neurosci Rep (2015) 15:511
DOI 10.1007/s11910-014-0511-3

MOVEMENT DISORDERS (M OKUN, SECTION EDITOR)

An Update on the Use of Botulinum Toxin Therapy in Parkinson's Disease

Reversa Mills · Laxman Bahroo · Fernando Pagan

Published online: 20 November 2014

Abstract Botulinum toxin (BoNT) has gained widespread use in a variety of neurological conditions. Parkinson's disease is a complex neurodegenerative disorder manifested by motor and non-motor symptoms that can cause significant disability. BoNT has been used to effectively treat a variety of symptoms related to Parkinson's disease. This review will examine the current therapeutic indications of BoNT use in the following disorders related to Parkinson's disease: cervical dystonia, blepharospasm and lid apraxia, focal hand dystonia, foot dystonia, laryngeal dystonia, oromandibular dystonia, camptocormia, hand and jaw tremor, sialorrhea, hyperhidrosis, dysphagia, constipation, and overactive bladder.

Keywords Parkinson's disease · Non-motor symptoms · Botulinum toxin · Cervical dystonia · Foot dystonia · Focal hand dystonia · Laryngeal dystonia · Oromandibular dystonia · Blepharospasm · Lid apraxia · Camptocormia · Tremor · Sialorrhea · Hyperhidrosis · Dysphagia · Constipation · Overactive bladder

Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disorder that may be characterized by the following cardinal motor features: rest tremor, bradykinesia, rigidity, and loss of postural reflexes. The pathological hallmark of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta and by the presence of alpha synuclein-positive neuronal inclusions known as Lewy bodies though there is degeneration in several motor and non-motor brain circuits. PD is the second most common neurodegenerative disorder following Alzheimer's disease.

In the USA, there are over 60,000 individuals diagnosed with PD every year and there are over 1,000,000 individuals living with PD. According to an analysis in 2009, the prevalence rates of diagnosed PD in the United States (US) population by age range from 0.01 % under the age of 45 to 1.2 % over the age of 65 [1]. Undiagnosed PD remains an issue and as a result the prevalence rates are likely higher than reported. This analysis also concluded that approximately $14 billion in medical expenses was consumed annually [1]. This was an estimated $8.1 billion in excess of the cost predicted for a population without PD [1]. As the size of our elderly population continues to increase, it is expected that the economic burden of chronic diseases such as PD will continue to rise [1]. Given that we have no treatments at this time to cure or slow the progression of PD, it is imperative that we provide treatments to help improve the quality of life of patients with PD [1].

PD is a disorder marked not only by motor features but also by the presence of non-motor symptoms including sleep disorders, fatigue, pain, urinary dysfunction, constipation, sialorrhea, cognitive dysfunction, and depression/anxiety (Table 1). The effect of non-motor symptoms on quality of life can be more significant than the motor features [2, 3]; therefore, it is essential that we recognize these non-motor symptoms to help alleviate these symptoms and improve the quality of life for patients with PD.

This article is part of the Topical Collection on *Movement Disorders*

R. Mills · L. Bahroo · F. Pagan (✉)
Movement Disorders Division, Department of Neurology, Georgetown University Hospital, 3900 Reservoir Rd, NW, 7 PHC, Washington, DC 20007, USA
e-mail: FPOGAN01@gunet.georgetown.edu

R. Mills
e-mail: reversa.mills@gunet.georgetown.edu

L. Bahroo
e-mail: LXBY@gunet.georgetown.edu

Table 1 Summary of common non-motor symptoms in Parkinson's disease and prevalence (%) data from the PRIAMO study

Domains	Domain prevalence (%) PRIAMO *N*=1072	Non-motor symptoms
Sensory issues	94.7	Pain (shoulder, back pain, dystonia)
		Parasthesias
		Anosmia
		Visual disturbance (diplopia, blurred vision)
Sleep disorders	64.1	Sleep fragmentation
		Rapid eye movement (REM) sleep behavior disorder
		Restless legs syndrome
		Excessive daytime sleepiness
		Altered sleep-wake cycle
Fatigue	58.1	
Autonomic issues	88.3	Orthostatic hypotension
		Urgency/nocturia
		Erectile dysfunction
		Sweating
		Rhinorrhea
		Sialorrhea
		Dry eyes
Neuropsychiatric	66.8	Depression
		Anxiety
		Panic attacks
		Apathy/loss of motivation
		Fear, panic attacks
		Dependent personality
		Hallucinations
		Confusion
		Cognitive impairment
Gastrointestinal	61	Dysphagia
		Constipation
		Gastric reflux
		Nausea

Table 1 adapted from [2] Barone P, et al. Movement Disorders. 2009;24:1641–1649 and [3] Chaudhuri KR, et al. Parkinsonism Related Disorders. 2011;17:717–723

Botulinum Toxin Treatment for Non-motor Symptoms in Parkinson's Disease

The motor symptoms of PD including tremor, bradykinesia, rigidity, and gait difficulty can generally improve with dopaminergic therapy, anticholinergic agents, and surgical options. However, many of the non-motor features and other disabling symptoms of PD including dysarthria, postural instability, freezing of gait, and autonomic disability are not as responsive to these conservative treatments [4, 5]. Botulinum toxin (BoNT) has been successfully used to treat a variety of symptoms related to PD including cervical dystonia, foot dystonia, focal hand dystonia, laryngeal dystonia, oromandibular dystonia, blepharospasm and lid apraxia, camptocormia, hand and jaw tremor, sialorrhea, hyperhidrosis, dysphagia, constipation, and overactive bladder [5, 6, 7••, 8–10] (Table 2).

Botulinum Toxin

Clostridium (*C.*) *botulinum* is the bacterium that releases the most potent neurotoxin known and is responsible for causing botulism. There are seven different serotypes of *C. botulinum* (A–G), but only the serotypes A, B, and E cause human botulism via colonization of the lower GI tract after ingestion of contaminated food. Botulism can present as muscle weakness, paralysis, dysarthria, dysphagia, constipation, and urinary retention. Death can occur in up to 10–25 % of cases [11].

BoNT inhibits the release of acetylcholine (ACh) at the neuromuscular junction (NMJ) thereby blocking neuromuscular conduction and muscle contraction. The normal release of ACh at the NMJ occurs through the formation of the synaptic fusion complex of ACh vesicles bound to the presynaptic membrane by soluble *N*-ethylmaleimide-sensitive

Table 2 Common disorders treated with botulinum toxin and level of evidence for the safety and efficacy of botulinum toxin use

Disorders treated with botulinum toxin	Level of evidence of safety and efficacy
Dystonia	
Cervical dystonia	Level A recommendation
Blepharospasm and lid apraxia	Level A recommendation
Focal hand dystonia	Level B recommendation
Laryngeal dystonia	Level C recommendation
Oromandibular dystonia	Level C recommendation
Lower limb dystonia	Level U recommendation
Camptocormia	Level U recommendation
Tremor	
Hand and jaw tremor	Level U recommendation
Secretory disorders	
Hyperhidrosis	Level A recommendation
Sialorrhea	Level B recommendation
Gastrointestinal and genitourinary disorders	
Overactive bladder	Level A recommendation
Dysphagia	Level U recommendation
Constipation	Level U recommendation

Level A: established as effective (requires at least two consistent class I studies); Level B: probably effective (requires at least one class I study or at least two consistent class II studies); Level C: possibly effective (requires at least one class II study or two consistent class III studies); Level U: inadequate or conflicting data, treatment is unproven

Adapted from:

[5] Jankovic, J. Toxicon.2009;54:614–623.

[7••] Hallett, M et al. Toxicon. 2013;67:94–114.

[8] Simpson, DM et al. Neurology. 2008;70:1699–1706.

[9] Naumann, M et al. Toxicon. 2013;67:141–152.

AAN Classification of Quality of Evidence for Clinical Trials (see AAN classification of evidence for therapeutic intervention on the Neurology Web site at *www.neurology.org/site/misc/NeurologyFiller.pdf*) is shown as follows:

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. The following are required:

a. Primary outcome(s) clearly defined

b. Exclusion/inclusion criteria clearly defined

c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias

d. Relevant baseline characteristics presented and substantially equivalent among treatment groups or appropriate statistical adjustment for differences

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority

2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)

3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment

4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers

Class II: A randomized controlled trial in a representative population that lacks one criterion from a–d above OR a prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d.

Class III: All other controlled trials including well-defined natural history controls or patients serving as own controls in a representative population, where outcome assessment is independently assessed or independently derived by objective outcome measurement

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion. Studies not meeting class I, II, or III criteria including consensus or expert opinion.

factor attachment protein receptor (SNARE) proteins. SNARE proteins form a *trans* complex of three proteins including syntaxin 1, SNAP-25, and synaptobrevin which mediate the docking and exocytosis of ACh vesicles at the presynaptic nerve terminal. The mechanism of action of the various serotypes of BoNT are similar in that all cleave the SNARE proteins; however, BoNT A, C, and E cleave SNAP-25 and BoNT B, D, F, and G cleave synaptobrevin [12].

Formulations of Botulinum Toxin

BoNT type A was first used clinically for the treatment of strabismus in 1977 [11]. The US Food and Drug Administration (FDA) approved BoNT type A for the treatment of strabismus, blepharospasm, and hemifacial spasm in patients 12 years or older in 1989. In 2000, it was approved for the treatment of cervical dystonia, and in 2002, it received approval for cosmetic purposes [11].

There are currently four neurotoxin products approved for therapeutic use in the USA. The type A formulations include Onabotulinumtoxin A (Botox, Allergan Inc.), Abobotulinumtoxin A (Dysport, Ipsen Ltd), and Incobotulinumtoxin A (Xeomin, Merz Pharmaceuticals). The one available BoNT type B is Rimabotulinum B (Myobloc, Solstice Neurosciences Inc).

Onabotulinumtoxin A is approved for the treatment of chronic migraine, upper limb spasticity in adult patients, cervical dystonia in adult patients, severe axillary hyperhidrosis, urinary incontinence due to detrusor overactivity, blepharospasm associated with dystonia, and strabismus in patients 12 years of age or older. Abobotulinumtoxin A is indicated for the treatment of cervical dystonia in adults, and Incobotulinumtoxin A is approved for the treatment of adults with cervical dystonia and blepharospasm. Rimabotulinum B is approved for the treatment of cervical dystonia in adults [13•]. Each neurotoxin product has its own unique characteristic based on molecular weight, complexing proteins, onset of action, and diffusing properties. Therefore, it is important to note that these agents are not therapeutically interchangeable [13•].

In this review, we will describe the most common clinical uses of BoNT therapy in PD. The injection technique, preparation, and dosage of each type of BoNT will not be described as this is beyond the scope of this publication.

Dystonia

Dystonia is defined as a movement disorder characterized by sustained or intermittent, involuntary muscle contractions causing twisting, repetitive movements, or abnormal postures [5, 14, 15•]. The etiology of dystonia can be varied and includes idiopathic causes, secondary dystonia, or genetic in origin [13•]. Focal dystonia affects a specific area of the body and can present as cervical dystonia, limb dystonia, focal hand dystonia, laryngeal dystonia, oromandibular dystonia, blepharospasm, and/or camptocormia [13•]. Dystonia is common in PD patients and is present in up to 60 % of patients, with a predilection for young-onset PD [16, 5]. Dystonia can also occur as a motor complication of levodopa therapy, and dystonic contractions can occur with wearing off and as a peak-dose dyskinesia [17, 5].

Cervical Dystonia

Cervical dystonia (CD) is also known as spasmodic torticollis and is the most common form of focal dystonia resulting from involuntary contractions of muscles in the neck and shoulders. CD is characterized by abnormal posturing of the head and neck in the form of tilting, flexion, or extension movements of the head combined with elevation or anterior placement of the shoulders [18]. CD may present as a sustained posture, spasm, jerks, or tremor.

CD is classified according to the dominant head position or movement. Rotary (simple) torticollis is the most common type with other patterns including laterocollis, retrocollis, and complex torticollis [19]. Anterocollis is the most common posture associated with parkinsonism, specifically PD and multiple system atrophy [5]. Neck or shoulder pain is present in up to 70 % of patients [19]. Although spontaneous remissions of CD have been reported, in the majority of cases, CD is a lifelong disorder that waxes and wanes in severity and in some cases may progress to segmental or generalized dystonia [18].

BoNT is considered the most effective treatment for CD. Based on the results of eight double-blind, randomized controlled clinical trials meeting the criteria for class I studies, the efficacy and safety of BoNT types A and B for the treatment of CD have been established [7••, 8]. These studies provided level A evidence supporting all four BoNT for the treatment of CD [7••, 8]. The most common side effects reported in these studies included dysphagia and neck weakness. The dosing equivalency between the four brands of neurotoxin has not been well established, and controlled randomized comparative dosing trials would be beneficial for clinicians.

Blepharospasm and Lid Apraxia

Blepharospasm is a focal dystonia characterized by involuntary, intermittent, or persistent forceful eyelid closure due to spasmodic contractions of the orbicularis muscles. Benign essential blepharospasm describes the involuntary contractions of only the orbital and periorbital muscles. However, some patients may also have spasm of other facial, oromandibular, pharyngeal, laryngeal, or cervical muscles, which is a form of cranio-cervical dystonia called Meige syndrome. Blepharospasm typically begins in the fifth to seventh decade of life and is more common in women [18]. Blepharospasm usually occurs in more advanced stages of PD but can also occur in atypical parkinsonism.

In the presence of parkinsonism, blepharospasm is often associated with apraxia of eyelid opening, defined as an intermittent inability to voluntarily open the eyelids due to levator inhibition, abnormal contraction of the pretarsal orbicularis oculi, or eyelid freezing [5]. BoNT has a

longstanding history in the treatment of blepharospasm and is considered a first-line therapy. In an evidenced-based review of the current clinical data available, it was concluded that Onabotulinumtoxin A and Incobotulinumtoxin A are effective in the treatment of blepharospasm (level A recommendation) and Abobotulinumtoxin A is probably effective (level B recommendation). There were no quality studies to confirm the efficacy of Rimabotulinumtoxin B contributing to a level U recommendation [7••].

Upper Extremity Dystonia

Focal dystonia in the upper extremities often commences in the hands and is usually task specific. As the disorder progresses, the dystonia can have segmental spread and affect other tasks [18]. The most common upper extremity finding is Parkinsonian writer's cramp characterized by an isolated grip on the pen and minor flexion of the arm in contrast to abnormal contractions of the fingers and arm as seen in typical dystonic writer's cramp [20]. Striatal hand characterized by metacarpophalangeal flexion, interphalangeal joint extension, and ulnar deviation may also be seen in untreated PD patients with advanced disease [21].

BoNT is currently the treatment of choice for focal hand dystonia. The evidence to support the use of BoNT for limb dystonia (upper extremities) is based on the data from one class I study [22] and one class II study [23] of Abobotulinumtoxin A and two class II studies of Onabotulinumtoxin A. [24, 25]. The most common side effect reported was focal weakness. Currently, there are no published randomized, double-blind controlled studies with the use of Incobotulinumtoxin A or Rimabotulinumtoxin A. In an evidence-based review of BoNT in the treatment of focal hand dystonia, both Abobotulinumtoxin A and Onabotulinumtoxin A were considered to be possibly effective (level B recommendation); however, there was insufficient evidence to confirm the efficacy of Incobotulinumtoxin A and Rimabotulinumtoxin B (level U recommendation) [7••]. Although all of these formulations are currently used in clinical practice, further studies are needed to establish dosing equivalency of all four brands and the effectiveness of Incobotulinumtoxin A and Rimabotulinumtoxin B.

Lower Limb Dystonia

Foot dystonia is the most common dystonia present at the onset of PD and may present as the initial manifestation of the disease [26, 5]. In young-onset PD, foot dystonia often presents as exercise-induced toe cramping that can progress to inversion of the foot and disability. The presence of exercise-induced foot dystonia should raise the suspicion for young-onset PD [20]. Striatal deformities of the foot with unilateral equinovarus dystonic posture of the foot and extension of the great toe can be seen in early-onset PD and up to 10 % of untreated patients with advanced PD [21]. Foot dystonia has also been associated with levodopa therapy as wearing off dystonia and peak-dose dyskinesia [17]. "Off" "dystonia has been reported to occur in approximately 30 % of patients treated with longstanding levodopa therapy [20].

In an open-label pilot study, BoNT was used to treat "off" painful dystonia induced by levodopa in 30 patients with PD. All patients had improvement in pain in 10 days with no reported side effects [27]. There are currently no class I studies confirming the efficacy and safety of BoNT for the treatment of foot dystonia. Although BoNT is widely used off label for the treatment of foot dystonia, further studies are needed to provide high-quality evidence to support BoNT as an effective treatment modality.

Laryngeal Dystonia

A hallmark feature of PD is hypophonia characterized by reduced voice intensity and speech audibility. Individuals with PD commonly present with many other speech and voice impairments including spasmodic dysphonia, which is a task-specific focal dystonia of the larynx caused by irregular and uncontrolled vocal spasms disrupting the normal flow of speech. There are two main types of spasmodic dysphonia. Adductor spasmodic dysphonia is characterized by irregular hyperadduction of the vocal folds during speech resulting in a strained voice. Abductor spasmodic dysphonia is characterized by irregular abnormal abductor spasms during speech resulting in breathy interruptions or whispering. Some patients may have signs of both adductor and abductor spasms.

BoNT has been used for the treatment of both forms of laryngeal dystonia for over 30 years. There is one class I study that supports the use of Onabotulinumtoxin A for the treatment of adductor spasmodic dysphonia that showed improvement in the measured outcomes of 13 patients treated with BoNT type A [28]. The main side effects reported were excessive breathiness, mild bleeding, and vocal fold edema. There are several class III studies [29–32] of Onabolutinumtoxin A and one class III study [33] of Rimabotulinumtoxin B. Based on the evidence of these studies, Onabotulinumtoxin A was considered to be possibly effective (level C recommendation) for the treatment of adductor laryngeal dystonia, and a level U recommendation was given for the other three formulations due to insufficient data [7••]. More studies are needed to determine the appropriate dosing recommendations for the various types of BoNT and to establish the effectiveness of BoNT in the treatment of abductor spasmodic dysphonia [7••].

Oromandibular Dystonia

Oromandibular dystonia (OMD) is characterized by involuntary repetitive spasms mainly involving masticatory muscles but often includes lingual and pharyngeal muscles [34]. Clinically, OMD can be classified as having jaw-closing, jaw-opening, jaw-deviation dystonia, or a combination of these irregular movements. OMD can be idiopathic, tardive, or secondary to other movement disorders [34, 35]. Bruxism is a form of OMD presenting clinically as jaw clenching and tooth grinding and can result in tooth destruction, jaw pain, and headaches. Bruxism can be seen in patients with parkinsonism and can significantly affect quality of life due to its effect on speech and swallowing and cosmetically can be socially embarrassing [34].

BoNT has been used to treat OMD and has been most effective in treating jaw-deviation and jaw-closing dystonia as well as bruxism. Injections are typically given into bilateral masseters and temporalis muscles for these types of OMD. Jaw-opening dystonia is more difficult to treat and usually includes injections in the external pterygoid as well [18]. Based on the evidence of one class II study with Onabotulinumtoxin A [36] and one class II study with Abobotulinumtoxin A [37], these toxins are considered possibly effective (level C recommendation) whereas there was insufficient data to determine the efficacy of Inconobotulintoxin A and Rimabotulinumtoxin B (level U recommendation) for the treatment of OMD [7••]. However, more studies are needed to evaluate the treatment response between the different formulations of BoNT and the various subtypes of OMD.

Camptocormia

Camptorcormia is characterized by abnormal posture of the trunk manifested by anteflexion of the thoracolumbar spine that can be seen on sitting or more noticeably with walking that resolves in the recumbent position [5, 38]. Camptocormia is seen in a wide range of disorders including neurodegenerative disorders, dystonias, peripheral nervous system, and musculoskeletal disorders. The exact pathophysiology of camptocormia is still not fully understood. The prevalence in PD has been reported between 4.1 and 17.6 % [38]. Camptorcormia is a disabling condition that can severely impair mobility with complete loss of ambulation, causing patients to be wheel-chair bound.

The treatment of camptocormia has been difficult as levodopa and anti-spasmodic agents have been of limited benefit. BoNT has been used in the treatment of this condition. In one study of patients with camptocormia, 9 of 11 patients with PD and camptocormia received BoNT injections with Onabotulinumtoxin A into the rectus abdominus muscles with notable improvement in 4 of the 9 patients [39]. There is currently insufficient evidence to support or disprove the use of BoNT for camptocormia. More quality studies are needed to establish the efficacy and safety of BoNT therapy for this condition.

Hand and Jaw Tremor

Tremor is the most common presenting feature in PD and can be the most difficult symptom to treat. PD patients can present with a resting tremor as well as a postural and kinetic tremor which is often more troublesome as this re-emergent tremor can interfere with various tasks including holding a cup or a newspaper as well as other activities of daily life. In addition to the hand tremor, PD patients can often have tremor affecting the chin, lips, jaw, and tongue [5]. Although treatment with levodopa and dopamine agonists can significantly improve the cardinal features of PD, tremor can be more difficult to respond to conventional therapy. Anticholinergic medications can also be used to treat tremor in PD; however, these medications have severe side effects including urinary retention, xerostomia, and cognitive dysfunction [40].

Given PD tremor can be focal and asymmetric in presentation, BoNT may be beneficial for the treatment of PD-related tremor. There have been limited studies investigating the efficacy of BoNT in the treatment of PD-related tremor. Four studies with relatively small sample sizes have reported the use of BoNT in PD-related tremor [40–44]. These studies showed no significant changes in clinical rating scales or other objective measurements in patients with PD-related tremor. However, BoNT has been shown to be effective in the treatment of essential hand tremor based on the evidence of two double-blind placebo-controlled studies [45, 46].

In an open-label pilot study, injection of BoNT into the bilateral masseter muscles of three PD patients resulted in significant improvement in jaw tremor [47]. BoNT is currently not indicated or widely accepted as a treatment for PD tremor. There is currently insufficient published data to confirm the effectiveness of BoNT, and further studies are needed to demonstrate efficacy of BoNT for the treatment of PD-related tremor.

Sialorrhea

Sialorrhea or drooling is defined as the overflow of saliva from the mouth due to excessive production of saliva, inability to retain saliva within the mouth, or impaired swallowing [48]. Sialorrhea is a common symptom of PD affecting nearly 75 % of patients [5]. Drooling can negatively impact a patient's quality of life due to social embarrassment, infection of skin around the mouth, and increased risk of aspiration-related lung infections [49]. Sialorrhea in PD is not likely due to increased saliva production but rather to dysregulation of salivary function as a result of dysfunction of the salivary

parasympathetic ganglia in combination with impaired swallowing and forward head posture [50]. Oral anticholinergic agents are effective for the treatment of sialorrhea but are frequently associated with side effects and not well tolerated in patients with PD.

The mechanism of action of BoNT is not limited to the neuromuscular junction and may extend to the inhibition of the release of acetylcholine at autonomic nerve terminals, thereby reducing saliva production and outflow from the salivary glands [51]. Several studies provide evidence for the safety and efficacy of BoNT type A in the reduction of sialorrhea in PD [52–54]. In a double-blind, placebo-controlled, parallel group study, BoNT type B was injected into the parotid and submandibular glands of patients with PD and effectively improved sialorrhea [55]. Another study evaluated BoNT type A versus type B in the treatment of cervical dystonia and found a significant increase in dry mouth in patients treated for cervical dystonia with BoNT type B as compared to BoNT type A [56]. Possible side effects of BoNT include dysphagia and xerostomia. Ultrasound-guided injections may improve the efficacy of BoNT treatment of sialorrhea [57]. Based on the level of evidence, Abobotulinumtoxin A and Rimabotulinumtoxin B are considered probably effective for the treatment of sialorrhea (level B recommendation); however, there is insufficient published data to confirm the efficacy of Inconobotulinumtoxin A (level U recommendation) [9].

Hyperhidrosis

Hyperhidrosis (excessive sweating) is common in PD and a recent analysis reported hyperhidrosis in 64 % of patients with PD as compared to 12.5 % of controls [58]. Patient's symptoms occurred more often during "off" periods and in "on" periods with dyskinesias and did not seem to correlate with severity of disease. Patients also reported significant social and emotional disturbance due to hyperhidrosis.

Although BoNT has not been specifically studied for the treatment of sweating disturbances related to PD, there has been research confirming the efficacy of BoNT for the treatment of essential hyperhidrosis. Essential hyperhidrosis is described as excessive sweating of the palms, feet, or axillae [5, 59]. In a review of neurotoxin treatment of secretory disorders, a level A recommendation was given for the use of BoNT in the treatment of axillary hyperhidrosis [9]. Future research is needed to validate the efficacy and safety of BoNT therapy for hyperhidrosis related to PD.

Dysphagia

Oropharyngeal dysphagia is well recognized in patients with PD. Swallowing difficulties can occur early in the course of the disease and is often under reported by patients. History and examination frequently underestimate the severity and prevalence of dysphagia in PD as compared to videofluoroscopy [50]. A number of reports suggest that videofluoroscopy identified silent aspiration occurring in 15–20 % of asymptomatic PD patients and 36 % of symptomatic PD patients [60–62]. In a study examining a non-invasive technique to detect subclinical swallowing difficulties, asymptomatic patients with PD were found to have a prolonged oral and pharyngeal phase with multiple swallow attempts [50]. There are multiple theories for the etiology of dysphagia in PD and include achalasia, impairment of the motor nucleus of the vagus, presence of Lewy bodies in the myenteric plexus of the esophagus, and forward neck posture [5].

Achalasia is defined as the loss of peristalsis and an inability of the lower esophageal sphincter to reach maximal relaxation [63]. Pneumatic dilation of the distal esophagus is a commonly applied non-surgical therapy for achalasia. Heller's cardiomyotomy is the standard surgical therapy and involves an incision on the serosal surface of the esophagus under the gastroesophageal junction [63]. Since 1995, several studies have demonstrated the effectiveness of endoscopic injections of BoNT into the lower esophageal sphincter quadrants for the treatment of achalasia [64–69]. Side effects reported were mild and included transitory chest pain, gastroesophageal reflux, and cutaneous rash [63]. Advantages of BoNT therapy over pneumatic dilation or cardiomyotomy are fewer complications of the technique, safer to be used in high-risk patients with multiple co-morbidities, and the ability to treat patients in an outpatient setting [63]. However, further studies are needed to confirm the safety and efficacy of BoNT use for dysphagia.

Constipation

Constipation is defined as less than three bowel movements per week and an occurrence of one of the following in a minimum of 25 % of the time: hard bowel movements, difficulty having a bowel movement, or sense of inadequate defecation [70]. Constipation is five times more common in PD than in the normal population and is considered one of the most bothersome non-motor symptoms of PD [5, 71]. Constipation in PD may be due to slow transit, pelvic floor dysfunction, or a combination of both. Pelvic floor dysfunction is characterized by functional obstruction at the pelvic outlet due to failure of the puborectalis muscle to relax during defecation or paradoxical contraction [70].

The paradoxical puborectalis contraction may represent a form of focal dystonia and has been suggested as a possible mechanism of constipation in PD [72, 5]. The effectiveness of BoNT for the treatment of constipation in PD has been demonstrated in two open-label studies using transrectal ultrasound guidance to inject the puborectalis muscle [73, 74].

Both studies showed a decrease in anal tone during straining on assessment with anorectal manometry. Further double-blind, placebo-controlled, randomized trials are needed to establish the safety and efficacy of the use of BoNT in the treatment of constipation in patients with PD.

Overactive Bladder

Bladder dysfunction is one of the most common autonomic disorders seen in PD with a reported prevalence of 38 to 71 % [75]. However, it is difficult to distinguish the effects of PD on bladder dysfunction versus the results of prostatic hyperplasia and stress urinary incontinence, also seen in men and women over age 65. Overactive bladder is the most common form of bladder dysfunction in PD and leads to nocturia, which has been reported in over 60 % of PD patients [76]. The prevalence of urinary frequency is 33–54 %, and urinary incontinence is 26 % in men and 28 % in women [76].

Detrusor overactivity is considered to be the main contributing factor causing overactive bladder in PD patients [75]. There are several reports supporting the use of BoNT injections for the treatment of overactive bladder associated with neurogenic detrusor overactivity [77–79]. BoNT therapy has been shown to increase bladder capacity and improve urgency and incontinence. BoNT therapy for the treatment of neurogenic detrusor overactivity was given a level A recommendation by the Therapeutics and Technology Assessment Subcommittee of the AAN, based on the review of two class I studies [10].

Side Effects of Treatment

In a summary of published studies of efficacy, safety, and side effect profile of long-term BoNT therapy, the most common side effects reported for BoNT treatment for cervical dystonia include dysphagia, neck muscle weakness, hoarseness, and dry mouth [80]. Frequently reported adverse events for blepharospasm include ptosis, facial asymmetry, dry eyes, and injection site bruising [80]. These adverse events associated with long-term exposure to BoNT therapy were minor and self-limiting. In addition to weakness of injected muscles, local pain, and bruising, systemic side effects have been reported including flu-like symptoms. Flu-like symptoms have been reported in 1.7–20 % of patients treated with BoNT type A and in 5–55 % of patients treated with BoNT type B [81]. It is possible that the increased frequency of flu-like symptoms seen in BoNT type B could be due to the higher antigenicity seen with BoNT type B compared to type A, although this theory has not been proven. The mechanism of flu-like symptoms following BoNT is not clearly identified but may be due to the introduction of a foreign protein with BoNT injections inciting an inflammatory response [82]. Although previously thought that immunogenicity was a major factor of non-responsiveness to BoNT treatment, more often a lack of response may be due to other factors including inadequate dosing or incorrect muscle selection [80]. Long-term treatment with BoNT can provide safe and effective symptomatic treatment and may also provide long-term benefits that modify the natural course of the disease [80, 83].

Treatment Alternatives

BoNT is considered a first-line therapy for the treatment of cervical dystonia, blepharospasm, and focal dystonia due to its effectiveness and decreased potential for systemic side effects [8]. Oral medications are recommended for segmental and generalized dystonia and can also be used as adjunctive therapy to BoNT for more symptomatic relief [15]. Oral medications that can be used to treat dystonia include trihexyphenidyl, baclofen, benzodiazepines, carbidopa-levodopa, muscle relaxants, sodium oxybate, tetrabenazine, clozapine, carbamazepine, oxcarbazepine, zolpidem, and pregabalin [15]. Surgical treatments for dystonia refractory to medications and BoNT therapies include deep brain stimulation, selective peripheral denervation, intrathecal baclofen infusions, and orofacial plastic surgeries. Other non-pharmacologic treatments include physical therapy, devices, or braces that utilize sensory tricks such as dental braces or eyelid crutches attached to glasses, transcranial magnetic stimulation, and transcranial alternating current stimulation [15]. Further studies are needed to confirm the efficacy and tolerability of these non-invasive treatments.

Conclusion

PD is a progressive neurodegenerative disorder characterized by a multitude of motor and non-motor symptoms that can have a significant impact on quality of life. Since the discovery of botulinum neurotoxin and its inhibitory action on neuromuscular transmission, the application of the use of BoNT has grown to encompass a wide variety of diseases. Various bothersome symptoms of PD including dystonia, involuntary spasms, and autonomic and urinary dysfunction have been shown to be amenable to BoNT therapy. BoNT is the treatment of choice for cervical dystonia, focal hand dystonia, blepharospasm, axillary hyperhidrosis, and detrusor overactivity. Further studies are needed to establish the efficacy of BoNT treatment for foot dystonia, abductor spasmodic dysphonia, camptocormia, PD-related tremor, dysphagia, and constipation. There is also a need for a more standardized dosing recommendation for the treatment of the various disorders with regard to dilution optimization for the various

formulations of BoNT, which may be beneficial in improving response rates to treatment and limiting side effects. BoNT therapy has the potential to radically alter the lives of individuals with PD through symptomatic improvement, and all avenues of research should be approached to further advance our understanding of its current and future applicable use.

Compliance with Ethics Guidelines

Conflict of Interest Reversa Mills declares no conflict of interest.

Laxman Bahroo has received consultancy fees from Merz and honoraria payments and paid travel accommodations from Allergan. Dr. Bahroo has also received consultancy fees, honoraria payments, and paid travel accommodations from Ipsen and US World Meds. Fernando Pagan has received board membership payments from TEVA, US World Meds, Lunbeck, and Merz. Dr. Pagan has also received consultancy fees from TEVA, US World Meds, Lunbeck, Merz, and Acadia. He also has received grants from US World Meds, Merz, Teva, and Medtronic as well as honoraria payments from TEVA, US World Meds, Lunbeck, Merz, Acadia, and Novartis. Dr. Pagan also has received paid travel accommodations from Teva, Acadia, Lunbeck, US World Meds, and Merz.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A. The current and projected economic burden of Parkinson's disease in the United States: economic burden of PD in the US. Mov Disord. 2013;28:311–8.
2. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009;24:1641–9.
3. Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: the non-motor issues. Parkinsonism Relat Disord. 2011;17:717–23.
4. Diamond A, Jankovic J. Treatment of advanced Parkinson's disease. Expert Rev Neurother. 2006;6:1181–97.
5. Jankovic J. Disease-oriented approach to botulinum toxin use. Toxicon. 2009;54:614–23.
6. Sheffield JK, Jankovic J. Botulinum toxin in the treatment of tremors, dystonias, sialorrhea and other symptoms associated with Parkinson's disease. Expert Rev Neurother. 2007;7:637–47.
7. •• Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon. 2013;67:94–114. *This review provided recommendations for the therapeutic use of botulinum toxin based on various levels of evidence of available clinical studies supporting the efficacy and safety of each indication. Botulinum toxins were evaluated by the serotype A and B and also each formulation was studied individually. Recommendations based on the level of clinical evidence were presented for the treatment of various movement disorders including blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, limb dystonia, laryngeal dystonia, tics and essential tremor.*
8. 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.
9. Naumann M, Dressler D, Hallett M, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. Toxicon Off J Int Soc Toxinology. 2013;67:141–52.
10. 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.
11. Lacy BE, Weiser K, Kennedy A. Botulinum toxin and gastrointestinal tract disorders: panacea, placebo, or pathway to the future? Gastroenterol Hepatol. 2008;4:283.
12. Charles D, Gill CE. Neurotoxin injection for movement disorders. Contin Minneap Minn. 2010;16:131–57.
13. • Truong D. Botulinum toxins in the treatment of primary focal dystonias. J Neurol Sci. 2012;316:9–14. *This article reviews each formulation of Botulinum toxin type A and B for the treatment of various forms of focal dystonia. Clinical trials are presented comparing the safety, efficacy and duration of effect of the various formulations of botulinum toxin. Botulinum toxin therapy is considered to be first line therapy for the treatment of focal dystonia.*
14. Albanese A et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord Off J Mov Disord Soc. 2013;28:863–73.
15. • Thenganatt MA, Jankovic J. Treatment of dystonia. Neurotherapeutics. 2014;11:139–52. *This review details the various treatment options for dystonia including oral medications, botulinum toxin, surgical procedures including Deep Brain stimulation, physical and other types of therapies. Clinical trials of botulinum toxin in the treatment of various forms of dystonia are presented with varying levels of supporting evidence. This article concluded that a combination of therapies is most effective in the treatment of dystonia.*
16. Jankovic J, Tintner R. Dystonia and parkinsonism. Parkinsonism Relat Disord. 2001;8:109–21.
17. Jankovic J, Stacy M. Medical management of levodopa-associated motor complications in patients with Parkinson's disease. CNS Drugs. 2007;21:677–92.
18. Hallett M, Benecke R, Blitzer A, Comella CL. Treatment of focal dystonias with botulinum neurotoxin. Toxicon. 2009;54:628–33.
19. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. Mov Disord Off J Mov Disord Soc. 1991;6:119–26.
20. Tolosa E, Compta Y. Dystonia in Parkinson's disease. J Neurol. 2006;253 Suppl 7:VII7–13.
21. Ashour R, Tintner R, Jankovic J. Striatal deformities of the hand and foot in Parkinson's disease. Lancet Neurol. 2005;4:423–31.
22. Kruisdijk JJM, Koelman JHTM, OngerboerdeVisser BW, de Haan RJ, Speelman JD. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. J Neurol Neurosurg Psychiatry. 2007;78:264–70.
23. Contarino MF, Kruisdijk JJM, Koster L, et al. Sensory integration in writer's cramp: comparison with controls and evaluation of botulinum toxin effect. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2007;118:2195–206.
24. Tsui JK, Bhatt M, Calne S, Calne DB. Botulinum toxin in the treatment of writer's cramp: a double-blind study. Neurology. 1993;43:183–5.
25. Yoshimura DM, Aminoff MJ, Olney RK. Botulinum toxin therapy for limb dystonias. Neurology. 1992;42:627–30.

26. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord Off J Mov Disord Soc. 2005;20 Suppl 11:S11–16.
27. Pacchetti C, Albani G, Martignoni E, et al. 'Off' painful dystonia in Parkinson's disease treated with botulinum toxin. Mov Disord Off J Mov Disord Soc. 1995;10:333–6.
28. Troung DD, Rontal M, Rolnick M, Aronson AE, Mistura K. Double-blind controlled study of botulinum toxin in adductor spasmodic dysphonia. Laryngoscope. 1991;101:630–4.
29. Adams SG, Hunt EJ, Irish JC, et al. Comparison of botulinum toxin injection procedures in adductor spasmodic dysphonia. J Otolaryngol. 1995;24:345–51.
30. Finnegan EM, Luschei ES, Gordon JD, Barkmeier JM, Hoffman HT. Increased stability of airflow following botulinum toxin injection. Laryngoscope. 1999;109:1300–6.
31. Ludlow CL, Naunton RF, Sedory SE, Schulz GM, Hallett M. Effects of botulinum toxin injections on speech in adductor spasmodic dysphonia. Neurology. 1988;38:1220–5.
32. Wong DL, Adams SG, Irish JC, et al. Effect of neuromuscular activity on the response to botulinum toxin injections in spasmodic dysphonia. J Otolaryngol. 1995;24:209–16.
33. Adler CH, Bansberg SF, Krein-Jones K, Hentz JG. Safety and efficacy of botulinum toxin type B (Myobloc) in adductor spasmodic dysphonia. Mov Disord Off J Mov Disord Soc. 2004;19:1075–9.
34. Sinclair CF, Gurey LE, Blitzer A. Oromandibular dystonia: long-term management with botulinum toxin: management of OMD with botulinum toxin. Laryngoscope. 2013;123:3078–83.
35. Lee KH. Oromandibular dystonia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104:491–6.
36. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. Neurology. 1987;37:616–23.
37. Lee SJ, McCall WD, Kim YK, Chung SC, Chung JW. Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial. Am J Phys Med Rehabil Assoc Acad Physiatr. 2010;89:16–23.
38. Peeraully T, Tan E-K. Camptocormia in Parkinson's disease: dystonia or myopathy? Basal Ganglia. 2012;2:1–3.
39. Azher SN, Jankovic J. Camptocormia: pathogenesis, classification, and response to therapy. Neurology. 2005;65:355–9.
40. Rahimi F, Bee C, Debicki D, et al. Effectiveness of BoNT A in Parkinson's disease upper limb tremor management. Can J Neurol Sci. 2013;40:663–9.
41. Jankovic J, Schwartz K. Botulinum toxin treatment of tremors. Neurology. 1991;41:1185–8.
42. Pullman SL, Greene P, Fahn S, Pedersen SF. Approach to the treatment of limb disorders with botulinum toxin A. Experience with 187 patients. Arch Neurol. 1996;53:617–24.
43. Trosch RM, Pullman SL. Botulinum toxin A injections for the treatment of hand tremors. Mov Disord Off J Mov Disord Soc. 1994;9:601–9.
44. Henderson JM, Ghika JA, Van Melle G, Haller E, Einstein R. Botulinum toxin A in non-dystonic tremors. Eur Neurol. 1996;36:29–35.
45. Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord Off J Mov Disord Soc. 1996;11:250–6.
46. 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.
47. Schneider SA, Edwards MJ, Cordivari C, Macleod WN, Bhatia KP. Botulinum toxin A may be efficacious as treatment for jaw tremor in Parkinson's disease. Mov Disord Off J Mov Disord Soc. 2006;21:1722–4.
48. Meningaud J-P, Pitak-Arnnop P, Chikhani L, Bertrand J-C. Drooling of saliva: a review of the etiology and management options. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101:48–57.
49. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79:368–76.
50. Pinnington LL, Muhiddin KA, Ellis RE, Playford ED. Non-invasive assessment of swallowing and respiration in Parkinson's disease. J Neurol. 2000;247:773–7.
51. Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG. Long-lasting benefits of botulinum toxin type B in Parkinson's disease-related drooling. J Neurol. 2009;256:563–7.
52. Lipp A, Trottenberg T, Schink T, Kupsch A, Arnold G. A randomized trial of botulinum toxin A for treatment of drooling. Neurology. 2003;61:1279–81.
53. 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 Off J Mov Disord Soc. 2003;18:685–8.
54. Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG. Botulinum toxin type A for drooling in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord Off J Mov Disord Soc. 2006;21:704–7.
55. 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.
56. Tintner R, Gross R, Winzer UF, Smalky KA, Jankovic J. Autonomic function after botulinum toxin type A or B: a double-blind, randomized trial. Neurology. 2005;65:765–7.
57. Dogu O, Apaydin D, Sevim S, Talas DU, Aral M. Ultrasound-guided versus 'blind' intraparotid injections of botulinum toxin-A for the treatment of sialorrhoea in patients with Parkinson's disease. Clin Neurol Neurosurg. 2004;106:93–6.
58. Swinn L, Schrag A, Viswanathan R, et al. Sweating dysfunction in Parkinson's disease. Mov Disord Off J Mov Disord Soc. 2003;18:1459–63.
59. Murray CA, Cohen JL, Solish N. Treatment of focal hyperhidrosis. J Cutan Med Surg. 2007;11:67–77.
60. Bushmann M, Dobmeyer SM, Leeker L, Perlmutter JS. Swallowing abnormalities and their response to treatment in Parkinson's disease. Neurology. 1989;39:1309–14.
61. Bird MR, Woodward MC, Gibson EM, Phyland DJ, Fonda D. Asymptomatic swallowing disorders in elderly patients with Parkinson's disease: a description of findings on clinical examination and videofluoroscopy in sixteen patients. Age Ageing. 1994;23:251–4.
62. Mari F, Matei M, Ceravolo MG, et al. Predictive value of clinical indices in detecting aspiration in patients with neurological disorders. J Neurol Neurosurg Psychiatry. 1997;63:456–60.
63. Gui D, Rossi S, Runfola M, Magalini SC. Botulinum toxin in the therapy of gastrointestinal motility disorders. Aliment Pharmacol Ther. 2003;18:1–16.
64. Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology. 1996;110:1410–5.
65. Neubrand M, Scheurlen C, Schepke M, Sauerbruch T. Long-term results and prognostic factors in the treatment of achalasia with botulinum toxin. Endoscopy. 2002;34:519–23.
66. Mikaeli J, Fazel A, Montazeri G, Yaghoobi M, Malekzadeh R. Randomized controlled trial comparing botulinum toxin injection to pneumatic dilatation for the treatment of achalasia. Aliment Pharmacol Ther. 2001;15:1389–96.
67. D'Onofrio V, Miletto P, Leandro G, Iaquinto G. Long-term follow-up of achalasia patients treated with botulinum toxin. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2002;34:105–10.
68. Ghoshal UC, Chaudhuri S, Pal BB, et al. Randomized controlled trial of intrasphincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. Dis Esophagus Off J Int Soc Dis Esophagus ISDE. 2001;14:227–31.

69. Annese V, Bassotti G, Coccia G, et al. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. GISMAD Achalasia Study Group. Gut. 2000;46:597–600.
70. Brisinda G, Bentivoglio AR, Maria G, Albanese A. Treatment with botulinum neurotoxin of gastrointestinal smooth muscles and sphincters spasms. Mov Disord. 2004;19:S146–56.
71. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Parkinsonism Relat Disord. 2011;17:10–5.
72. Mathers SE, Kempster PA, Swash M, Lees AJ. Constipation and paradoxical puborectalis contraction in anismus and Parkinson's disease: a dystonic phenomenon? J Neurol Neurosurg Psychiatry. 1988;51:1503–7.
73. 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.
74. 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.
75. Sakakibara R, Tateno F, Nagao T, et al. Bladder function of patients with Parkinson's disease: bladder function of patients with PD. Int J Urol. 2014;21:638–46.
76. Sakakibara R, Shinotoh H, Uchiyama T, et al. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci Basic Clin. 2001;92:76–85.
77. Giannantoni A, Rossi A, Mearini E, et al. Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. J Urol. 2009;182:1453–7.
78. Giannantoni A, Conte A, Proietti S, et al. Botulinum toxin type A in patients with Parkinson's disease and refractory overactive bladder. J Urol. 2011;186:960–4.
79. Kulaksizoglu H, Parman Y. Use of botulinum toxin-A for the treatment of overactive bladder symptoms in patients with Parkinsons's disease. Parkinsonism Relat Disord. 2010;16:531–4.
80. Ramirez-Castaneda J, Jankovic J. Long-term efficacy and safety of botulinum toxin injections in dystonia. Toxins. 2013;5:249–66.
81. Baizabal-Carvallo JF, Jankovic J, Pappert E. Flu-like symptoms following botulinum toxin therapy. Toxicon Off J Int Soc Toxinology. 2011;58:1–7.
82. 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.
83. Jankovic J. Botulinum toxin in clinical practice. J Neurol Neurosurg Psychiatry. 2004;75:951–7.