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Standardized algorithm for muscle selection and dosing of botulinum toxin for Parkinson tremor using kinematic analysis

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Abstract

Background: Inadequate efficacy and significant side effect profile makes pharmacological treatment of Parkinson's disease (PD) tremor challenging. Personalized dosing of botulinum toxin type A (BoNT-A) using tremor analysis has shown efficacy and safety for treating upper limb tremor. This study incorporated a novel, standardized treatment algorithm for determining injection pattern and BoNT-A dosing, customizable by the physician, in PD patients with disabling tremor in one or both arms.

Methods: This open-label study included 47 PD participants (25 "De-novo" and 22 "L-dopa") who received 4 serial BoNT-A treatments with follow-ups at 6 weeks post-treatment over 42 weeks. The treatment algorithm utilized kinematic tremor analysis of each participant's whole arm tremor and determined the physician's injection pattern of BoNT-A. Endpoints included changes in angular tremor amplitude, Fahn-Tolosa-Marin (FTM C) tremor scale, Movement Disorder Society-Unified Parkinson's disease rating scale (MDS-UPDRS) tremor-related score, tremor-related quality of life questionnaire, Likert ratings of perceived weakness, and maximal grip strength.

Results: BoNT-A significantly ($p < 0.05$) improved tremor amplitude (41.6%), quality of life (23.0%), UPDRS tremor score (29.6%), and arm function (FTM C; 24.6%) for both treatment cohorts from weeks 6 to 42. Maximum grip strength was reduced between 7.4% and 23.0% at follow-up visits and did not impact activities of daily living. Efficacy was obtained with first injection and remained without adjustment over two serial injection in 45% of participants.

Conclusions: This is the first study to use a fully standardized treatment algorithm for personalization of BoNT-A injection patterns for disabling PD tremor over serial treatments. A sustained alleviation of tremor severity and improved arm function and quality of life fulfills an important unmet need for the treatment of PD tremor. This study demonstrated that BoNT-A can be administered as a monotherapy in tremor-dominant PD or as an add-on therapy for refractory PD tremor.

Keywords: botulinum toxin type A, kinematics, Parkinson's disease, tremor

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Introduction

Tremor occurs in more than 75% of Parkinson's disease (PD) patients and can significantly worsen their quality of life (QoL), both physically and psychosocially.[1] Tremor causes functional interference in more than 60% of PD patients during daily activities such as dressing, fine motor skills, and writing.[2] High dosages of levodopa and anticholinergic medications (e.g. trihexyphenidyl) may improve refractory tremor, but adverse effects such as motor fluctuations/dyskinesias, and cognitive dysfunction and blurred vision, respectively, are poorly tolerated.[3] Surgical approaches such as neurostimulation and ablative therapies can improve tremor and QoL, however variability in beneficial effects, lack of sustained long-term benefit, and permanent surgical adverse effects such as ataxia, brain bleeding, speech and balance

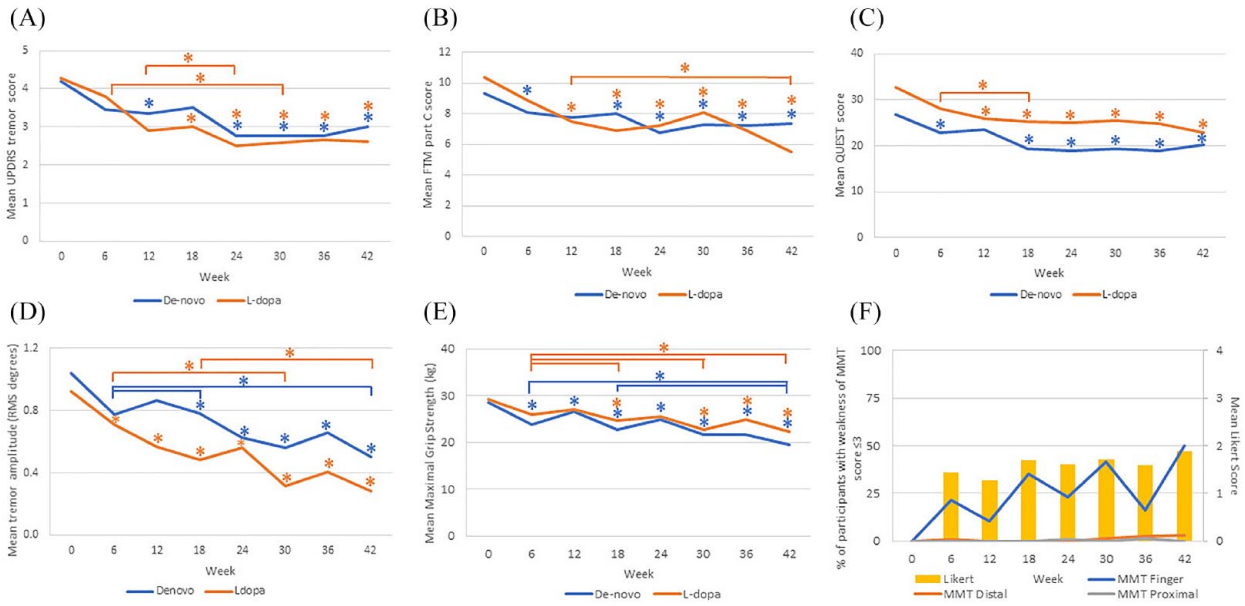

Figure 1. In the "De-novo" and "L-dopa" cohorts, mean changes in (A) tremor severity, (B) functional disability caused by tremor, (C) QoL measures, (D) kinematic wrist tremor, (E) maximal grip strength, and (F) percentage of total participants who had MMT rating ⩽3 in the finger extensor muscle (blue), distal/wrist (orange, and proximal/bicep (grey) and mean Likert score rating participant-perceived weakness (yellow bar) are plotted.

Mean Likert score included severity of perceived weakness ratings in finger drop/wrist/forearm and bicep muscle groups. Statistically significant reductions compared to week 0, or comparisons otherwise stated by a line, are denoted by a coloured asterisk (*) representing "De-novo" (blue) or "L-dopa" (orange) treatment groups.

FTM, Fahn-Tolosa-Marin; MMT, manual muscle testing; QoL, quality of life; QUEST, Quality of Life in Essential Tremor questionnaire; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's disease rating scale.

disturbances are seen in 20–40% of patients.[4,5] Considering this, several recent studies have reported beneficial outcomes using botulinum toxin type A (BoNT-A) injections as a more targeted approach to reduce rest and postural PD tremors and functional disability caused by essential tremor (ET).[6–9] When the injection pattern of BoNT-A is customized to the tremor characteristics of each patient, it yields better efficacy as compared with a fixed-dose approach.[7–10] Accurate selection of muscles to treat with BoNT-A along with tailored dosing for each muscle is crucial for significant functional improvements.

Needle-guided techniques (e.g. electromyography [EMG], electrical stimulation), ultrasound, or surface anatomy are used for accurate muscle targeting for injection. However, these techniques do not aid to objectively determine BoNT treatment patterns.[11] Techniques such as muscle palpation, EMG measurement of muscle tremor, or multijoint kinematic tremor analysis are required to identify tremulous muscles for determining injection patterns.[10,12] Currently there are no standardized assessment methods for the selection of muscle groups to be targeted by BoNT-A for determining tremor treatment pattern without producing excessive arm weakness.

This study used our previously published[7,13] fully standardized treatment algorithm based on kinematic tremor analysis to treat disabling upper limb PD tremor over four serial treatments.

Methods

This open-label, phase II pilot study was conducted at the London Movement Disorders Centre with approval by Western University Health Sciences Research Ethics Board (REB#107433) and registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02668497). The authors confirm that all ongoing and related trials for this drug/intervention are registered. Participants provided signed written informed consent prior to study initiation. Study design and analysis are displayed in the CONSORT flowchart (Supplemental Figure 1). A convenience sampling of 48 PD participants with functionally

debilitating arm tremor in either one or both arms were recruited from the London Movement Disorders Center in London, Ontario, Canada. Four injections of BoNT-A (incobotulinumtoxinA; Xeomin®) were administered every 12 weeks starting on week 0; follow-up visits occurred at peak effect of BoNT-A (6-weeks after each injection), thus a total of eight visits occurred over 42 weeks.

All included study participants had a clinical diagnosis of PD with mild to severe or refractory arm tremor, as determined by clinical exam, and participants reported arm tremor as their primary and most disabling symptom, either *de novo* (PD drug naïve) or stable on oral medications for at least 3-months. Newly diagnosed PD participants who were not started on levodopa therapy ("De-novo") and tremor was their primary and most debilitating symptom and PD participants optimized on levodopa medication ("L-dopa") for symptomatic treatment for their other cardinal motor symptoms but tremor is not optimally alleviated were recruited. Exclusion criteria included: a history of stroke or amyotrophic lateral sclerosis, underlying arm muscle weakness or any related compartmental muscle syndrome, history of allergic/side effect reaction to botulinum toxin, contradictions per the Xeomin® drug monograph and pregnant women.

Clinical outcome measures included: Movement Disorder Society-Unified Parkinson's disease rating scale (MDS-UPDRS)-items rating severity of rest, postural and action tremor, the Fahn-Tolosa-Marin tremor rating scale part C (functional interference caused by tremor), and the tremor-related QoL questionnaire – Quality of Life in Essential Tremor (QUEST). Hand weakness was monitored using a Baseline® hydraulic hand dynamometer (White Plains, NY) to measure maximal grip strength, manual muscle testing (MMT) assessed finger, wrist and elbow flexor/extensor strength, and a Likert style participant-reported rating of arm muscle weakness [0: no weakness; 1: slight weakness in non-injected muscles (e.g. finger drop); 2: mild weakness in injected muscles; 3: moderate weakness in injected muscles; 4: severe weakness in injected muscles with functional loss].[7,14]

Kinematic tremor assessment and analysis was conducted while on no medications ("De-novo") and while "L-dopa" participants were in their "ON" state at each visit as previously described;[14,15] tremor assessments were conducted within 1–2 h of levodopa dose intake. Wireless goniometer and torsiometer motion sensors (Biometrics Ltd.) were placed over the wrist, elbow and shoulder joints and along the inside of the forearm to capture tremor as participants performed a series of six scripted tasks that simulate natural postures over three trials: two tasks with arm rested on their lap or supported by armrest, two tasks with arms outstretched with palms facing downwards or inwards, and two tasks involving holding an empty cup or a cup with a 1-pound (0.454 kg) weight in their most tremulous position. Kinematic recording was initiated when tremor either at rest or those with a re-emergent tremor was noticeable visible by the assessor. The DataLITE sensor acquisition system (PC Software version 8.7) collected the data and was processed using a software algorithm written in MatLab® (V.2014b) that provided tremor characteristics for each joint: amplitude of tremor [angular root mean squared (RMS degrees)], directional breakdown of muscle groups, and separation into each planes of motion for the wrist, elbow, and shoulder.[7,14–16]

For the first treatment, an injection pattern was determined using our treatment algorithm[7,13] with physician oversight to confirm muscle and dosage parameters. This algorithm[7] is based on the injector's own clinical experience and insight on appropriate starting dose and muscle selection gained from the previous study.[14–16] Subsequent modifications to BoNT-A injection patterns were based on changes in tremor amplitude and participant perceived benefit and weakness.[7] Total BoNT-A dosages ranged from 20 to 390 U per arm. Injections were performed using a needle [1 inch (2.54 cm) long 30g] under electromyographic (EMG; Myoguide® portable EMG machine, Bolton, ON, Canada) guidance.

Primary endpoints were changes in tremor amplitude at each joint over the eight visits. Secondary endpoints were tremor-related clinical scale measures. Statistical analysis (IBM® SPSS® v.20) was performed to analyze kinematic and clinical data. Participants were grouped based on medication state, "De-novo" or "L-dopa". Both PD cohorts were recruited to investigate whether BoNT-A was efficacious as a monotherapy for "De-novo" participants or as an adjunct therapy for "L-dopa" participants. A non-parametric Friedman one-way repeated measures analysis of variance (ANOVA) test using confidence intervals of 95% ($\alpha = 0.05$) with *post hoc* Bonferroni corrections for multiple comparisons was performed to compare between baseline (week 0) to

all time-points (weeks 6–42), at peak effect (weeks 6, 18, 30, 42) and at re-injection (weeks 0, 12, 24, 36).[7] Differences in tremor severity (measured clinically and kinematically) between groups for each time-point were determined by a separate independent samples Mann–Whitney *U* test; a null hypothesis that tremor severity was not statistically different between PD cohorts ($p = 0.05$).

Results

Demographics

Of the consented 48 participants, 47 subjects met study criteria (Supplemental Figure 1) and their demographics and baseline scores are outlined in Table 1. Four "De-novo" and four "L-dopa" participants withdrew from the study due to lack of tremor relief and/or excessive muscle weakness.

In total, 38 (81%) participants received BoNT-A injections in all muscle groups at the wrist, elbow, and shoulder. Individual muscle dosages injected per wrist/forearm, elbow and shoulder muscle groups ranged from 5 to 20 U, 15 to 40 U, and 10 to 50 U, respectively, in a mean number of 11 muscles (ranging from 7 to 13). Mean total dose per arm joint is displayed in Table 2. A total of 21 (48%) participants maintained the same injection pattern for the first two treatment cycles before adjustment was required. Ten (27%) participants kept the same dosing pattern for all four treatment cycles. Overall, 18 (41%) participants required an increased dose and five (11%) participants required a reduction in dose after the first treatment.

Clinical outcomes

Tremor severity between PD cohorts was not statistically significant over the treatment course. Mean tremor severity in "De-novo" participants was significantly reduced by 32.6% ($\chi^2 = 24.454$; $p = 0.001$) after the second injection (from weeks 24 to 42) (Figure 1A). Tremor severity of the "L-dopa" participants was significantly reduced by 41.4% [$\chi^2(7) = 29.376$; $p < 0.005$] after the second injection and continued to be reduced by a mean 38.5% ($p < 0.005$) after the third injection (from weeks 30 to 42). Arm functionality [$\chi^2(7) = 14.366$; $p = 0.045$] and QoL (QUEST) [$\chi^2(7) = 17.430$; $p = 0.015$] was significantly improved by a mean 24.9% from weeks 18 to 42 in the "De-novo" cohort (Figure 1B, C). In the "L-dopa" cohort, both arm functionality [$\chi^2(7) = 23.644$; $p = 0.001$] and QoL [$\chi^2(7) = 18.577$; $p = 0.01$] significantly improved by a mean 24.3% 12-weeks after the first injection and maintained a mean 28.8% improvement from weeks 18 to 42.

Kinematic outcomes

Wrist tremor severity between PD cohorts was not statistically different over the 42-week study. Mean wrist angular tremor amplitude across all six scripted tasks was significantly reduced by 24.9% [$\chi^2(7) = 26.713$; $p = 0.001$] 6-weeks after the second injection and was further reduced by 43.6% ($p < 0.005$) after the third injection from weeks 24 to 42 in the "De-novo" cohort (Figure 1D). In the "L-dopa" cohort, mean angular wrist tremor amplitude was significantly reduced by 23.4% [$\chi^2(7) = 38.593$; $p = 0.004$] 6-weeks after the first injection and was further reduced by 52.8% ($p < 0.005$) from weeks 12 to 42. Mean % change in wrist tremor severity over the treatment course (weeks 6–42) was observed to be 14.1% greater in the "L-dopa" cohort, although this was not statistically significant.

Mean elbow tremor amplitude was significantly reduced by 29.2% [$\chi^2(7) = 21.676$; $p = 0.003$] and by 50.1% [$\chi^2(7) = 42.134$; $p < 0.005$] over the treatment course (weeks 6–42) in "De-novo" and "L-dopa" cohort, respectively. Similarly, mean shoulder tremor amplitude was significantly reduced by 33.6% [$\chi^2(7) = 14.588$; $p = 0.042$] and by 42.0% [$\chi^2(7) = 45.491$; $p < 0.005$] over the treatment course in the "De-novo" and "L-dopa" cohorts, respectively.

Tolerability to BoNT-A

In the "De-novo" cohort, mean maximal grip strength was significantly reduced by 17.0% [$\chi^2(7) = 73.795$; $p = 0.004$] 6-weeks after the first injection, but returned to a mean change of 7.4% ($p = 0.041$) at 12-weeks for the second injection cycle, then grip strength reduced by 23.0% ($p < 0.005$) from weeks 18 to 42 (Figure 1E). In the "L-dopa" cohort, mean grip strength was significantly reduced by 16.0% [$\chi^2(7) = 53.987$; $p < 0.005$] at week 18 and then by 20.4% ($p < 0.005$) from weeks 30 to 42.

Out of the 313 total follow-up assessments of MMT in all participants, 36.1% (113/313) of assessments had finger extensor weakness (MMT rating of ≤ 3) in either hand at any time-point,

Table 1. Demographics and baseline measures of quality of life (QUEST), arm functionality (FTM part C) and tremor severity for all participants.

Patient ID	Study arm	Arm(s) injected	Gender	Age	Motor-dominant hand	Total daily levodopa dose (mg)	Baseline Scores			
							Summed tremor MDS-UPDRS score* (/12)	Mean Wrist tremor amplitude (RMS degrees)	QUEST score (/120)	FTM part C sub-score for functional disability (/32)
1	De-novo	Right	M	71	R		6	2.6	44	19
2	L-dopa	Left	F	65	R	400	0	0.7	33	6
3	De-novo	Right	M	74	R		2	0.4	34	16
4	De-novo	Both	M	67	R		6 (R); 4 (L)	1.3	19	10
5	De-novo	Left	F	55	R		5	0.9	28	6
6	L-dopa	Both	M	61	R	1000	7 (R); 6 (L)	1.7	38	20
7	De-novo	Left	F	78	R		3	0.2	14	2
8	De-novo	Both	F	81	R		3 (R); 3 (L)	0.6	19	7
9	L-dopa	Left	M	80	R	500	6	0.9	25	7
10	L-dopa	Both	M	74	R	400	6 (R); 4 (L)	0.7	37	14
11	L-dopa	Left	M	77	R	1000	4	1.0	0	0
12	L-dopa	Left	M	73	L	800	6	1.8	38	9
13	L-dopa	Left	M	70	R	1000	2	0.3	27	8
14	De-novo	Right	M	70	R		3	1.6	22	7
15	L-dopa	Both	M	81	R	400	4 (R); 3 (L)	0.6	43	10
16	De-novo	Right	F	73	R		7	0.9	22	8
17	L-dopa	Both	M	67	R	570	7 (R); 6 (L)	2.2	77	22
18	L-dopa	Right	M	83	R	800	5	0.6	18	13
19	De-novo	Left	M	64	R		8	4.2	45	8
20	De-novo	Right	M	57	R		2	0.8	12	5
21	De-novo	Right	M	78	R		3	0.5	7	4
22	L-dopa	Right	M	75	R	750	6	1.2	27	10
23	L-dopa	Left	M	60	R	400	3	0.2	22	6
24	L-dopa	Both	M	63	R	750	4 (R); 2 (L)	0.7	15	13
25	L-dopa	Left	M	66	L	800	3	0.4	44	8
26	L-dopa	Both	M	85	R	600	2 (R); 4 (L)	0.4	32	9

(Continued)

Table 1. (Continued)

Patient ID	Study arm	Arm(s) injected	Gender	Age	Motor-dominant hand	Total daily levodopa dose (mg)	Baseline Scores			
							Summed tremor MDS-UPDRS score* (/12)	Mean Wrist tremor amplitude (RMS degrees)	QUEST score (/120)	FTM part C sub-score for functional disability (/32)
27	L-dopa	Left	M	67	R	400	4	0.2	35	7
28	L-dopa	Both	M	80	R	850	4 (R); 5 (L)	0.8	31	13
29	L-dopa	Right	F	63	R	800	5	3.2	42	19
30	De-novo	Both	M	87	R		5 (R); 2 (L)	0.2	40	16
31	De-novo	Right	F	60	R		4	0.7	25	7
32	De-novo	Left	M	79	R		2	0.3	18	5
33	De-novo	Both	M	79	R		6 (R); 4 (L)	1.3	47	14
34	L-dopa	Both	M	69	R	300	4 (R); 4 (L)	0.4	45	13
35	L-dopa	Left	M	68	R	400	4	0.2	30	6
36	De-novo	Left	M	64	R		5	1.1	10	6
37	De-novo	Right	M	67	R		8	3.1	51	18
38	De-novo	Both	F	77	R		4 (R); 2 (L)	0.7	33	9
39	L-dopa	Right	M	83	R	800	3	0.1	8	6
40	De-novo	Right	M	75	R		5	0.3	22	17
41	De-novo	Right	M	71	R		4	0.9	19	9
42	De-novo	Right	M	71	R		4	1.5	58	16
43	De-novo	Right	M	67	R		2	0.4	18	6
44	De-novo	Right	M	72	R		2	0.6	20	4
45	De-novo	Right	M	69	R		6	1.9	19	10
46	De-novo	Left	M	75	R		6	0.5	25	5
47	L-dopa	Left	M	70	R	800	5	1.5	52	9
De-novo	25	5 Both	6F	71.2 ± 7.6	0L	N/A	4.4 ± 1.9	1.1 ± 1.0	26.8 ± 13.6	9.4 ± 5.0
L-dopa	22	8 Both	2F	71.8 ± 7.7	2L	660 ± 228	4.3 ± 1.7	0.9 ± 0.8	32.7 ± 16.0	10.4 ± 5.2

F, female; FTM, Fahn-Tolosa-Marin tremor rating scale; L, left; M, male; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's disease rating scale; QUEST, Quality of Life in Essential Tremor questionnaire; R, right.
*Indicates summed rest, postural and action tremor severity scores.

Table 2. Mean total arm dosages and mean dosages allocated to wrist, elbow, and shoulder muscle groups for all four injection cycles are shown for "De-novo" and "L-dopa" participant cohorts.

"De-novo"	Total arm dose (U)				Wrist total dose (U)				Elbow total dose (U)				Shoulder total dose (U)			
	Week 0 (1st injection) (*n* = 47)	Week 12 (2nd injection) (*n* = 44)	Week 24 (3rd injection) (*n* = 40)	Week 36 (4th injection) (*n* = 37)	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Unilateral Mean	154	160	186	191	58	65	71	71	48	50	54	54	50	56	71	70
SD	60	82	85	80	18	26	33	35	17	19	22	20	33	36	32	32
Bilateral Mean	138	119	133	140	49	55	54	57	41	47	44	46	48	37	42	45
SD	47	62	35	49	18	17	20	28	12	14	15	16	27	20	4	7
"L-dopa"	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Unilateral Mean	139	169	157	165	47	56	57	58	42	46	48	50	54	59	60	62
SD	52	75	51	46	17	22	19	19	15	18	18	17	23	26	23	23
Bilateral Mean	129	127	123	119	50	46	47	43	39	39	40	37	46	53	52	52
SD	48	51	46	43	16	16	15	13	11	11	12	13	23	21	17	19
Range* (min-max)	55–260	60–325	55–390	65–390	35–80	25–115	25–150	15–150	30–80	30–90	20–100	20–100	0–100	0–120	0–140	0–140

*Includes total dose per participant (unilateral and those treated bilaterally).
SD, standard deviation; U, botulinum toxin type A unit.

whereas BoNT-A injected into targeted wrist muscles caused mild weakness in 1.9% (6/313) of assessments (Figure 1F). Proximal weakness (elbow muscles) occurred in one "L-dopa" participant at third and fourth re-injections. The mean Likert score was 1.6 ± 0.7 (median = 1.0) indicating slight weakness in non-injected muscles (e.g. finger drop) and mild weakness in injected muscles over the treatment course (Figure 1F). At follow-ups, the mean Likert score was 1.8 ± 0.8 (median = 2.0). A Likert score $\geqslant 1$ representing the presence of unwanted muscle weakness was reported by a mean 80.3% (36/45) of participants over the treatment course. A Likert score of 3 (moderate weakness) was reported in 50.0% (11/22 including 12 bilaterally treated) of "L-dopa" participants compared with 24.0% (6/25) of "De-novo" participants; a rating of 3 occurred more than once in 18.1% (4/22) of "L-dopa" participants (all were treated bilaterally) and 12.0% (3/25) of "De-novo" participants. However out of the 17 participants who scored a 3/4 on the Likert scale (marked perceived weakness), six participants withdrew due to functional impairment but demonstrated minimal weakness from objective assessment (MMT $\geqslant 3$).

Discussion

This is the first study to customize BoNT-A injection pattern determination using our treatment algorithm and kinematic tremor analysis of each PD participant's whole arm tremor over four serial treatments. Significant improvements in functional ability and QoL were reported in "De-novo" and in "L-dopa" (treatment-refractory tremor) cohorts following the first injection, with an observed trend of tremor reduction being on average 14.1% greater in the "L-dopa" cohort over the treatment course (weeks 6–42). Interestingly, our previous study of kinematic-guided BoNT-A therapy for PD tremor did not produce sustained QoL and functional improvements,[14] thus highlighting the importance of automating tremor assessment and treatment pattern determination. This immediate QoL and functional improvement in our present study contrasts results reported by another group with a combined 35 years of experience treating upper limb tremor with BoNT-A where three injection cycles were required for treatment optimization.[12,17] As compared with using multi-joint kinematics in our study, only accelerometry-based injection patterns produced significant tremor reduction, but functional benefit was reported in only two (13.3%) patients.[18] In the first single-injection, randomized-control trial (RCT) involving EMG technology for identifying tremulous muscles in PD, a significant tremor reduction with a low incidence of hand weakness was reported.[10] In contrast to our study, QoL changes were similar to the placebo group and no functional outcomes were observed.[10] Although these previous studies confirm the short- and long-term benefits of BoNT-A therapy for reducing tremor, kinematic tremor data generated from these technologies (EMG or ultrasound) still requires clinical interpretation to generate injection patterns and assessments do not mimic activities of daily living. Multi-joint tremor analysis utilized in our studies enabled the generation of a fully standardized treatment algorithm, which may have contributed to the early and sustained functional and QoL improvements.[7]

Finger extensor weakness is a common side effect as observed in prior tremor-BoNT-A treatment studies due to either the spread of BoNT-A from targeted muscles or mistargeting. However, finger weakness was not viewed to be functionally disabling to terminate treatment.[14] Although the implementation of the treatment algorithm in the current study did reduce the incidence of finger drop as compared with the pilot study,[14] there is an opportunity to improve targeting of the supinator and extensor carpi muscles by using ultrasound and by reducing diffusion by hyper-concentrating BoNT-A during reconstitution (e.g. 0.5 cc saline to 100 U BoNT-A).

Wrist/hand weakness, assessed using the MMT, affected 1.9% of all participants, which was similar to Mittal *et al.*'s RCT study who reported 6.6% of patients had disabling hand weakness.[10] Nonetheless, our study had 8/47 (four "L-dopa" and four "De-novo") participants who withdrew due to weakness (6/47) or lack of benefit (2/47). Customized-dose injections have been shown to be superior to fixed-dose approaches as fixed-dosages resulted in 30–80% of participants developing functionally interfering hand weakness while 15–57% experienced mild to moderate finger drop.[9,19] Our fully standardized treatment approach ultimately reduced the incidence of hand weakness; however, the incidence of slight to moderate finger extensor weakness was comparable and was present for >4 weeks. In addition to using EMG, ultrasound needle guidance technique may help improve the delivery of BoNT-A

into the muscle belly and ultimately minimize mistargeting. The "L-dopa" cohort averaged a lower total dose that relates to lower tremor severity but resulted in a higher incidence of participants perceiving moderate unwanted muscle weakness, which occurred mainly in those treated bilaterally, compared with the "De-novo" cohort. It is possible these "L-dopa" participants are more advanced in their disease course and perceptual deficits in distinguishing between muscle weakness, bradykinesia, and rigidity.[20] This was revealed in differences between the mild objective MMT measures of weakness and more severe participant-perceived weakness (Likert scale).

Many participants (48%) did not require any adjustments to their injection pattern for two treatments and 27% of participants did not require any modifications to their injection pattern over the four treatment cycles. Similarly, in our ET study that utilized the same algorithm to aid in customization of muscle and dose patterns, 29% of participants required no changes to their treatment pattern over 3 serial treatments.[7] The treatment algorithm is currently optimized for mild to moderate tremor to produce efficacy at the lowest possible dose, however those with more severe tremor, large muscles, or higher adiposity (increased diffusion from target muscle) may require increased dosages at subsequent treatments. These factors could be considered for further optimizing our treatment algorithm such as by adding arm circumference measurements.

This study is limited by the lack of a placebo-controlled arm as serial treatments limits a placebo-response in participants;[10] however, a single-dose, placebo-controlled study investigating the same protocol used in in this study demonstrated efficacy and safety of our treatment algorithm for BoNT-A injections in ET patients.[13] Although this was a single-injector study, the injector was blinded to all study assessments and all injection pattern calculations/modifications to minimize bias; for safety, the injector confirmed treatment pattern prior to administering BoNT-A.

Assessing the pattern of multi-joint tremor is difficult for any injector. Using kinematic analysis and our treatment algorithm standardizes the assessment of tremor and simplifies injection pattern determination. This treatment approach could be used as a teaching tool and transferred easily amongst injectors. Furthermore, early efficacy sustained over all serial treatments reported in our study suggests BoNT-A is an important option as a mono- or adjunct-therapy for PD tremor. Once assessment variability is removed, techniques such as EMG and ultrasound for localization and changing concentration of BoNT-A reconstitution can further minimize weakness profile. Future studies should focus on placebo-controlled, serial treatments applying a standardized and customized dosing approach to target muscles at an appropriate dose relating to the severity of tremor at each arm joint.

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Conflict of interest statement

Ms. Samotus report no conflict of interests. Dr. Jog is a scientific advisor and receives research financial support from the following companies: AbbVie, Allergan Inc., Boston Scientific, Ipsen, MDDT Inc., Medtronic, Merz Pharma, Novartis, and Teva Pharmaceuticals. Mr. Lee is a former researcher at the London Movement Disorders Centre and now is a MDDT Inc. employee, and a scientific advisor for Merz Pharma. Dr. Jog and Mr. Lee are commercializing medical technologies based on this research with registered trademarks for TremorTek®, Hinge Diagnostics®, and have issued patents (PCT/CA2013/000804, PCT/CA2014/050893) assigned to MDDT Inc. Both Mr. Lee and Dr. Jog are shareholders of MDDT Inc.

Ethics statement

The study reported in this manuscript has been approved by the Western University Health Sciences Research Ethics Board (REB#107433) and have, therefore, been performed in accordance with the World Medical Association Declaration of Helsinki. All persons gave their informed written consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study were omitted. The study was prospectively registered at ClinicalTrials.gov (NCT02668497).

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Supplemental material

Supplemental material for this article is available online.

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