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Use of botulinum toxin in Parkinson's disease

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ABSTRACT

Botulinum toxin has emerged as an important therapeutic intervention within the realm of movement disorders, especially for focal and generalized dystonias. Botulinum toxin has additionally been used for a variety of symptoms associated with parkinsonism. In this review, we will specifically evaluate use of botulinum toxin in idiopathic Parkinson's disease. We will discuss symptoms including sialorrhea, limb, dystonia, tremor, dyskinesias, freezing of gait, camptocormia, pisa syndrome, urinary dysfunction, constipation, dysphagia, eyelid opening apraxia, and blepharospasm.

1. Introduction

Botulinum toxins, produced by the non-aerobic Clostridia bacteria, inhibit the release of acetylcholine from the presynaptic terminal by affecting SNARE and SNAP proteins [1]. Four different preparations are currently FDA approved in the U.S.A. including onabotulinum toxin A (Botox), incobotulinum toxin A (Xeomin), rimabotulinum toxin B (Myobloc), and abobotulinum toxin A (Dysport). Botulinum toxin was first used for the treatment of focal and segmental dystonias including blepharospasm and cranial-cervical dystonias in the 1980s. Botulinum toxin has been used for aspects of parkinsonism including tremor, sialorrhea, camptocormia, overactive bladder and pain. The 2016 AAN guidelines cite Level A evidence for a variety of toxins for use in cervical dystonia, upper and lower limb spasticity and chronic migraine. There is level B evidence for blepharospasm [2]. In this review, we will specifically discuss the use of botulinum toxin in idiopathic Parkinson's disease (PD).

2. Sialorrhea

Sialorrhea is observed in 40–80% of patients with advanced PD. Swallowing dysfunction with oropharyngeal dysphagia from bradykinesia can contribute to drooling in addition to severe hypomimia and stooped posture. Certain medications such as cholinesterase inhibitors and atypical antipsychotics used for cognition and psychosis can aggravate drooling. Pooling of saliva poses a risk of aspiration and infection. Use of anticholinergics is often limited by intolerable side effects. Botulinum toxin injections have been shown to improve sialorrhea in PD patients. A common side effect of botulinum toxin injections is dry mouth [33].

Lagalla et al. enrolled 32 PD patients in a double-blind, randomized, placebo-controlled trial studying onabotulinum toxin. Each patient received 50 units of onabotulinum toxin to each parotid gland versus placebo. Outcomes assessed included visual analogue scales for drooling frequency and patient embarrassment, UPDRS ADL subscores for drooling and dysphagia, and saliva production by weight. There were significant improvements between baseline and 1 month. 37% of toxin treated patients had UPDRS salivation score less than 2 (moderate excessive saliva, minimal drooling) versus 6% in the placebo group. Saliva production weights improved on average from 2.7 g to 1.3 g in the treatment group [3].

Mancini et al. included 20 parkinsonian patients (14 PD, 6 MSA) in a double-blind, randomized, placebo-controlled trial studying abobotulinum toxin. Each patient receiving toxin was injected under ultrasound guidance with about 145 units in each parotid and about 80 units in each submandibular gland. There was a significant reduction in Drooling Severity Scores at 1 week with benefit lasting on average about one month [4].

In studies for cervical dystonia, botulinum toxin type B was often noted to be associated with a high incidence of dry mouth as a side effect. The heavy chain of the B toxin has an increased affinity for secretory gland cholinergic acceptors. Multiple studies have demonstrated benefit of B toxin on sialorrhea. Dashtipour et al. published a literature review including 6 studies using BoNT-B for sialorrhea, with dosing between 1500 and 4000 units. All studies demonstrated a statistically significant benefit compared to placebo. A multicenter, double-blind RCT of 54 PD patients treated with botulinum toxin B demonstrated significant improvement in Drooling Frequency and Severity Scores and salivary flow rate across three treatment groups with dosing ranging from 1500 to 3500 units [5,6].

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Recently, incobotulinum toxin A was studied for sialorrhea in a small randomized, double-blind, placebo-controlled, cross-over study of 10 PD patients. In this study, there was no significant change in saliva production by weight or with Drooling Frequency and Severity scores. Dosing for this study was 20 units per parotid and 30 units per submandibular gland [7]. As compared to other studies, this study used lower dosing of toxin which may have affected efficacy. Additionally, there may have been additional benefit if the parotid glands were injected in addition to targeting the submandibular glands.

In general, treatment of sialorrhea with botulinum toxin appears safe and efficacious. Most frequently, this involves injections in both parotid and submandibular glands. Dry mouth can be a common side effect of salivary gland injections with botulinum toxin, but is rarely problematic in patients with baseline sialorrhea.

3. Limb dystonia

Dystonia has been reported to affect 30% of PD patients and 60% of those with onset younger than 40 years old. Most commonly, dystonia can affect the feet as an off phenomenon [8].

Pachetti et al. treated 30 PD patients with painful foot dystonia in an open label study with botulinum toxin under EMG guidance. Approximately 40 IU of onabotulinum toxin was injected per muscle group, divided in two sites, based on foot posture. Muscles included the tibialis posterior, tibialis anterior, gastrocnemius, flexor digitorum longus, and extensor hallucis longus; the median dose was 70 IU per patient. All patients noted improvement in pain within 10 days, and no local or distant side effects were noted. 21/30 patients had no pain for 4 months with decreased intensity of dystonic spasm. 7/30 patients with "on" foot dystonia noted improvement in foot posture with walking [9].

Rieu et al. enrolled 46 PD patients with prolonged (> 1 h per day) unilateral or bilateral toe plantarflexion in a randomized, double-blind, placebo-controlled trial comparing EMG-guided incobotulinum toxin injections of flexor digitorum longus (FDL), flexor digitorum brevis (FDB) and placebo. In those receiving toxin, 100IU was injected into either FDL or FDB as the first site based on randomization, and placebo was injected into the second site. Placebo patients received two placebo injections into FDL and FDB. Patients received two sets of injections three months apart. Injections targeted the more severely affected side if bilateral foot dystonia was present. The Clinical Global Impression of Change, the primary variable, was significantly improved in the incobotulinum toxin group (3.14 at 6 weeks, 2.90 at 18 weeks; $p = 0.039$). There was a significant reduction in pain, dystonia severity, and the Burke-Fahn-Marsden lower limb score in the incobotulinum toxin group compared to baseline scores; however, there was no significant difference when compared with the placebo group. This lack of significance was postulated to be secondary to low sample size and limited injection sites [10].

Patients with more persistent abnormal striatal limb deformities, such as striatal hand or foot, have also been treated with botulinum toxin. Giladi described 2 PD patients with both on and off striatal toe with 80–90% improvement with 50–70 units of onabotulinum toxin; EHL weakness was present but without significant gait impairment [11].

Dystonic clenched fist can be seen as a rare late complication of PD with associated loss of function, pain and poor palm hygiene. Abobotulinum toxin has been used as treatment of dystonic fist. One open-label study of 14 patients, 7 with idiopathic PD, noted muscle relaxation in all patients treated with toxin and mild-moderate posture improvement and pain relief in 5 PD patients. Three moderately to severely affected patients were able to gain mild functional benefit [12].

One open-label study looked at 6 PD patients who developed painful foot dystonia following deep brain stimulation surgery. All patients either required assistance with walking or were unable to stand independently. The primary outcome was the Burke Fahn Marsden Dystonia (BFMD) scale score. Following botulinum toxin injections, all six patients were able to walk briskly and had significant improvement in pain scores. Five of 6 patients had an improvement in BFMD scores by 2 points while one patient had improvement from a score of 4 to 0. Dosing ranged from 250 to 400 units; injection pattern varied depending on patient presentation [13].

As noted in the above studies, pain is often significantly improved following botulinum toxin injections for dystonia. One retrospective study of 160 parkinsonian patients noted that 50.6% had received injections with an indication of pain; of these, 77.6% was dystonic in nature versus 22.4% musculoskeletal. Subjective CGI scores were used as the primary assessment. Of the 117 PD patients included, 81% noted subjective benefits (CGI score +1 or greater) for pain, with 53.4% rating pain as very much improved [14].

As a treatment for limb dystonia, botulinum toxin can significantly improve pain as well as dystonic posturing. A consensus of the above studies suggests that pain was more consistently improved with toxin therapy, and functional improvement was variable but possible.

4. Tremor

Unlike other cardinal Parkinson's symptoms, tremor may be more refractory to standard pharmacologic treatments such as levodopa. Other medications for tremor including anticholinergics and amantadine are more commonly associated with side effects such as cognitive dysfunction. Botulinum toxin has not been widely adopted for Parkinson's tremor treatment. In prior studies looking at patients with ET or PD, onabotulinum toxin treatment was limited by weakness in 30–70% of patients. Some of this may be attributed to rigid protocols in regards to fixed dosing and predetermined injection sites [15].

Rahimi et al. studied 28 PD patients in an open label study of incobotulinum toxin for rest tremor. Their goal was to use kinematic guidance to target more active muscles to individualize injections; doses varied from 75 to 390 units per patient. Commonly injected muscles were flexor carpi ulnaris, extensor carpi ulnaris, pronator teres, pronator quadratus, flexor carpi radialis, extensor carpi radialis, and supinator. The injection patterns varied by treatment period depending upon kinematic guidance. There was a significant reduction in UPDRS rest tremor (baseline 2.7 versus 2.0 and 2.1 at weeks 16 and 32, $p = 0.014$) and Fahn-Tolosa-Marin tremor severity scores; no significant change in UPDRS action tremor. However, 57% had 3rd digit weakness, and 25% had decreased grip strength. Most patients described this as slight to mild, though 21% withdrew from the study due to weakness [16].

Mittal et al. described 30 PD pts with moderate-severe tremor enrolled in a randomized, double-blind, placebo-controlled crossover study. The injection pattern was customized based on the clinical features of each patient's tremor and administered under EMG guidance. The most commonly injected muscles, having been injected in 60% or more patients, were the lumbricals, flexor carpi radialis, flexor digitorum superficialis, flexor carpi ulnaris, pronator, biceps, triceps, extensor carpi radialis, and extensor digitorum. Each patient received about 7–12 injections, with a total of 85–110 units per patient. When undergoing incobotulinum toxin injections, the UPDRS rest tremor score, the primary outcome, decreased from an average of 3 points to 0–1 points at weeks 4 and 8. Grip strength was not statistically significantly different between the placebo and treatment groups. Two patients in the toxin group had moderate to severe weakness that was interfering compared to one in the placebo group. Eight additional patients experienced weakness after incobotulinum toxin treatment which was either not perceived by the patient or subtle and non-interfering [15].

There is a case series of 3 PD patients with jaw tremor treated with abobotulinum toxin. The patients received 60–200 units, divided into each masseter; one patient had additional injections in the mentalis. All patients had improvement of tremor at follow-up with benefit lasting

up to 3–4 months. No side effects were noted in this cohort [17].

In patients with poorly controlled PD limb tremor, botulinum toxin injections can be considered, but can be limited by weakness as a side effect even with individualized injection patterns.

5. Dyskinesias

Levodopa-induced dyskinesias can affect 45–85% of patients within a few years of starting treatment with L-dopa. Dyskinesias can occur both at peak-dose and with wearing off of levodopa effect. Aside from titrating levodopa dosing to address dyskinesias, the main pharmacologic option for the treatment of dyskinesias is amantadine which can be associated with possible cognitive and other anticholinergic-like side effects.

Treatment of dyskinesias with botulinum toxin has not been extensively studied. Espay et al. enrolled 12 PD patients with bothersome cervical-predominant levodopa-induced dyskinesias in a randomized, double-blind, placebo-controlled crossover trial. However, the study was prematurely terminated due to study concerns with excessive neck weakness. The primary outcome was change in the Goetz dyskinesia rating scale (GDRS) score. Those that did receive treatment with botulinum toxin did note improvement in GDRS scores for resting but not action-induced dyskinesias [18].

Thus far, there has not been sufficient data to support botulinum toxin injections for effective treatment of cervical dyskinesias.

6. Freezing of gait

In the later stage of Parkinson's disease, about 40–60% of patients can experience freezing of gait. The pathophysiology is poorly understood. It is postulated that this may be a dystonic manifestation with dis-synchronized contractions of agonist and antagonist muscles in the lower extremities. Freezing of gait is considered to be unresponsive to medical therapy with dopaminergics.

In 1997, Giladi et al. first reported an improvement in freezing of gait in a PD patient injected with botulinum toxin for foot dystonia. In 2001, the Giladi group described a cohort of 10 parkinsonian patients, 7 of whom had idiopathic PD, who were injected with botulinum toxin in an open label study for freezing of gait (FoG). Patients received a total of 100–300 units with one injection into the soleus, the lateral gastrocnemius, and the medial gastrocnemius; additional muscles were included if foot dystonia was present. Five patients received bilateral injections, and the remaining 5 had unilateral injections. Seven of 10 patients had some improvement in FoG, while 4 patients reported marked improvement. The mean duration of benefit was 6 weeks [19].

Gurevich et al. published a follow-up randomized, double-blind, placebo controlled study with 11 PD patients with FoG. Six patients received 150 units of onabotulinum toxin divided evenly in the soleus and lateral and medial heads of the gastrocnemius, and 5 patients received saline. Improvement was only noted in the saline group at week 16; there was no significant improvement in the toxin group according to UPDRS ADL, UPDRS motor, subjective CGI-C or Freezing of Gait Questionnaire scores. Three patients in the toxin group and 2 patients in the saline group complained of leg weakness, though this was not detectable on clinical exam. Two patients in the toxin group had increased fall frequency while 1 patient had decreased frequency [20].

Fernandez et al. studied the use of rimabotulinum toxin for FoG in a double-blind, placebo controlled trial. Nine patients received 5000 units divided into 4 sites in the gastrocnemius-soleus complex in the predominantly affected leg; 5 patients received placebo. In the B toxin group, 1 patient was “much improved,” 2 were “minimally improved,” 2 were “minimally worse,” and 4 patients were unchanged according to CGI scores. There was no significant change in UPDRS II/III scores, Visual Analogue Scale, or Webster Step-Seconds scores [21].

A more recent study by Vastik and colleagues in 2016 enrolled 11 PD patients with FoG in an open label trial. Patients received 50 units of botulinum toxin into each tensor fascia latae. Eight of 11 patients had a significant decline in freezing of gait scores. Time up and go scores showed a decline in 6 patients, increase in 3 patients and was unchanged in 1 patient; this was not significant at week 4. CGI scores were significantly improved with 6 patients noting moderate to marked improvement [22].

These studies of freezing of gait demonstrated inconsistent benefit with botulinum toxin. Additionally, these studies were limited by small sample sizes. The more recent 2016 study showed more promising results with tensor fascia latae injections, but larger controlled studies are still needed.

7. Camptocormia

Camptocormia occurs in 3–7% of patients with Parkinson's disease. This involuntary axial flexion occurs while upright and can increase while walking. Many use a degree of flexion of at least 45° of the thoracolumbar spine to define camptocormia [34]. Muscles postulated to contribute to camptocormia include the abdominal external and internal obliques for the upper subtype and the rectus abdominus and iliopsoas for the lower subtype. Camptocormia has a variable response with dopaminergic therapies and deep brain stimulation. Botulinum toxin use has been studied due to the theory that camptocormia may be a form of axial dystonia. The tendency to resolve when supine, when leaning against a support, or when wearing a backpack can be suggestive of a sensory trick [34].

Azher and Jankovic described 9 PD patients treated with botulinum toxin A injected into the rectus abdominus for camptocormia; four patients had improvement lasting eight weeks [23]. Fietzek et al. described 10 patients treated with US-guided Incobotulinum toxin A injections to the iliopsoas or rectus abdominus with a mean of 210 units. In this group, there was no significant improvement in camptocormia [38]. Van Coelln et al. treated 3 PD and 1 MSA patients with 500–1500 units of Abobotulinum toxin A to each side of the iliopsoas. Two patients had worsened posture, and 2 had subtle improvement [39].

Variable results in the above small studies may be related to difficult access of muscles for injection versus appropriateness of muscle selection. The above series did not include abdominal oblique injections. Additionally, sample sizes and dosing may not be adequate in the above mentioned papers to come to conclusions of therapeutic intervention with toxins. This additionally suggests complexity of this syndrome and central control of abnormal posture that is difficult to treat with any form of therapy.

8. Pisa syndrome

Pisa syndrome (PS) is observed in about 10% of patients with Parkinson's disease and presents with lateral trunk flexion. Similar to camptocormia, this tends to improve in a supine position, and has limited improvement with dopaminergic therapy [35].

Tassorelli and colleagues enrolled 26 PD patients with PS in a randomized, placebo-controlled trial of incobotulinum toxin for PS. Patients also had a four week rehabilitation program following injections. All patients were screened with an EMG protocol assessing abdominal, paravertebral and iliopsoas muscles in supine and upright positions. Up to six sites for injection were selected if there was involuntary tonic activity longer than 500 ms. Patients were randomized to placebo, with 4–6 injections of saline, versus incobotulinum toxin injections, ranging from 50 to 200 IU per patient. Lateral trunk inclination was significantly reduced versus baseline in the toxin treatment group following the rehabilitation period as well as at 3 month follow-up. As compared to the group's prior study looking at rehabilitation alone, there were additional improvements in pain intensity, UPDRS score, camptocormia and trunk range of motion in the toxin group [36].

Artusi et al. described 15 patients undergoing onabotulinum toxin

injections for PS with greater than 10° of lateral flexion; 2 patients were excluded who were undergoing concomitant rehabilitation. Patients underwent T1-weighted axial MRI to assess atrophy of paraspinal and non-paraspinal axial muscles. Patients were injected under ultrasound and EMG guidance if pathological muscular hyperactivity was noted on EMG on standing in addition to absence of atrophy on MRI. Dosing ranged from 50 to 75 units per paraspinal muscle and 25–50 units per non-paraspinal muscle, with an average dose of 151.9 ± 53.5 units. The responder rate was 84.6% with average improvement of lateral flexion by 40% and pain/discomfort improving about 52% [35].

There are few studies assessing botulinum toxin injections for Pisa syndrome. However, the studies currently published suggest possible efficacy in their small cohorts. Larger, multi-center randomized clinical trials are needed to determine definitive efficacy of toxin injections for Pisa syndrome.

9. Urinary dysfunction

Genitourinary symptoms including nocturia, frequency, urgency and incontinence are common in PD patients. Lower urinary tract symptom prevalence ranges from 27 to 64% of patients. Neurogenic overactive bladder is the most common presentation for PD patients, likely related to altered nigrostriatal signaling to the pontine micturition center through the periaqueductal gray. This is also often compounded by age-associated idiopathic overactive bladder and benign prostatic hypertrophy. Medications such as anticholinergic agents are frequently poorly tolerated. Onabotulinum toxin has been in use for urinary dysfunction in patients with spinal cord injuries and multiple sclerosis [24,25].

Anderson et al. enrolled 20 patients in an open-label study for patients with PD with neurogenic bladder and incontinence with no improvement on antimuscarinics. Each patient received 100 units of onabotulinum toxin injected into 10–20 submucosal intra-detrusor bladder sites within the lower hemisphere of the bladder, with 2–3 sites being in the trigone. King's Health Questionnaire part III (bladder) scores decreased significantly at months 1 and 3 post-treatment. Three-day voiding diaries and American Urological Association (AUS) symptoms scores showed a decrease in mean incontinence scores by at least 50% in the six months following treatment. 57% of patients had moderately to markedly improved symptoms. Two patients required alpha-blocking agents to assist bladder emptying, but no patients required catheterization [25].

Vurture et al. described 24 PD patients analyzed in a retrospective study after receiving intradetrusor injections of onabotulinum toxin. All patients were refractory or intolerant to anticholinergics and/or mirabegron. Each patient received 5 units injected into 20 sites throughout the bladder wall and trigone. A second set of injections totaling 100–200 units was offered for those with partial or complete inefficacy. In this cohort, 79.2% of patients endorsed improved overactive bladder symptoms, with 29.1% having complete resolution of incontinence. Most patients did not require pads after treatment, compared to median daily pad use of three prior to treatment. Two patients experienced worsened symptoms after the first treatment, but noted clinical improvement with repeat injections of 100 units. The complication rate was higher in this cohort with 25% of patients developing urinary tract infections and 12.5% requiring catheterization for high post-void residuals. At 17-month follow-up, 45.8% of patients were continuing to receive injections versus 37.5% on medications alone and 8.3% undergoing sacral neuromodulation [24].

Botulinum toxin is approved for treatment of neurogenic bladder symptoms. In PD patients specifically, there can be improvements in overactive bladder. Patients should be made aware of possible side effects in regards to urinary retention and infection risk.

10. Constipation

Gastrointestinal dysfunction is one of the most common non-motor symptoms in PD. Defecatory dysfunction is five times more common in Parkinson's disease as compared to the general population, with about 60% of patients affected. Constipation in Parkinson's disease may have contributions both from slow transit as well as outlet obstruction. Outlet obstruction has been attributed to focal dystonia of the pelvic floor with failure of puborectalis relaxation or paradoxical contraction.

There are two open-label studies using onabotulinum toxin for prominent outlet-type constipation. Both studies used 100 units of botulinum toxin injected into two sites in the puborectalis muscle under transrectal ultrasound guidance. In the Albanese et al. study, manometry, defecography and EMG were utilized before and after treatment. Anal tone during straining and anorectal angle were improved at 1 month [26]. In the Cadeddu et al. study, patients were assessed by manometry and defecography. At 1 and 2 months, pressure with straining was reduced and anorectal angle improved. Ten of eighteen patients subjectively improved in 2 months, with five patients having resolution of their symptoms at 1 month. Of the eight non-responders, higher dosing of 200 units was used with four patients noting symptomatic improvement [27]. In these studies, there were no noted side effects reported.

Further studies are necessary to study the efficacy of botulinum toxin injections for constipation; however, the small studies currently published demonstrate possible benefit.

11. Dysphagia

Dysphagia occurs in more than 50% of PD patients. All phases of swallowing can be affected. Hyperactivity can be noted at the upper esophageal sphincter which can result in aspiration. Botulinum toxin has been used in patients noted to have absence of cricopharyngeal inhibition. Restivo et al. described 4 PD patients injected with abobotulinum toxin A, 30 units per cricopharyngeal muscle. All four patients noted improvement in swallowing within 48 h, supported by improvement on videofluoroscopic and EMG studies. Benefits lasted 16–20 weeks [28].

A later open-label study of 34 patients with clinical dysphagia included 7 patients with PD; 15 units of onabotulinum toxin were injected into one cricopharyngeal muscle. Only 2 of 7 patients with PD had improvement by Dysphagia Severity Score. It was postulated that PD patients may have more issues with pharyngeal delay time in addition to absent cricopharyngeal inhibition. In contrast, 6 of 9 PSP and 4 of 4 MSA-P patients improved, suggesting more prominent cricopharyngeal hyperactivity [29]. Neither study noted significant side effects with the above dosing.

Botulinum toxin injections may be more beneficial for atypical parkinsonian syndromes with prominent cricopharyngeal hyperactivity, as compared to idiopathic Parkinson's disease but further study is needed.

12. Eyelid opening apraxia and blepharospasm

Apraxia of lid opening (ALO), the intermittent ability to open the eyes without orbicularis oculi contraction, can be seen in parkinsonian disorders, more commonly atypical syndromes. This can be associated with frontalis contraction. Botulinum toxin has been shown to be effective in patients with blepharospasm in conjunction with ALO as well as isolated ALO [30].

There is a case report of use of botulinum toxin in a 73 year old patient with PD with ALO. Twenty units total was injected in two sites close to the lash line to target the pretarsal orbicularis oculi. This patient experienced significant improvement in visual function, lasting 2–3 months [31].

One retrospective study included 64 patients with primary and

secondary blepharospasm, treated with either Onabotulinum toxin A or Rimabotulinum toxin B. Of the secondary patients, 12 patients had PD, 8 of whom had developed blepharospasm following deep brain stimulation. There was comparable duration and magnitude of benefit noted between groups [32].

There is insufficient evidence currently to conclude efficacy on use of botulinum toxin for ALO. As with injections for blepharospasm, common side effects of ALO can include ptosis.

13. Other uses

Based on non-Parkinson's literature, botulinum toxin may be beneficial for symptoms including cervical dystonia, laryngeal dystonia, oromandibular dystonia and hyperhidrosis [37].

14. Summary

Botulinum toxin appears efficacious for the treatment of sialorrhea, focal limb dystonia and blepharospasm. Use of botulinum toxin for tremor and overactive bladder may be considered if standard pharmacologic treatments are ineffective; preliminary data for outlet-obstruction constipation is promising. There is limited data to support the use of botulinum toxin for camptocormia, freezing of gait, levodopa-induced dyskinesias, apraxia of lid opening and dysphagia.

Appendix

Study	Type of Study	Toxin Type	Total Patients	Dosing Units	EMG US	Outcome Measures*	Results	Adverse Events**
Sialorrhea								
Lagalla et al, 2006 [3]	Double-blind, randomized, placebo-controlled trial	Onabotulinum toxin A	32 total 16 toxin 16 placebo	50 units per parotid gland	No	VAS-D VAS-FD VAS-SD UPDRS II Patient satisfaction Dental roll weights	Improved VAS scores ($p < 0.0001$-0.01) Improved ADL-drooling ($p < 0.0001$) 88% satisfaction Decreased saliva weight at 1 month ($p < 0.0001$)	1 mild, transient swallowing difficulty
Mancini et al, 2003 [4]	Double-blind, randomized, placebo-controlled trial	Abobotulinum toxin A	20 total (14 PD, 6 MSA) 10 toxin 10 placebo	146.25 units per parotid gland 78.75 units per submandibular gland	US	DFSS	Improved drooling score at 1 week ($p = 0.005$), average benefit 1 month	None reported
Chinnapongse et al, 2012 [6]	Double-blind, randomized, placebo-controlled trial	Rimabotulinum toxin B	54 total 14 1500 units 12 2500 units 13 3500 units 15 placebo	500, 1000, or 1500 per parotid gland 250 units per submandibular gland	No	Safety DFSS CGI-C PGI-C UPDRS II Salivary flow rate	Improved drooling score at 4 and 8 weeks in all toxin groups ($p < 0.05$) Decreased salivary rates in all groups ($p < 0.02$, $p < 0.0033$) Improved CGI, PGI and UPDRS II scores	4 dry mouth 1 breath odor 1 change in saliva 1 tongue coating 1 trismus 1 dysguesia
Narayanaswami et al, 2016 [7]	Double-blind, randomized, placebo-controlled crossover study	Incobotulinum toxin A	10 total	20 units per parotid gland 30 units per submandibular gland	No	Salivary weight DFSS UPDRS II UPDRS III	No significant change in salivary weight or secondary outcome measures	1 difficulty chewing and tongue control 1 viscous saliva
Limb Dystonia								
Pachetti et al, 1995 [9]	Open-label	Onabotulinum toxin A	30 with painful 'off' foot dystonia	40-100 units total, median 70 units 40 units per injected muscle, chosen by foot posture	EMG	McGill pain questionnaire Subjective response	30/30 improved pain ($p = 0.024$) 21/30 with no pain for 4 months 7/30 improved 'on' dystonia with walking	None reported
Rieu et al, 2017 [10]	Double-blind, randomized, placebo-controlled parallel study	Incobotulinum toxin A	45 total with dystonic toe plantarflexion 13 FDL 16 FDB 16 placebo	100 units in either flexor digitorum longus or brevis	No	CGI-C BFMD score VAS PDQ39	Moderate improvement CGI-C at 6 and 18 weeks ($p = 0.039$) Significant improvement in pain ($p < 0.001$, $p = 0.002$), severity ($p < 0.001$, $p = < 0.001$) and BFM score ($p = 0.026$, $p = 0.001$) at 6 and 18 weeks in toxin group compared to baseline scores; no significant difference compared to placebo group	9 falls (2 in placebo group) 1 transient loss sensation
Giladi et al, 1994 [11]	Case series	Onabotulinum toxin A	2 with striatal toe	50-70 units in extensor hallucis longus	No	Subjective response	80-90% subjective and objective improvement	Moderate EHL weakness
Cordivari et al, 2001 [12]	Case series	Abobotulinum toxin A	14 total with dystonic clenched fist (7 PD, 3 CBD, 4 CRPS)	220-1200 units total in varying injection sites	EMG	Assessed muscle relaxation, pain, posture, function	14/14 mild-moderate posture improvement 4/7 PD patients with functional improvement 5/7 PD patients with improved pain	None reported
Gupta et al, 2106 [13]	Case series	Onabotulinum toxin A	6 total with foot dystonia impairing gait following deep brain stimulation	250-400 units total in varying injection sites	EMG	BFMD score VAS UPDRS leg scores TUG 6MWT Gait velocity and cadence GAS	6/6 able to walk independently 6/6 with significant pain improvement 5/6 with 2 point BFMD improvement 1/6 with 4 point BFMD improvement	None reported

Bruno et al, 2016 [14]	Retrospective chart review	Onabotulinum toxin A (96%) Incobotulinum toxin A (4%)	160 total (117 PD, 14 PSP, 16 MSA, 6 CBS, 7 NOS) with history of dystonia injections	100-600 units total in varying injection sites, for pain (50.6% patients)	EMG	CGI-C	81% of PD patients with improvement in CGI score > =1 for pain 53.4% of PD patients rated pain 'very much improved'	4 transient weakness
Tremor								
Rahimi et al, 2015 [16]	Open-label	Incobotulinum toxin A	28 total with limb rest tremor	75-390 units total in varying injection sites based on kinematic tremor measurements	EMG	UPDRS III 20-21 FTM scale Likert scale	UPDRS item 20 (rest tremor severity) significantly reduced at 16 and 32 weeks (p = 0.006, p = 0.014) No significant difference UPDRS item 21 (action tremor severity) FTM tremor severity significantly reduced at week 6 (p = 0.024)	57% 3rd digit weakness 25% decreased grip strength
Mittal et al, 2017 [15]	Double-blind, randomized, placebo-controlled crossover study	Incobotulinum toxin A	30 total with limb rest tremor	85-110 units total across 7-12 varying injection sites	EMG	UPDRS III 20-21 NIHCGC tremor severity score PDQL PGI-C Ergometer strength	UPDRS item 20 and 21 scores significantly decreased at 4 and 8 weeks (p < 0.001, p = 0.01) Significant improvement in NIHCGC (p < 0.001) and PGIC (p < 0.001) No significant difference in PDQL or grip strength	16 decreased grip (6 in placebo group) 3 moderate-severe weakness (1 in placebo group)
Schneider et al, 2006 [17]	Case series	Abobotulinum toxin A	3 total with jaw tremor	60-200 units total divided into each masseter; 1 patient including mentalis	EMG	Subjective response	3/3 improvement at 4 and 9 weeks post-injection	None reported
Dyskinesias								
Espay et al, 2011 [18]	Double-blind, randomized, placebo-controlled crossover study	Onabotulinum toxin A	12 total with cervical dyskinesias	200 units total 25 units in each sternocleidomastoid 50 units in each splenius capitis, divided 25 units in each trapezius	EMG	GDRS score CGI-C UPDRS IV 32-34	Study prematurely terminated due to safety concerns Improvement in resting but not action-induced dyskinesias	2 head drop with moderate dysphagia
Freezing of Gait								
Giladi et al, 2001 [19]	Cross-sectional study	Onabotulinum toxin A	10 total (7 PD, 1 vascular parkinsonism, 1 Parkin gene, 1 gait disorder NOS)	100-300u total in one or both gastrocnemius and soleus, +/- tibialis posterior, +/-extensor hallucis longus	EMG	CGI-C	7/10 with some improvement 4/10 with marked improvement, mean of 6 weeks 2/7 with no effect	1 transient leg weakness
Gurevich et al, 2007 [20]	Double-blind, randomized, placebo-controlled trial	Onabotulinum toxin A	11 total 6 toxin 5 placebo	300 units total 50 units in the lateral and medial heads of each gastrocnemius 50 units in each soleus	EMG	UPDRS II FOG-Q CGI-C	No improvement in the toxin group Significant increase in fall frequency in the toxin group (p < 0.05)	5 leg weakness (2 in placebo group), not clinically detectable 2 increased fall frequency
Fernandez et al, 2014 [21]	Double-blind, randomized, placebo-controlled trial	Rimabotulinum toxin B	14 total 9 toxin 5 placebo	5000 units divided in four sites in the gastrocnemius-soleus complex in more affected leg	No	UPDRS II UPDRS III VAS CGI-C Modified Webster Step-Seconds test	No significant differences between groups	2 dry mouth 1 increased festination
Vastik et al, 2016 [22]	Open-label	Botulinum toxin A	11	50 units in each tensor fascia latae	EMG	FOG-Q TUG UPDRS Hoehn and Yahr CGI fMRI	8/11 with improved FOG-Q scores (p < 0.001) Significant improvement CGI scores (p < 0.005) No significant change in TUG	None reported
Camptocormia								
Azher et al, 2005 [23]	Case series	Onabotulinum toxin A	16 total (11 PD) 9 PD with toxin	300-600 units in the rectus abdominis	No	UPDRS	4/9 with marked improvement 3/9 with no improvement	None reported
Fietzek et al, 2009 [38]	Open-label	Incobotulinum toxin A	10	100-300 units in either the rectus abdominis or iliopsoas based on hip or lower trunk flexion	US	Goal attainment Change in posture UPDRS III TUG	No noted improvement	2 sore muscles
Van Coelln et al, 2008 [39]	Case series	Abobotulinum toxin A	4 total (3 PD, 1 MSA-P)	500-1500 units in each side of the iliopsoas	US	Change in posture	2 subtle-mild benefit 1 slight worsened posture 1 significantly worsened	1 injection site pruritis 3 mild hip flexion weakness 1 moderate hip flexion weakness impacting ADLs
Pisa Syndrome								
			26 total		EMG			None reported

Tassorelli et al, 2014 [36]	Double-blind, randomized, placebo-controlled trial	Incobotulinum toxin A		50-200 units total in varying sites in abdominal, paravertebral or iliopsoas muscles		Lateral and anterior flexion and range of motion UPDRS III FIM VAS	Lateral and anterior trunk flexion improved in toxin group ($p = 0.044$, $p = 0.001$) Improvements in pain, UPDRS, and FIM ($p = 0.001$, $p = 0.001$, $p = 0.001$)	
Artusi et al, 2018 [35]	Open-label	Onabotulinum toxin A	15	152 units total mean dose 50-75 units per paraspinal muscle 25-50 per non-paraspinal muscle	EMG US	Change in posture VAS	84.6% responder rate Significant improvement of flexion ($p < 0.001$) and pain ($p < 0.001$)	None reported
Urinary Dysfunction								
Anderson et al, 2014 [25]	Open-label	Onabotulinum toxin A	20	100 units in 10-20 submucosal intradetrusor sites	No	KHQ AUA symptom score 3-day voiding diary Post-void residuals Urodynamics	Improvement in KHQ bladder symptoms at 1 and 3 months ($p < 0.02$) Improved diary and AUA scores ($p < 0.05$, $p = 0.006$) Decreased incontinence episodes ($p < 0.05$) 57% with moderate to marked improvement	2 required alpha-blocking agents for bladder emptying
Vurture et al, 2018 [24]	Open-label	Onabotulinum toxin A	24	100 units in 20 sites in the bladder wall and trigone	No	Overactive bladder symptoms Post-void residuals Change in urgency Pad use	79.2% improved 29.1% resolved incontinence (< 0.001) Pad use decreased from 3 to 0 ($p = 0.016$)	25% UTIs 12.5% required catheterization
Constipation								
Albanese et al, 2003 [26]	Open-label	Onabotulinum toxin A	10	100 units in the puborectalis muscle	US	Manometry Defecography EMG	Reduced tone during straining ($p = 0.00001$) Anorectal angle increased ($p = 0.0004$)	None reported
Cadeddu et al, 2005 [27]	Open-label	Onabotulinum toxin A	18	100 units in two sites of the puborectalis muscle	US	Manometry Defecography	Symptomatic improvement at 1 and 2 months in 8 and 10 patients ($p = 0.002$, $p = 0.0003$) 5 with resolved symptoms at 1 month Straining pressure reduced ($p = 0.00001$) Anorectal angle increased ($p = 0.00001$)	None reported
Dysphagia								
Restivo et al, 2002 [28]	Case series	Abobotulinum toxin A	4	30 units per cricopharyngeal muscle	EMG	Clinical exam EMG Videofluoroscopy	4/4 with improvement through week 20	None reported
Alfonsi et al, 2010 [29]	Open-label	Onabotulinum toxin A	34 total (7PD, 9 PSP, 4 MSA-P, 1 MSA-C, 2 MS, 10 stroke, 1 ataxia telangiectasia)	15 units in one cricopharyngeal muscle	EMG	DSS EMG	Improvement in dysphagia ($p < 0.001$), but only 2/7 PD patients improved versus 6/9 PSP and 4/4 MSA-P patients	None reported
Apraxia of Lid Opening								
Lepore et al, 1995 [31]	Case report	Onabotulinum toxin A	1	20 units in pretarsal orbicularis oculi	No	Subjective response Clinical exam	Improved visual function for 2-3 months	None reported
Martinez-Ramirez et al, 2014 [32]	Retrospective chart review	Onabotulinum toxin A Rimabotulinum toxin B	64 total (41 primary, 23 secondary blepharospasm with 12 PD)	39.3-57.2 units in varying injection sites	No	Duration of benefit Peak dose improvement	Similar efficacy for primary and secondary blepharospasm ($p = 0.88$)	8 Bruising 3 Dry eyes 3 Ptosis 1 Redness 4 Diplopia 1 Pain

* Assessments: Visual Analogue Scale (VAS), Unified Parkinson's Disease Rating Scale (UPDRS), Drooling Frequency and Severity Scale (DFSS), Clinical Global Impression of Change (CGI-C), Patient Global Impression of Change (PGI-C), Burke-Fahn-Marsden Dystonia (BFMD), Parkinson's Disease Questionnaire-39 (PDQ-39), Timed Up and Go (TUG), 6 Minute Walk Test (6MWT), Goal Attainment Scale (GAS), Fahn-Tolosa-Marin (FTM), NIH Collaborative Genetic Criteria (NIHCGC), Parkinson's Disease Quality of Life (PDQL), Goetz Dyskinesia Rating Scale (GDRS), Freezing of Gait Questionnaire (FOG-Q). Functional Independence Measure (FIM), King's Health Questionnaire (KHQ), American Urological Association (AUA), Dysphagia Severity Scale (DSS)
** Adverse events are noted for toxin-treated patients unless otherwise noted

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