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Review article

Botulinum toxin for the treatment of tremor

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ABSTRACT

Tremor is a key clinical feature of several common neurological disorders. Adequate management of tremor has been an unmet need in clinical practice. Most of the anti-tremor medications have limited efficacy and are associated with undesirable adverse effects, especially in elderly patients. Several studies have reported good outcomes with the use of botulinum neurotoxin (BoNT) for the treatment of tremor. This article aims to systematically review these studies and to highlight the role of BoNT in the management of tremor. A PubMed search was performed in August 2018 to identify articles pertinent to this review.

Majority of the studies that have assessed the efficacy of BoNT in tremor, enrolled patients with essential tremor (ET), Parkinson's disease (PD), and dystonic tremor. Results of these studies suggest clinically meaningful improvement in hand tremor in both ET and PD and vocal tremor in ET after BoNT therapy. Additionally, BoNT has been reported to be efficacious in alleviating head and palatal tremor, tremor in multiple sclerosis, and proximal positional tremor. It is apparent that BoNT injections tailored to the needs of individual patients yield better efficacy and lower adverse effects compared to fixed-muscle-fixed-dose approach. BoNT individualized approach adds to the armamentarium for patients who have medically refractory tremors or those who are unable to tolerate the anti-tremor medications. The studies are limited and mostly open-label; thus, randomized placebo-controlled studies are needed to prove the efficacy of BoNT in various tremor conditions.

1. Introduction

Tremor is an involuntary, rhythmic, oscillatory movement of a body part [1]. It is one of the hallmark features of the two most common movement disorders i.e. essential tremor (ET), and Parkinson's disease (PD). Other movement disorders in which tremor may dominate the clinical presentation include dystonia (dystonic tremor), certain spinocerebellar ataxias, Wilson's disease, primary writing tremor (PWT), and primary orthostatic tremor (POT) [2,3]. Additionally, tremor may be a manifestation of multiple sclerosis (MS) [4,5]. Tremor may interfere with the activities of daily life and may lead to social embarrassment [6].

Adequate management of tremor is an unmet need in patients with the aforementioned pathologies. Although levodopa or dopamine receptor agonists in PD and beta-blockers or primidone in ET are often effective in ameliorating tremor, the improvement may be only partial or may be limited by the emergence of undesirable side effects. Similarly, deep brain stimulation (DBS) and thalamotomy which are effective surgical approaches in the management of tremor, may not be applicable to all patients with troublesome or disabling tremors [7,8]. In one survey, involving 1418 patients with ET, only 11.8% of the respondents were satisfied with their care [9].

Considering these limitations of medical and surgical therapies, several studies have explored the use of botulinum neurotoxin (BoNT) for the management of tremor, particularly in focal tremors. The mechanism by which BoNT improves tremor is not well understood but may be partly due to temporary weakness in the involved muscles by inhibiting the release of acetylcholine from the presynaptic terminals and thus, blocking the neuromuscular transmission. BoNT also blocks the presynaptic motor end plate of gamma motor neurons of intrafusal fibers and restores presynaptic inhibition between forearm antagonist muscles by inhibiting the input into the spinal cord via the Ia afferents [10]. In addition, BoNT can transiently alter the excitability of the cortical motor areas by reorganizing the inhibitory and excitatory intracortical circuits, likely originated through peripheral mechanisms. Hence, BoNT has an effect on the tremor by dampening the peripheral oscillations at the muscle level, spindle fibers affecting the reciprocal inhibition at spinal cord level, and central level at the cortical motor areas [11,12]. The muscle afferents influence the central motor structures such as motor cortex, thalamus, and the cerebellum. It is possible

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Table 1
Results of search for articles from PubMed using various key words and their combinations.

Key words and combinations	Number of publications in PubMed		
	Total	Included	Excluded
Tremor AND Botulinum toxin	302	26	276 (not in English: 33, not relevant: 194 case reports/case series with < 5 subjects: 36 review articles: 13)
Essential tremor AND Botulinum toxin	117	20	97 (not in English: 17, not relevant: 70, case reports/case series with < 5 subjects: 6 review articles: 4)
Tremor AND Parkinson's disease AND Botulinum toxin	67	7	60 (not in English: 12, not relevant: 39, case reports/case series with < 5 subjects:4 review articles: 5)
Tremor AND Multiple sclerosis AND Botulinum toxin	11	2	9 (not in English: 3, not relevant: 3 case reports/case series with < 5 subjects: 0 review articles: 3)
Tremor AND Wilson's disease AND Botulinum toxin	2	0	2 (not in English: 0, not relevant: 2, case reports/case series with < 5 subjects: 0 review articles: 0)
Dystonic tremor AND Botulinum toxin	54	2	52 (not in English: 6, not relevant: 39 case reports/case series with < 5 subjects: 1 review articles: 6)
Writing tremor AND Botulinum toxin	19	3	16 (not in English: 0, not relevant: 13 case reports/case series with < 5 subjects: 2 review articles: 1)
Palatal tremor AND Botulinum toxin	24	2	22 (not in English: 3, not relevant: 13 case reports/case series with < 5 subjects: 5 review articles: 1
Proximal Tremor AND Botulinum toxin	8	1	7 (not in English: 2, not relevant: 5 case reports/case series with < 5 subjects: 0 review articles: 1)
Neuropathic Tremor AND Botulinum toxin	4	0	4 (not in English: 0, not relevant: 4 case reports/case series with < 5 subjects: 0 review articles: 0)
Rubral tremor AND Botulinum toxin	70	0	70 (not in English: 10, not relevant: 60 case reports/case series with < 5 subjects: 0 review articles: 0)

Total number of articles included for review after removing the duplicates: 35
Total number of articles included from the reference sections of the shortlisted articles:0
Final number of articles include for review: 35

that reduced input in one of these central structures might lead to a reduction of central oscillatory activity and consequently to a reduction of the tremor [10].

This indication, although not yet approved by the US Food and Drug Administration, further expands the spectrum of therapeutic applications of BoNT in the treatment of movement disorders and other neurologic and non-neurologic disorders [13,14]. In this article, we comprehensively review the studies that have assessed the efficacy of BoNT in the management of tremor of different etiologies, focusing on the dose of BoNT, muscle selection, injection techniques, and outcomes.

2. Methods

In August 2018, the authors used PubMed to search for the pertinent literature using the terms “Botulinum toxin” and “Tremor” with additional search terms being, “Essential tremor”, “Parkinson's disease”, “Multiple sclerosis”, “Writing tremor”, “dystonic tremor”, “rubral tremor”, “vocal cord tremor” and “cerebellar tremor”. This search yielded 658 articles (Table 1). During the initial screening of the abstracts/full texts, the articles that were not relevant to this review, case reports, case series with < 5 patients, and articles published in languages other than English were removed, leaving 63 remaining articles. The references from these articles as well as full-text articles/abstracts from authors' personal collections were also thoroughly searched for any additional articles (Table 1). The duplicate articles were removed and in total, 35 articles pertaining to this topic were included for this review (Table 1).

The efficacy of BoNT for the management of tremor in several diseases has been extensively evaluated in randomized double-blind, placebo-controlled studies (RCT) and in open-label studies (OL). We found a total of 10 published studies evaluating the role of BoNT in ET patients with hand tremor (3 RCT and 7 OL), seven studies on PD tremor (1 RCT and 6 OL), two studies on hand tremor in MS (1 RCT and 1 OL), two studies on head tremor in ET (1 RCT and 1 OL), one OL study on dystonic head tremor, two OL studies on essential palatal tremor, two OL studies on task-specific hand tremor (primary writing tremor and musician tremor). There is one OL study on each proximal upper limb tremor and jerky position-specific upper limb tremor.

2.1. *BoNT for the treatment of essential hand tremor [Table 2]*

ET is one of the most common neurological diseases with the estimated prevalence of ~4% and with bimodal age at onset with peaks around 2nd and 6th decade of life [15,16]. Clinically, patients have 4–12 Hz kinetic tremor of both hands, but the tremor may also involve other body parts such as head, face, jaw, voice, and legs [17–19]. The kinetic tremor in ET is usually observed during voluntary actions such as writing, eating, drinking, and while pouring water into a cup. The first line medications for ET has not changed over the last three decades and includes beta-blockers such as propranolol and one of the antiepileptic medications especially primidone or topiramate. Approximately 50–60% of the patients with ET achieve sustained improvement with these medications. However, these medications often cause side effects, especially in the elderly population. DBS targeting the ventral intermediate nucleus of the thalamus is effective against tremor in ET but carries a 3%–4% risk of post-operative complications that include intracerebral hemorrhage, peripheral or intracerebral infection, and other problems [20,21].

There are few OL studies [22–25], where a small number of ET patients with hand tremor were injected with BoNT using surface anatomical landmarks or EMG guidance. In one such study, Trosch et al. [22] injected up to 8 hand and arm muscles under the guidance of surface and needle EMG. Three of the 14 ET patients (21%) had > 50% reduction in tremor amplitude and five patients (~40%) had moderate to marked subjective functional improvement after the injections, although the difference did not reach statistical significance. Pullman et al. [23]. published their experience with 17 patients in which only three patients had marked improvement in tremor. Injections were given in different muscles on the basis of tremor activity on EMG with adjustments in dose and techniques.

In 1996, Jankovic et al. [26]. conducted the first randomized double-blind placebo-controlled study to assess the efficacy of BoNT in 25 patients with ET (BoNT arm: 13, placebo arm: 12). Two forearm extensors i.e. extensor carpi ulnaris (ECU) and extensor carpi radialis (ECR) and two forearm flexors i.e. flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU) were injected at low dose (extensors: 10U each) and high dose (flexors: 15U each) in all the patients under EMG guidance.

Table 2
Summary of studies on use of BoNT for treatment of essential hand tremor.

Authors	Diagnosis	Subjects	Placebo	BoNT type	Amounts and muscles	Result	Adverse event	Class of evidence
[22]	ET	14	No	Ona-A	Surface and needle EMG used in customized approach to inject mean 108 units in up to 8 muscles.	3 (21%) had > 50% reduction in tremor amplitude. 5 had moderate to marked subjective improvement in functional benefit.	NA	Class III
[23]	ET	17	No	Ona-A	Needle EMG guided injections (mean 108.6 Units)	3/17 had > 50 reduction in tremor amplitude and marked subjective improvement	NA for ET patients. Overall tremor patient 4-/5 hand weakness in ~2/3rd patients	Class III
[26]	ET	25	Yes	Ona-A	50 U, wrist flexors and extensors	Significant reduction on tremor in BoNT treated patients after 4-weeks, compared to placebo-treated patients.		Class II
[24]	ET	20	No	Abo-A	1-2 muscles based on EMG (FCR, Biceps, Triceps, ECR) 25–175U	Significant improvement in severity of tremor as well as the functional disability associated with the tremor.	Finger extension weakness in 15% patients.	Class III
[27]	ET	130	Yes	Ona-A	Low dose group: 10 U in ECR, ECU; 15 U in FCR,FCU. High Dose group: 20 U in ECR, ECU; 30U in FCR, FCU.		Hand weakness in 30% (13/43) of the low-dose group and in 70% (31/45) of the high-dose group	Class III
[28]	ET	24	No	Inco-A	Kinematic analysis of tremor amplitude at wrist, elbow and shoulder joint injecting 4–13 muscles (70–300U per limb)	Significant reduction in total FTM score and QUEST score suggesting improvement in tremor and the quality of life	At 6 weeks, significant hand weakness was seen. No functional arm weakness. 12.5% had severe weakness, 30% reported moderate weakness.	Class III
[29]	ET- above patients with long term follow-up	24	No	Inco-A	Kinematic analysis of tremor amplitude at wrist, elbow and shoulder joint injecting 4–13 muscles (70–300U per limb)		8% (2/24) participants withdrew due to bothersome weakness while 8% (2/24) withdrew due to experiencing no functional benefit and no weakness.	Class III
[31]	ET- treatment Monotherapy	10	No	Inco-A	As above, 6–13 muscles (70–300U per limb). 6 injections -long term follo-up in drug naive patients	Action and postural tremor, quality of life and functional tasks on FTM-C improved with subsequent injections	Significant weakness on muscle grip testing but no functional arm weakness at 6 week after each injection.	Class III
[32]	ET	28	yes	Inco-A	Customized approach, EMG guidance 8–12 muscles (~100 units)	FTM tremor score, Archimedes spirals significantly improved at 4 and 8 weeks.	No significant hand weakness.	Class I
[27]	ET	53	No	Ona-A	Individualized injections, mostly in forearm flexors muscle. Avoided forearm extensor	Follow up for ~2.5 years for all patients (n = 91) with consistent and > 80% improvement in peak effect rating scale.	None of the patients had severe of disabling hand weakness	Class III

BoNT: Botulinum neurotoxin, **ECR**: Extensor carpi radius, **ECU**: Extensor carpi ulnaris, **EMG:** Electromyography, **ET**: Essential tremor, **FCR**: Flexor carpi radialis, **FCU:** Flexor carpi ulnaris, **FTM**: Fahn-Tolosa-Marin tremor rating scale, **Inc-A**: IncobotulinumtoxinA, **NA**: Not available, **Ona-A**: OnabotulinumtoxinA, **QUEST**: Quality of life in essential tremor questionnaire.
Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
The following are also required:
a. concealed allocation.
b. primary outcome(s) clearly defined.
c. exclusion/inclusion criteria clearly defined.
d. adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.
e. For non inferiority 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 non-inferiority., 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 clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

Table 3
Summary of studies on the use of BoNT for treatment of essential head and voice tremor.

Authors	Diagnosis	Subjects	Placebo	BoNT type	Amounts and muscles	Result	Adverse event	Class of evidence
[25]	Essential Head tremor	8	No	Ona-A	NA	Significant improvement in tremor	Transient neck weakness and dysphagia	Class III
[38]	Essential Head tremor	10	Yes	Ona-A	Bilateral SCM (40 units each) and splenius capitis (60 units each). Total 200U.	Moderate to marked improvement in 50% patient in study group. No improvement statistically in clinical and subjective rating,	7 patient had neck weakness and 3 patients had swallowing difficulty	Class III
[37]	Head tremor-Dystonic and non-dystonic	43 (14 non-dystonic, 29 dystonic)	No	Abo-A	Non-dystonic: mean 400U in bilateral splenius capitis, Dystonic: 3 neck muscles	Significant improvement in subjective response, clinical rating and accelerometric recording at 2–3 weeks.	Dysphagia in dystonic tremor (5 patients), non-dystonic (2 patients).	Class III
[42]	Voice tremor	10	No	Ona-A	Vocalis (unilateral: 15U or bilateral 2.5U, crossed over)	Substantial Subjective benefit	Increased breathiness (no difference between unilateral and bilateral injections	Class III
[43]	Voice tremor	15	No	Ona-A	Thyroarytenoid (1–2.5U)	Beneficial in 50–65% patients based on the mode of evaluation	Breathy and week voice, hoarseness, swallowing difficulty	Class III
[44]	Voice tremor	13	No	Ona-A	Vocalis (1.5U each)	Improvement in all patients	Breathiness and dysphagia	Class III
[45]	Voice tremor	16	No	Ona-A	Thyroarytenoid (1U) for horizontal tremors and additional 2.5 U in strap muscles for vertical tremors	Significant improvement in all patients	Hoarseness (when injected to thyroarytenoid), no side effects with strap muscle injection	Class III
[46]	Voice tremor	7	No	Ona-A vs. IA	0.83 U in each adductor complex	IA did not provide more improvement than BoNT	Details not available	Class III
[47]	Essential voice tremor and dystonic tremor	Essential: 5 Dystonic: 10	No	Abo-A vs Propranolol	15 U to Left thyroarytenoid muscle	Dystonic vocal tremors responded significantly to treatment with botulinum toxin but not oral propranolol. Essential vocal tremors did not respond significantly to either treatment	Details not available	Class III

Abo-A: Abobotulinumtoxin A**, BoNT**: Botulinum neurotoxin, **IA**: Injection augmentation, **NA**: Not available, **Ona-A**: OnabotulinumtoxinA, **SCM**: Sternocleidomastoid, Class I, II, III, IV- refer to Table 2 footnote.

After a 4-week follow up, 75% of BoNT treated patients reported mild to moderate improvement in tremor compared to 27% of the placebo-treated patients. Moreover, there was > 30% reduction in tremor amplitude in nine of 12 BoNT-treated subjects and in one of the nine placebo-treated subjects, highlighting the efficacy of BoNT in ameliorating hand tremor in ET. Although 92% of the patients developed weakness in fingers and wrist (extensor > flexor), in none of the cases the weakness was irreversible, and none had any difficulty in carrying out activities of daily life. Later, in 2001, Brin et al. [27]. assessed the efficacy of onabotulinumtoxinA in a larger sample of ET patients (n = 133). Unlike the first RCT by Jankovic et al., in this study, there were two groups of patients in the treatment arm (low-dose group; n = 43 and high-dose group; n = 45). The low-dose group were injected a total of 50U of onabotulinumtoxinA (FCR:15U, FCU:15U, ECR:10U, ECU:10U) and the high-dose group were injected a total of 100 U (FCR:30U, FCU:30U, ECR:20U, ECU:20U). There was statistically significant improvement in postural tremor but its use in clinical practice was limited due to unacceptable weakness in the hand muscles. Thirty percent of the patients (13/43) in the low-dose group and 70% percent (31/45) of the patients in the high-dose group had developed hand weakness, particularly in the finger and hand extensors, after BoNT injection [27]. Pacchetti et al. [24]. injected 20 patients with ET in 1–2 forearm muscles and noticed improvement in tremor severity and functional disability and only 15% of the patients developed finger extensor weakness. In 2016, Samotus et al. [28]. studied hand tremor in patients with ET using sensor-based kinematic analysis at the shoulder, elbow, and wrist joint during various tasks to elicit action and postural tremor. The dosages of the BoNT injections were customized according to tremulous activity sensed by the goniometer. The authors published the 96-weeks follow up data of these patients who received total 6 injections at intervals of 16 weeks [29]. The results were consistent with those reported after the shorter follow up of 38 weeks. The authors also injected 10 treatment naïve patients with ET hand tremor and found significant improvement in action and postural tremor at peak effect (6 weeks) and subsequently improved tremor scores in the long-term follow-up (96 weeks) [30]. In a large retrospective review by Niemann and Jankovic [31], 91 patients with ET, PD or dystonic tremor received onabotulinumtoxinA injections using individualized approach and surface anatomy in the forearm flexors groups (FCR and FCU), avoiding the forearm extensor muscles to prevent hand and extensor finger weakness. Based on peak effect rating scale, more than 80% of the patients had moderate to marked benefit. Out of 1095 limbs injected, 134 (12.2%) were associated with some adverse effect, such as focal weakness but none of the patients had disabling weakness.

Recently, Mittal et al. published a randomized double-blind, placebo-controlled study of 28 patients from a single center where incobotulinumtoxinA was injected in upper limb muscles using a customized approach [32]. The authors injected 8–12 arm/forearm and hand muscles depending on the tremor activity based on clinical examination and needle EMG. There was statistically significant improvement in the Fahn-Tolosa-Marin (FTM) tremor score at 4 and 8 weeks in the incobotulinumtoxinA group compared to the placebo group ($p < 0.003$ and $p < 0.001$ respectively). Also, on the tremor severity scale (National Institutes of Health Collaborative Genetic Criteria tremor score severity), the BoNT-treated group had significant improvement compared to the placebo group at 4 weeks and 8 weeks ($p = 0.003$ and $p = 0.002$, respectively). Mild hand weakness was noted in 21% of patients, and one patient withdrew from the study due to disabling hand weakness.

Although BoNT in ET was not assessed in the most recent evidence-based practice guidelines by the American Academy of Neurology [33], it did receive level B evidence in another critical review [34]. It is likely that even higher recommendation can be accorded to this treatment as a result of more recent studies reviewed above.

2.2. BoNT in essential head tremor [Table 3]

In addition to tremor of the hands, patients with ET may also develop head tremor [19,35], which is usually less responsive than hand tremor to drug therapy [36]. Improvement of 30–50% in head tremor with propranolol and primidone have been reported in several studies [37,38]. There are two OL studies and one RCT yielding mixed results for the treatment of head tremor. In a study by Jankovic and Schwartz [25], 42 of 51 tremor patients had disabling head tremor of various types (essential, dystonic, or combined). Patients with lateral oscillation of the head were injected in both splenius capitis muscles and in one or both sternocleidomastoid muscles if there was an anterior-posterior component. Asymmetric dosages or additional neck muscle injections were often required in patients with dystonic tremor. Sixty-seven percent of the patients with head tremor reported a global improvement after BoNT therapy. In another study, Wissel et al. [37]. described 14 non-dystonic and 29 dystonic head tremor patients who received abobotulinumtoxinA with significant improvement in subjective response, clinical rating and accelerometric recording at 2–3 weeks following the injections. Pahwa et al. [38]. performed a small double-blind placebo-controlled trial in 10 patients with head tremor associated with ET and noted that 50% of the patients in the onabotulinumtoxinA group showed improvement based on the clinician rating compared with only 10% in the placebo group, but no significant difference was found in clinical ratings or accelerometric measurements of head tremor.

2.3. BoNT in essential voice tremor [Table 3]

Voice tremor (VT), the phonatory manifestation of ET, is one of the common symptoms of ET and may be observed in as many as 62% of the ET patients [15,39]. Often coupled with head tremor [40], it is a disabling and frequently socially embarrassing symptom of ET [41]. As VT usually does not respond to medical therapies, several studies have assessed the utility of BoNT in the treatment of VT.

Warrick et al. [42]. injected the vocalis muscles with onabotulinumtoxinA (15U if unilateral and 2.5U if bilateral, later crossed-over) and noted that three out of ten patients had objective improvement of their VT with bilateral injection and two out of nine with unilateral injections. Importantly, majority of patients in this study had subjective reduction in vocal effort that could be attributable to reduced laryngeal airway resistance. Hertegard et al. [43]. injected onabotulinumtoxinA to the thyroarytenoid muscles, and in some cases, to the cricothyroid or thyrohyoid muscles in 15 patients with essential VT. While the subjective evaluation revealed beneficial effect of BoNT in 67% of the patients, the perceptual evaluations demonstrated significant reduction in VT during connected speech ($p < 0.05$). Acoustic analysis demonstrated a nearly significant decrease in the fundamental frequency variations ($p = 0.06$) and a significant decrease in fundamental frequency during sustained vowel phonation ($p < 0.01$). The results of perceptual evaluation coincided most closely with the subjective judgments. Later, Adler et al. [44]. and Gurey et al. [45]. also reported significant subjective and objective improvement in VT after onabotulinumtoxinA injections. Gurey et al. customized the BoNT injection sites based on the type of laryngeal tremor observed in the recruited patients. While patients with horizontal laryngeal tremor received BoNT injections to both thyroarytenoid muscles, those with vertical laryngeal tremor underwent additional infrahyoid muscle injections. All patients had symptomatic improvement with reduced tremor amplitude and 50% of the patients developed post-injection hoarseness lasting 3–8 days without associated aspiration or dysphagia.

In a prospective cross-over trial, Estes et al. [46]. compared the efficacy of BoNT with that of injection augmentation (IA) with buffered hydrogel in patients with VT and reported that IA has no advantage over BoNT in the treatment of essential VT. Another study compared the efficacy of abobotulinumtoxinA to that of propranolol (80 mg/d) in 10 patients with dystonic VT and 5 patients with essential VT [47]. The

Table 4
Summary of the studies on the use of BoNT for tremor in Parkinson's disease.

Authors	Diagnosis	Subjects	Placebo	BoNT type	Amounts and muscles	Result	Adverse event	Class of evidence
[22]	PD	12	No	Ona-A	–	17% > 50% reduction on tremor amplitude. 5 had moderate to marked subjective improvement in functional benefit		Class III
[23]	PD	15	No	Ona-A	needle EMG guided injections (mean 107.5 Units)	2/15 had > 50% reduction in tremor amplitude and marked subjective improvement	NA for PD patients. Overall tremor patient 4-/5 hand weakness in ~2/3rd patients	Class III
[55]	PD	7	No	Inco-A	Individualized dose based on kinematic analysis, 4–6 muscles (80–200U)	UPDRS 20 (rest tremor) improved at 1,2,3 months post injection, UPDRS 21 (action/postural tremor) at 3 months post injection.	5/7 had hand weakness, one had disabling weakness and rest 4 had minor weakness.	Class III
[53]	PD	28	No	Inco-A	Individualized dose based on kinematic analysis	Significant improvement in UPDRS 20 and FTM tremor score.	25% mild grip weakness, 57% mild third finger weakness	Class III
[29]	PD	28	No	Inco-A	Kinematic analysis of tremor amplitude at wrist, elbow and shoulder joint injecting 4–13 muscles (70–300U per limb)	70% reduction in tremor amplitude by kinematics. Hand weakness reduced in follow up visits after decreasing dose.	< 5% had finger flexor weakness at 32, 54, 86 weeks. Reduction in maximal grip strength at 6 weeks.	Class III
[54]	PD	30	Yes	Inco-A	Customized approach, EMG guidance 8–12 muscles (~100 units)	Significant improvement in UPDRS (sections 16 and 20), PGIC, NIHCGC tremor severity score at 4 and 8 week, UPDRS section 21 at 8 week.	No significant hand weakness at 4 weeks in study group	Class I
[31]	PD	6	No	Ona-A	Individualized injections, mostly in forearm flexors muscle. Avoided forearm extensor	Follow up for ~2.5 years for all patients (n = 91) with consistent and > 80% improvement in peak effect rating scale.	None of the patients had severe of disabling hand weakness	Class III

BoNT: Botulinum neurotoxin, **EMG:** Electromyography, **Inc-A**: IncobotulinumtoxinA, **NA**: Not available, **NIHCGC:** National Institutes of Health Collaborative Genetic Criteria, **Ona-A**: OnabotulinumtoxinA, **PD**: Parkinson's disease, **PGIC:** Patient Global Impression of Change, **QUEST**: Quality of life in essential tremor questionnaire, **UPDRS**: Unified Parkinson's Disease Rating Scale, Class I, II, III, IV- refer to Table 2 footnote.

Table 5
Summary of the studies on the use of BoNT for the treatment of tremor in other diseases.

Authors	Diagnosis	Subjects	Placebo	BoNT type	Amounts and muscles	Result	Adverse event	Class of evidence
[58]	MS	23 (36 limbs)	Yes	Ona-A	Agonist and antagonist muscle in tremor subtype under EMG guidance (100 units)	Bain composite tremor score, writing score and Archimedes spirals improved at 6 and 12 weeks.	42% had weakness in hand muscles which improved in 2-weeks of time.	Class III
[57]	Cerebellar Tremor due to MS	5	No	Ona-A	Two muscles in forearm without EMG guidance 50U in both flexor and extensor group.	No statistically significant improvement in rest, postural and intention tremor.	All patients had hand weakness	Class III
[70]	Proximal Upper limb Tremor	19	No	Ona-A	Individualized muscles (upto 8 shoulder muscles)	63% moderate-marked improvement functional activity (drinking, feeding), 21% mild improvement, 15% no improvement.	1 patient had severe weakness, 3 had mild, non-disabling weakness.	Class III
[71]	Jerky, Position-Specific, Upper Limb Action Tremor	8	No	Abo-A	Individualized muscles; 3–6 muscles with mean dose of 190–300 IU	25% much improved, 50% improved and 25% no change.	3/8 had weakness with one patient having clinically significant shoulder weakness	Class III
[59]	Task Specific tremor - Musicians	5	No	BoNT	Based on location of hand tremor. tremor. Total dose of 10–120U or 5–25 U/muscle in 2–6 muscles.	4/5 patients reported improvement in tremor, 1/5 had no improvement.	–	Class III
[60]	Primary Writing Tremor	4	No	Ona-A	Small amount (10–12.5U) in 1–3 muscles.	All patients had moderate to marked improvement in symptoms	–	Class III
[64]	Orthostatic Tremor	7	Yes	Abo-A	Bilateral Tibialis Anterior muscles 200U	No significant improvement in electrophysiological or clinical assessment at 6 weeks	–	Class I
[67]	Essential Palatal Tremor	5	No	Abo-A	20–60U	All patients improved - clicking and tinnitus	–	Class III
[68]	Palatal tremor	5	No	Abo-A	5–15U soft palate	4/5 had improvement in tremor	1 patient had transient weakness	Class III

Abo-A: Abobotulinumtoxin-A**, BoNT**: Botulinum neurotoxin, **EMG:** Electromyography, **Inc-A**: IncobotulinumtoxinA, **MS:** Multiple sclerosis, **NA**: Not available, **Ona-A**: OnabotulinumtoxinA, Class I, II, III, IV- refer to Table 2 footnote.

study found significant improvement in dystonic VT after BoNT injections (15 U in left thyroarytenoid) compared with propranolol. Interestingly, patients with essential VT did not have significant improvement either with BoNT or with propranolol. However, results of this study need to be confirmed as interpretation of this study is limited by small sample size.

In majority of the aforementioned studies, the common side effects of BoNT injection were breathiness, hoarseness of voice, and dysphagia. However, these side effects improved within 1–2 weeks after the BoNT injection. In summary, BoNT appears to be a potential therapeutic option in patients with disabling VT.

2.4. BoNT in the management of tremor in PD [Table 4]

The spectrum of motor symptoms in PD can range from a purely akinetic-rigid subtype in which tremor is absent to a tremor-dominant subtype in which tremor is the earliest and the most prominent feature [48]. Patients with PD typically have a 4–6 Hz resting tremor, but it is the "re-emergent tremor" of PD that is most troublesome as this tremor interferes with patient's ability to hold objects [49,50]. The tremor in PD substantially impacts several domains of quality of life, from physical to psychosocial which adds psychosocial stress in more than 25% of patients [51]. Unlike other cardinal motor features of bradykinesia and rigidity, tremor in PD may be refractory to pharmacologic treatment or may require the use of high doses of levodopa, which can cause debilitating motor fluctuations (ON-OFF phenomena/dyskinesia). Anticholinergic medications (e.g., trihexyphenidyl hydrochloride) can help few patients with refractory PD tremor but their common adverse effects that include cognitive dysfunction, blurring of vision, and urinary retention are poorly tolerated by elderly individuals [52]. BoNT provides a good therapeutic option for such patients.

Currently, there are seven published studies (OL: 6, RCT:1) that have assessed the efficacy of BoNT in PD tremor [22,23,29,31,53–55]. Trosch et al. [22]. treated 12 individuals with PD injecting BoNT into the forearm muscles. They measured tremor amplitude and frequency with accelerometric recording. The mean amplitude reduction for the PD tremor group was 15%, with five patients demonstrating more than 50% amplitude reduction and one patient had 98% reduction. Five patients (38%) reported moderate to marked functional improvement. In another study by Pullman et. a. [23], 187 patients with limb disorders, of whom 15 had PD tremor, were injected with onabotulinumtoxinA. Only two of the 15 patients (13.3%) had major quantitative changes in tremor amplitude ($>$ 50% reduction) and reported satisfactory functional improvement.

In recent years, kinematic analysis has been utilized to understand the dynamic composition of hand tremor. In an OL study by Rahimi et al. [55], seven patients with PD were injected with incobotulinumtoxinA using kinematic analysis of the tremor. The results were promising with improvement in tremor for up to 3 months. After this pilot study, the authors studied the effects of incobotulinumtoxinA in PD tremor using the same technique involving a larger cohort ($n = 28$) [53]. The patients were followed after three injection visits, once in every 16 weeks, for a total of 48 weeks. A statistically significant decrease in the mean Unified Parkinson's Disease Rating Scale (UPDRS) item 20 (rest tremor) at week 16 ($p = 0.006$) and at week 32 ($p = 0.014$), and in the FTM tremor severity scores at week 6 were noted; however, 10 (36%) participants reported muscle weakness. The authors later published a long term follow up with six injections, once in every 16 weeks for 96 weeks [29] The mean BoNT-A dose was 174.1 $\pm$ 68.8 units, injected to a mean of 8.4 $\pm$ 1.9 muscles for 28 PD patients, 10 (34%) of whom either withdrew because of hand weakness, lack of benefit, or other reasons. Niemann and Jankovic [31] included six patients with PD out of a total of 91 patients with tremor treated with onabotulinumtoxinA. The mean dose injected in FCU and FCR aimed to control the postural rather than supination-pronation rest tremor was 47.9 $\pm$ 11.5 units and the patients were followed for 27 treatment visits. Similar to patients with ET, most of the patients with PD reported satisfactory response.

Mittal el. al. published the first RCT examining the role of BoNT in PD tremor [54], wherein the authors injected incobotulinumtoxinA in 8–10 upper limb muscles in a customized injection approach based on the tremor activity as seen on clinical examination and EMG activity. There was significant improvement in rest tremor on UPDRS rating at 4 and 8 weeks in BoNT group compared to the placebo group ($p < 0.001$). There was significant improvement in action/postural tremor on UPDRS rating at 8 weeks after BoNT treatment ($p = 0.01$). There was no statistically significant hand weakness in the study group ($p = 0.19$).

These studies provide evidence of meaningful improvement in PD tremor in short- and long-term follow up assessments after BoNT-A injections. BoNT injections administered in an individualized approach based on distribution, amplitude, and other features of the tremor hold promise in PD patients with troublesome tremor.

2.5. Use of BoNT in management of tremor in other conditions [Table 5]

2.5.1. Tremor in multiple sclerosis

Tremor is observed in approximately 25% of the patients with Multiple Sclerosis (MS) [56]. Tremor in MS patients leads to severe disability and poor quality of life [56]. There is one OL study and one RCT to study the role of BoNT to treat tremor in MS patients [57,58]. In the OL study involving five patients with MS tremor, two forearm muscles were injected without EMG guidance. However, there was no statistically significant improvement in the clinical rating scales. This study had few major limitations such as small sample size and fixed-dose protocol. These limitations were addressed in a study by Van der Walt et al. [58], in which the authors injected onabotulinumtoxinA under EMG guidance in one limb or both upper limbs in 23 MS patients (total 36 limbs) based on the tremor activity. This resulted in significant improvement in the clinical rating scores of hand tremor and ataxia. Although weakness was observed in 42% patients, it improved in all patients within 2-weeks.

2.5.2. Task-specific tremor and role of BoNT

The literature on efficacy of BoNT in task-specific tremor is sparse. In an OL study [59] of patients with musicians' tremor, BoNT was injected in five patients where 80% patients reported improvement in tremor. Total dose of 10–117.5 units of BoNT (unspecified type) was injected in 2–6 muscles (5–23.4 Units/muscle).

The response was apparently better than using primidone or propranolol, and no adverse events were reported. Papapetropoulos et al. [60] injected BoNT in 1–3 muscles with 10–12.5 units/muscle based on the muscle activity in four patients with PWT and all patients had moderate to marked improvement in symptoms. Three out of four patients had mirror dystonia (dystonic movements in resting dominant hand associated with writing with the non-dominant hand). Identifying mirror movement is a critical in selecting correct muscles for the injection with BoNT in patients with PWT and task-specific dystonias [61].

2.5.3. Orthostatic tremor

Orthostatic tremor is a high-frequency tremor ($>$ 13 Hz) of the legs when patient is standing or in supine position when forcefully pressing feet against a vertical platform [62]. It typically affects individuals in the 6th decade of life and it rarely responds to any medical therapy, although clonazepam may provide some relief [63]. In a small OL study of eight patients [64], authors injected 200 units of BoNT in bilateral tibialis anterior muscle with electrophysiologically confirmed orthostatic tremor. There was no improvement at 6 weeks, but injection to additional leg muscles, including thigh muscles, was apparently not attempted.

2.6. Palatal tremor

Palatal tremor or myoclonus is characterized by rhythmic movements of the soft palate, which may occur sporadically (essential myoclonus) or after brainstem or cerebellar lesion (symptomatic myoclonus) and may be associated with disturbing ear click or rhythmical movements of other body parts (myorhythmia) [65,66]. There are two small OL studies of 5 patients each with palatal tremor (total 10 patients), who received BoNT-A injections in soft palate with reported marked improvement in nine out of ten patients [67,68]. It should be, however, pointed out that many patients with palatal tremor (myoclonus) are later found to have functional (psychogenic) etiology [69].

2.7. Dystonic hand tremor

Niemann and Jankovic [31]. successfully treated 31 patients with dystonic tremor with onabotulinumtoxinA (the mean dose was 77.3U; range: 27.5–187.5U). An RCT study, utilizing mirror movement [61] to identify the most appropriate muscles to target, is needed.

2.8. Non-specific tremor

Proximal upper limb tremor due to mixed etiologies has been studied in two OL studies [70,71]. Kim et al. [70], injected 19 patients with onabotulinumtoxinA in shoulder muscles (~8 muscles) and reported that more than 60% patients had moderate to marked improvement in the proximal upper limb tremor with one patient suffering from severe hand weakness. In a smaller OL study [71], eight patients with position-specific jerky proximal tremor, 75% patients had improvement with BoNT injections.

3. A practical approach to BoNT injection for hand tremor

In this section, we summarize what we consider relevant for a practical approach to the injection of BoNT in patients with hand tremor.

3.1. BoNT in hand tremor

1. Examine the tremor in different positions; with hands at rest, at different postures, and during action (e.g. drawing a spiral and writing). Observe for tremor not only in the affected fingers, metacarpophalangeal joint, and wrist but also at the elbow and shoulder.
2. Muscle selection should be individualized and customized to the patients' tremor. For the patients who also have proximal tremor that may contribute to the motor impairment, the arm (biceps, triceps) and even shoulder (deltoid, pectoralis) muscles may need to be injected. If the tremor involves specific fingers without compensatory contraction and contributes to the motor impairment, then lumbricals and other distal hand muscles should be considered for injection.
3. Depending on the response to the tremor movements, the dose can be adjusted and other muscles can be selected for injection based on the response to prior injection.
4. If possible, the extensor muscles should be avoided as these muscles are sensitive to BoNT and their injection frequently causes wrist and finger extension weakness. If needed absolutely, low dose of BoNT and close follow-ups should be done to assess for any weakness.
5. For the task-specific dystonia and primary writing tremor, precaution should be taken to avoid injection in the compensatory muscle rather than dystonic muscle. Having the patient to write (or perform a specific task) with the contralateral, unaffected, hand may elicit dystonic mirror movement in the involved hand which can lead to more appropriate selection of target muscles.
6. The complexity of tremor assessment and the need for individualization implies that at the current stage, these injections should be performed only by those who are highly skilled injectors.

4. Techniques for muscle selection and injection

1. Manual examination: It is based on visual inspection and palpation of the muscles. Muscles are injected based on palpation and activation of muscle based on the anatomical landmarks.
2. Surface EMG: This physiological test may help in the identification of the involved muscles.
3. Accelerometry: Surface EMG can be combined with accelerometer to record the tremor amplitude and severity in particular hand positions or tasks [24].
4. Needle EMG: Needle EMG may help to identify target muscle and also demonstrate tremor activity in the muscle.
5. Ultrasound: This technique may help in direct visualization of the muscle for the muscle injection. Unfortunately, the tremor activity cannot be assessed on ultrasound. Needle EMG can be combined with ultrasound for both direct visualization of the muscle and assessing the tremor activity on EMG.
6. Kinematic analysis: Motion sensor devices placed over the forearm, wrist, elbow, and shoulder joints angular tremor amplitude simultaneously in multiple degrees of freedom such as flexion-extension (wrist, elbow, shoulder joints), pronation-supination, radial-ulnar deviations (wrist joint) and abduction-adduction deviations (shoulder joint) [28,29]. As per Rahimi et al., there is mutual agreement in muscle selection between visual inspection (by an experienced injector) and kinematic analysis of 36% and 53% in ET and PD patients, respectively.

5. Conclusion

Although the studies are limited and largely open-label, BoNT might be a useful tool in alleviating tremor irrespective of the etiology. Majority of the published studies are in patients with hand tremor in ET and PD, head and voice tremor in ET. It is apparent from the aforementioned studies that individualized injections i.e. accurate localization of the muscles and customization of BoNT dose and injection technique yields superior result compared to fixed-muscle-fixed-dose approach. BoNT therapy may play a crucial role in the management of tremors that are refractory to medical therapy or in patients who cannot tolerate the adverse effects of the anti-tremor medications or are not candidates for surgical treatment. BoNT injections using individualized approach adds to the therapeutic armamentarium for patients who have medically refractory tremor, those who are unable to tolerate the anti-tremor medications, and in those who are not or who are considered candidates for surgical intervention.

Conflicts of interest

The authors declare no conflicts of interest.

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