

Botulinum Neurotoxin A for Hand Tremors in Parkinson's Disease: A Meta-Analytic Study



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ABSTRACT

Background: Resting tremor is a prominent cardinal motor symptom of Parkinson's disease (PD). In some cases, the tremor may be refractory to dopaminergic and anticholinergic treatment. Multiple studies were previously done to evaluate the effectiveness of Botulinum Neurotoxin A (BoNT/A) with essential tremors and dystonia, but data regarding its use on tremors of PD is still lacking.

Objective: This meta-analytic study aims to determine the effectiveness of BoNT/A in treating tremors of patients with PD.

Data Sources: Researches were searched at PubMed, ScienceDirect and EBSCO Host.

Review Methods: Articles on the effect of BoNT/A on PD hand tremors were searched. Studies and data pertaining to non-PD tremors like essential tremors excluded in the analysis due to difference in pathophysiology. Standardized mean difference was used as the effect measure and was computed with Review Manager version 5.4 software.

Results: Three open label studies were used for final analysis in this study. Studies included are those pertaining to tremors due to PD. Pooled estimates showed a significant change in decreasing tremor score after BoNT/A injection.

Conclusion: Botulinum Toxin A injections can be used to manage PD tremors effectively.

Keywords: Botulinum neurotoxin A, Botox A, Btx, tremors, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a widespread progressive neurodegenerative disorder with a prevalence of 0.4% to 2% affecting mainly the elderly population. [1,2] It primarily manifests with resting tremors, bradykinesia, rigidity and postural instability.[1] But it also involves a myriad of symptoms, both motor and non-motor, such as dystonia, pain, sialorrhea, constipation, urinary dysfunction, cognitive impairment and depression to mention a few.[3] These symptoms occur because of the degeneration of dopaminergic neurons in the substantia nigra pars compacta and deposition of the Lewy bodies in the brain.[2] At the moment, there is no permanent cure for PD. Patient's with PD are only being treated symptomatically. The mainstay treatment is dopamine agonists (levodopa/carbidopa). These are used to substantially improve cardinal symptoms such as bradykinesia, rigidity, shuffling of gait and hypophonia, especially in the early stages of disease. Anticholinergic (biperiden) is also being utilized, especially if tremor is the predominant symptom.[1,4-6]

Resting tremor is a prominent cardinal motor symptom of PD. PD tremor is often described as "pillrolling" but this tremor is not isolated to the

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fingers. PD tremors may also involve the jaw, chin and tongue.[4,5,7] The wrist tremor may cause flexion-extension of the joint, or rotate and deviate it side to side. Tremors of the elbow become increasingly harder to manage.[4] Because of these symptoms, PD tremors may affect patients physically and activities of daily living including but not limited to writing, eating and dressing becomes a challenge, and patients may eventually require assistance. Severe cases of PD may also affect the patient's posture and sleep.[4] Then, it should be stressed equally that these limitations in activities of daily living may also cause psychosocial stress in some patients.[1,6]

We are seeing a number of PD patients being refractory to conventional treatment regimen. The treatment of PD symptoms with botulinum neurotoxin is being studied presently. There are seven well-known antigenically distinct serotypes of botulinum neurotoxins, but only types A (BoNT/A), B and E colonizes the human body.[4] Botulinum neurotoxin inhibits the release of acetylcholine (ACh) at the neuromuscular junction (NMJ) thereby preventing muscular contraction.[2,4,7-10] Botulinum neurotoxin is popularly known for its contribution to the aesthetic industry and is now gaining importance in the management of movement disorders.

The aim of this study is to determine the efficacy of BoNT/A in treating hand tremors from PD. With the mechanism of action of botulinum neurotoxin discussed as inhibitory to neuromuscular transmission, it may be considered for use in tremors[9] but mostly for the management of essential tremors as of the moment. Double-blind, placebo-controlled trials were conducted before on essential tremors and botulinum toxin with satisfactory results. Despite the growing amount of studies on the use of BoNT/A on tremors, it is still not as widely utilized. Currently, the use of botulinum toxin in tremors is still under Level U recommendation.[2] Therefore, this study aims to determine the efficacy of BoNT/A in controlling tremors, and to even expand its use by focusing only on hand tremors from PD.

METHODS

Review Question and Eligibility Criteria

This study included all possible experimental studies and trials on the effect of BoNT/A on PD tremors. The P.I.C.O.T. framework (*population, intervention,*

comparison, outcome and timeframe) was used in developing our clinical question, guide the literature search and evaluate eligibility of potentially relevant research papers.[11] In terms of the population of interest, we searched for studies that involved tremors in PD regardless of the respondent's age or sex. The intervention for these studies is botulinum toxin as the means to control or decrease the tremors from PD. The primary outcome of interest was a decrease in tremors. The studies used the Unified Parkinson's Disease Rating Scale (UPDRS) to assess the effect of BoNT/A on PD tremors. Some studies also utilized the Fahn-Tolosa-Marin tremor rating scale (FTM), Tremor Assessment Form (TAF) and National Institutes of Health Collaborative Genetic Criteria (NIHCGC). But for uniformity, only the UPDRS results were analyzed for this meta-analysis. This research did not impose any limitation on the date of publication of research papers. Only papers written in English were included in this study.

Data Items

The variable that was of primary interest in this present study was tremors in PD. We employed the P.I.C.O.T. framework in developing our clinical question, guiding our literature search and assessing eligibility of potentially relevant research articles.

Information Sources

The literatures used in this study were gathered through various search engines and online databases such as PubMed, Science direct and EBSCO Host. Other literatures were also given directly by one reviewer to the co-reviewer from his personal files of journals.

Search

The keyword search on databases was done with the following keywords: "*botulinum toxin AND parkinson disease AND tremor*", "*botox AND parkinson disease AND tremor*" and "*btx AND parkinson disease AND tremor*". The search was limited to articles on clinical trials on human data using BoNT/A on patients with tremors secondary to PD. Clinical trials which involved tremors not caused by PD were excluded. Articles which utilized botulinum toxin B were also excluded.

Study Selection

Two independent reviewers conducted literature search and eligibility assessment. Both reviewers extracted research data and performed quality assessment of the identified articles. Disagreements in judgment between the reviewers were resolved by discussion.

Title, keywords and abstract of publications identified according to the search strategies were independently screened by these reviewers. Inclusion criteria for title and abstract screening included trials or experimental studies on BoNT/A on PD tremors. The same reviewers independently scrutinized full-text researches for final inclusion in the study. Excluded research articles and reasons for their exclusion were recorded and tabulated. In instances of disagreement, these discrepancies were managed through a discussion.

Quality Appraisal and Assessment of Risk of Bias

The quality of the articles was critically appraised using the The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool.[12] The following were assessed: *Bias due to confounding, Bias in selection of participants into the study, Bias in classification of interventions, Bias due to deviations from intended interventions, Bias due to missing data, Bias in measurement of outcomes and Bias in selection of the reported result.* The ROBINS-I ranks as follows: low, moderate, serious and critical.

In the assessment of risks of biases across the selected researches, the Cochrane Risk-of-Bias tool was employed. The following aspects of the researches were assessed: *random sequence generation (selection bias), allocation concealment (selection bias), selective reporting (reporting bias), other sources of bias, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias).* Each study was rated as low risk, unclear risk or high risk of bias.

Summary Measures

The mean and standard deviation (SD) of tremor scores were utilized to calculate the standardized mean difference (std. MD) and was used in meta-analysis.

Data Analysis and Synthesis of Results

For visual presentation, forest plots were used to generate for each outcome to show variations among studies and pooled analyses. Test for heterogeneity was carried out based on Cochran's Q and I². As a guide, I² values of 25% may be considered low, 50% moderate and 75% high. For cases with moderate to high heterogeneity, a random effects model was used to provide a conservative mean difference estimate; otherwise the fixed effect model was preferred. Calculations were performed using Review Manager version 5.4 software. Publication bias was also evaluated using the same software. Cochran Q-value with p-value less than 0.05 was considered significant.

RESULTS

Study Selection

The search retrieved a total of 600 articles from year 2000 until 2018. Articles involving non-Parkinson tremors or other PD symptoms other than tremors were removed. After screening these publications, 28 remaining papers were screened for eligibility. From these articles, 23 were further removed due to the following: they were review articles, case reports and qualitative studies. The articles that were used in this study involved patients with hand tremors from PD refractory to conventional management as well as their most bothersome and disabling symptom. As presented in the PRISMA Flow Diagram of Study Selection (see Figure 1), a total of three articles were included in this meta-analytic study.

Study Characteristics

Table 1 summarizes the main characteristics of all included studies. All articles are open label studies and were conducted in Canada. A total of 61 participants' data were analyzed for meta-analysis, all diagnosed with PD and having tremors involving the upper limb. The table also illustrates that only BoNT/A was the administered intervention for all participants.

Synthesis of Results and Meta-Analysis

Unified Parkinson's Disease Rating Scale (UPDRS) was the parameter used in this meta-analysis since it

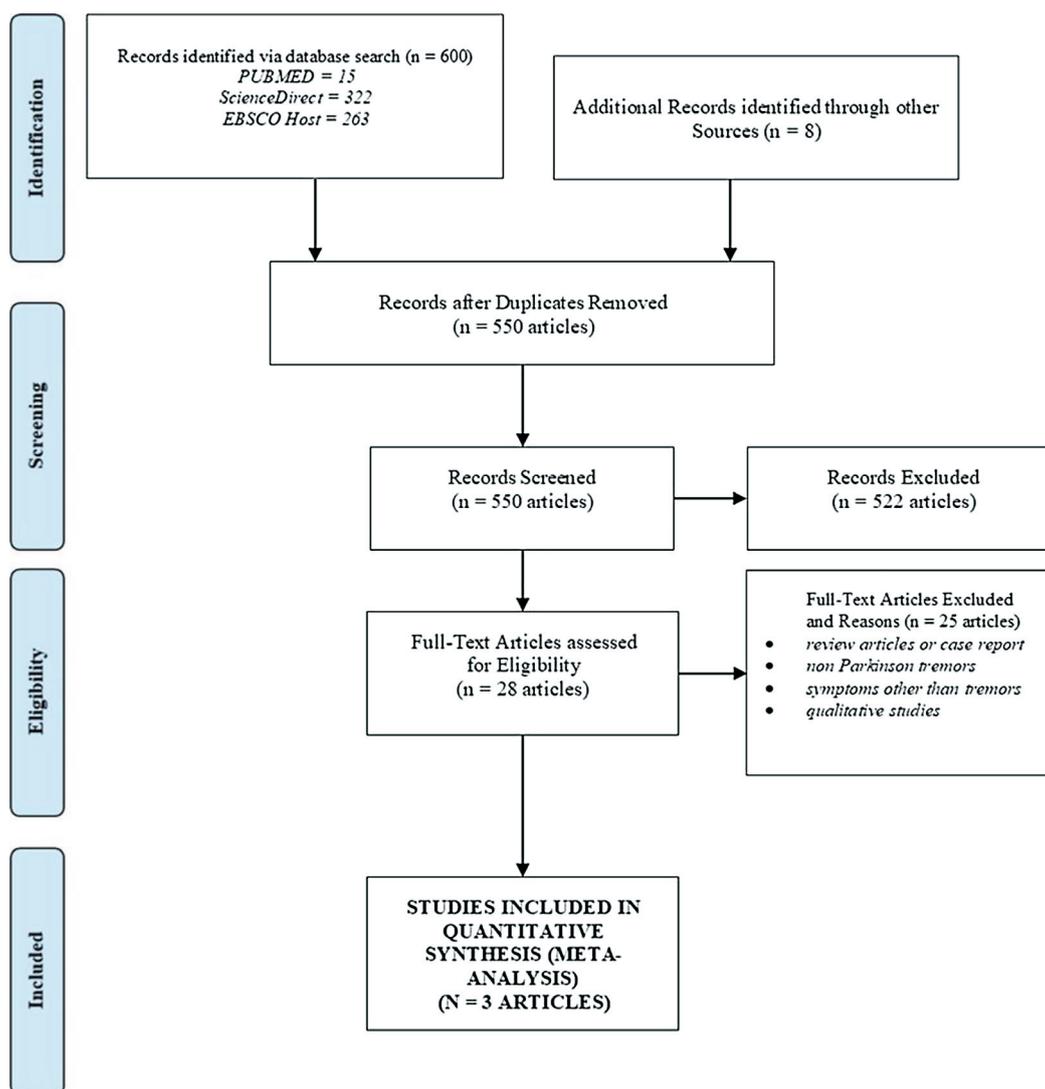


Figure 1. PRISMA Flow Diagram of Study Selection.

was the common parameter that was used in all the studies. Since PD tremors is the focus of the studies, only tremors part of the UPDRS (parts 20 and 21, pertaining to rest and action tremors, respectively) were used and analyzed, and not the total UPDRS score. A decrease in the UPDRS 20 and 21 scores meant an improvement in tremors. Effect of BoNT/A to the above outcomes were reported using the weighted mean difference.

UPDRS-20

Since significant heterogeneity was observed among the three reviewed studies in terms of UPDRS-20 scores ($I^2 = 79\%$, P -value = 0.009), random effects model was applied to calculate the pooled mean difference. Based on the results, mean UPDRS-20 after administration of BoNT/A is significantly lower than that prior to its administration (pooled mean

difference = -1.02, 95% confidence interval: -1.47 to -0.58, $Z = 4.49$, p -value <0.00001).

UPDRS-21

Since heterogeneity was not observed among the three reviewed studies in terms of UPDRS-21 scores ($I^2 = 0\%$, P -value = 0.82), fixed effects model was applied to calculate the pooled mean difference. Based on the results, mean UPDRS-21 after giving BoNT/A is significantly lower than that prior to its administration (pooled mean difference = -0.70, 95% confidence interval: -0.94 to -0.47, $Z = 5.84$, p -value <0.00001).

Risk of bias

All three studies were assessed as high risk of bias in terms of performance and detection

Table 1

Study, Year	Study Design, Country	Diagnosis/ Participants	Sample Size	Mean Age	Years with Tremor	Intervention/ Route of Administration	Outcome Measure	Primary Outcome	Result after BoNT/A injection
Rahimi, Bee, et al. (2013)	Open Label Canada	PD with upper limb tremors	10	59.7 years	5.6 years	BoNT-A 97±52 U (1 dose) IM	TAF UPDRS NIHCGC	Decrease in tremors, and reduction of tremor score	Mean combined UPDRS 20 and 21 of 2.1
Rahimi, Samotus et al. (2015)	Open Label, Single Center Canada	PD with upper limb (wrist and forearm) tremors	28	65.5 years	3.1 years	BoNT-A 186.7±79.5 U (3 doses – weeks 0, 16 and 32) IM	FTM UPDRS	Decrease in tremors, and reduction of tremor score	Mean UPDRS 20 of 2.1, and UPDRS 21 of 1
Samotus et al. (2017)	Open Label, Single Center Canada	PD with upper limb tremors	23	Not indicated		BoNT-A 174.1 U (6 doses) IM	FTM UPDRS	Decrease in tremors, and reduction of tremor score	Mean UPDRS 20 of 1.3, and UPDRS 21 of 0.8

PD - Parkinson’s Disease
IncoA, BoNT/A - Incobotulinum toxin A
 UPDRS - Unified Parkinson’s Disease Rating Scale
 NIHCGC - National Institutes of Health Collaborative Genetic Criteria
 TAF - Tremor Assessment Form
 FTM - Fahn–Tolosa–Marin scale
OnaBoNT-A - Onabotulinum Toxin A

bias. For reporting and other bias, all the studies were considered at low-risk of bias. Attrition bias assessments were all unclear.

Based on the ROBINS-I (Risk of Bias in Non-Randomised Studies of Interventions) tool, all of the studies were graded low-risk of bias.

DISCUSSION

This present meta-analytic study demonstrated the effect of BoNT/A in reducing tremors among patients with PD. Tremors, being a primary symptom of PD may arise early in the disease but may also be very resistant with present treatment. Thus, it can be very distressing to the patient. Tremors secondary to PD arise secondary to loss of dopaminergic neurons from degeneration of the substantia nigra pars compacta.

This study utilized the treatment with BoNT/A. Botulinum neurotoxin inhibits the release of

acetylcholine at the neuromuscular junction thereby preventing muscular contraction.[2] It can be gleaned from Figures 2 and 3 that the analysis of the pooled data showed significant improvement in the severity of hand tremors after administration of BoNT/A. It can be noted that the results favor the use of BoNT/A and denote the superior ability of BoNT/A in decreasing PD tremors. It proved that it is effective in reducing tremors through its mode of action.

But as with all other interventions, even with the benefits that BoNT/A to PD tremors as demonstrated in the trials, it does come with its drawbacks and side effects. Practitioners of BoNT/A must be wary of these possible side effects when administering BoNT/A to muscles and must educate patients regarding the following. The studies included in the meta-analysis demonstrated that the effect of BoNT/A is not immediate for some and may only be observed after one month.[4] Some participants

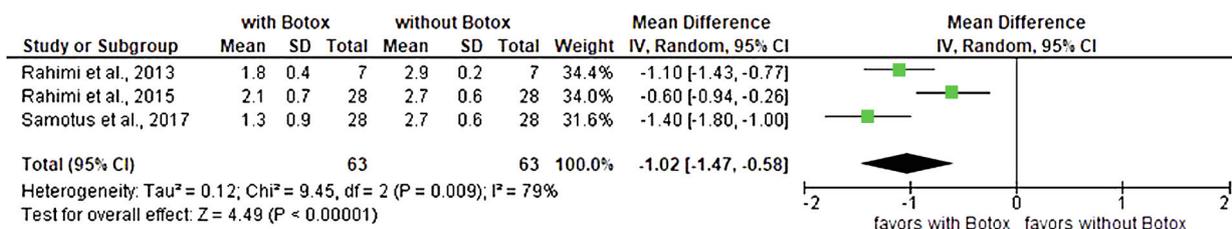


Figure 2: Comparison of UPDRS section 20 scores before and after Botulinum Toxin A injection

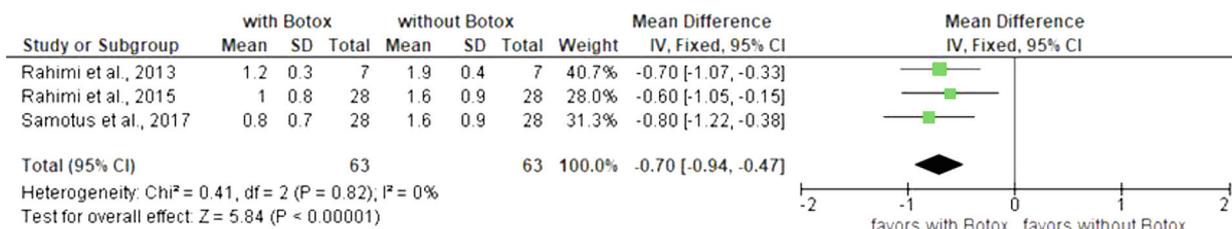


Figure 3: Comparison of UPDRS section 21 scores before and after Botulinum Toxin A injection

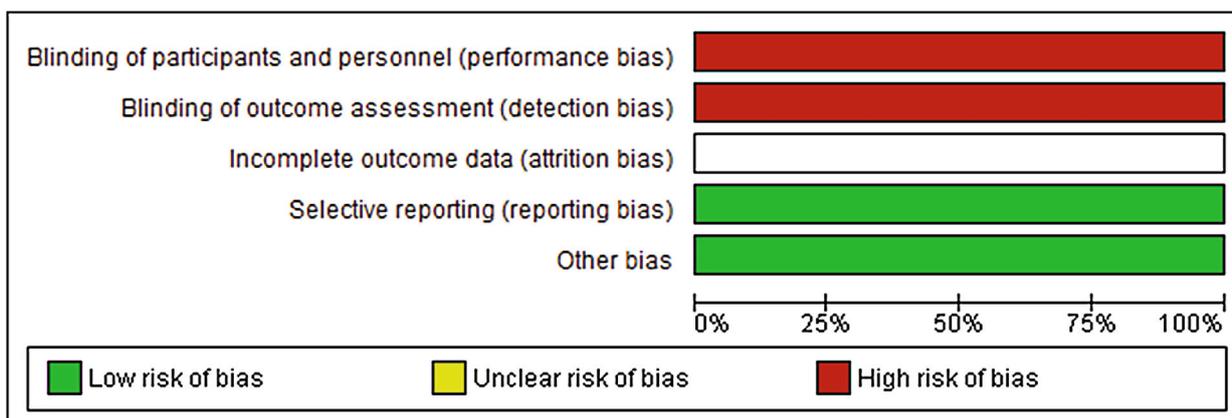


Figure 4: Risk of Bias Graph. Legends: Red for High risk; White for Unclear risk; Green for Low risk

did experience weakness of the muscle injected which may disrupt activities of daily living more, and participants stated that the weakness lasts for 2-3 months. Some also experienced weakness in muscle grip.[4,5] Quality of life improvement is not uniform in all of the participants across the studies. Some of the patients in the studies did express that overall quality of life still did not improve from the motor disability brought about by PD despite improvement of tremors after BoNT/A administration.[6]

Nevertheless, the studies included in the meta-analysis still bring hope to PD afflicted patients since they show significant results before and after BoNT/A administration. To further emphasize the benefits of BoNT/A in tremors, here are some of the additional results on other parameters in the studies not included in the data analysis of the meta-

analysis. Not only does BoNT/A improve the tremors of PD, but it also improves the patient's functionality. Because of the decrease in tremors, ability to perform tasks and chores such as pouring liquid or drawing has significantly become better. Social activities also significantly improved as patients were able to eat, perform hygiene and socialize.[6] Analysis of muscle tremors from PD by neurophysiologic studies also showed a significant quantitative decrease in the severity of tremors of the muscles affected.[6]

A paper by Mittal, et al.[1], a randomized, double-blind, placebo-controlled study, also investigating the benefits of BoNT/A on PD tremors could have been a good candidate for this meta-analysis. It almost has the same methodology as other papers in this study using UPDRS 20 and 21 to score resting and postural tremors before and after administration

	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Rahimi et al., 2013	-	-		+	+
Rahimi et al., 2015	-	-		+	+
Samotus et al., 2017	-	-		+	+

Figure 5: Risk of Bias Summary. Legends: Red for High risk; White for Unclear risk; Green for Low risk

of BoNT/A on patients with debilitating PD tremors refractory to medication. To keep the data analysis uniform and accurate, this study was excluded in this meta-analysis because it used the median to analyze its data as compared to other studies which used mean. Regardless, it still showed favorable results. The paper showed that BoNT/A showed significant decrease in rest tremor score at 4 and 8 weeks, and significant decrease in action/postural tremor score as well after 8 weeks. In this study, grip strength was also tested which likewise showed a weakness with the BoNT/A group but the weakness was not statistically significant compared to the placebo group. It also has additional parts of analyzing the tremor severity, patients’ perception of change, tremor effects on activities of daily living and quality of life quantitatively using the respective scales, and all showed significant changes with the BoNT/A group at 4 and 8 weeks compared to the placebo group.[1]

LIMITATION

As there are only few completed clinical trials regarding the use of BoNT/A in PD tremors, only a few clinical trials were included in this meta-analysis. Medical health professionals and researches are encouraged to conduct more clinical trials, preferably randomized controlled trials regarding the use of botulinum toxin in PD tremors as it presents to be a promising intervention for such patients.

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Rahimi et al., 2013	+	+	+	+	+	+	+	+
Rahimi et al., 2015	+	+	+	+	+	+	+	+
Samotus et al., 2017	+	+	+	+	+	+	+	+

Domains:
 D1: Bias due to confounding.
 D2: Bias due to selection of participants.
 D3: Bias in classification of interventions.
 D4: Bias due to deviations from intended interventions.
 D5: Bias due to missing data.
 D6: Bias in measurement of outcomes.
 D7: Bias in selection of the reported result.

Judgement
 - Moderate
 + Low

Figure 6: Risk of bias in non-randomised studies according to the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool.

CONCLUSION

In conclusion, patients with tremors secondary to PD, especially that affecting the limbs, may benefit from BoNT/A injection. It can be an adjunctive, replacement or substitute treatment to the population of PD patients with moderate to severe hand tremors resistant to conventional oral medications and those

in which quality of life is severely affected by their hand tremors. The dose may be dependent upon the muscle being injected and the severity of tremor. The expanding use of BoNT/A in different movement disorders can be a new stepping stone in further managing or developing new treatment protocols for movement disorders, not only for PD but also others.

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