

## Articles

# Treatment with Botulinum Neurotoxin Improves Activities of Daily Living and Quality of Life in Patients with Upper Limb Tremor

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## Abstract

**Background:** Botulinum neurotoxin's degree of effectiveness on upper limb tremor is subject to debate; although this treatment reduces the tremor's amplitude, a clear functional benefit has not been demonstrated. The objective of this study was to assess the effect of botulinum neurotoxin type A treatment on activities of daily living and quality of life in patients with upper limb tremor.

**Methods:** We retrospectively examined the medical records of 50 consecutive patients treated with botulinum neurotoxin for upper limb tremor that was refractory to oral medication. One month after the injection, the patient was evaluated according to the Quality of Life in Essential Tremor Questionnaire, and the Essential Tremor Embarrassment Assessment.

**Results:** Full data sets were available for 38 patients suffering variously from essential tremor ( $n = 21$ ), Holmes tremor secondary to a focal brain lesion ( $n = 8$ ), idiopathic dystonic tremor ( $n = 4$ ), primary writing tremor ( $n = 4$ ), and Parkinson's disease ( $n = 1$ ). The Quality of Life Essential Tremor Questionnaire and the Essential Tremor Embarrassment Assessment scores improved significantly ( $p < 0.001$ ) in the study population as a whole, and in the essential tremor and Holmes tremor subgroups.

**Discussion:** Botulinum neurotoxin treatment of patients with upper limb tremor is associated with improved quality of life and activities of daily living, irrespective of the tremor's etiology. Long-term treatment enables the physician to adjust the injection strategy to the patient's needs. Our study was limited by its retrospective design. The results must therefore be confirmed in a prospective, double-blind, placebo-controlled, randomized clinical trial.

**Keywords:** botulinum neurotoxin, upper limb tremor, activities of daily living, quality of life, Clinical Global Impression

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**Supplementary material:** To access the supplementary material, please visit the article landing page.

## Introduction

Upper limb tremor is a common movement disorder, with a range of etiologies and clinical presentations. The disorder often results in a marked impairment of activities of daily living (ADL).<sup>1</sup> There are consensus guidelines on the first-line treatment of the two main diseases that lead to upper limb tremor: essential tremor (ET)<sup>2,3</sup> and Parkinson's disease (PD)<sup>4</sup>. However,

the management of other causes of tremor is less well defined. In ET, the question of second-line treatment frequently arises in practice, and there are no guidelines on how many oral medications should be tried before considering botulinum neurotoxin (BoNT) injections or neurosurgery.

In fact, BoNT's poorly defined role in the treatment of upper limb tremor is mainly due to the lack of data on its efficacy in general and the

impact on quality of life (QoL) and ADL (i.e., functional benefit) in particular. The first double-blind trial in patients with ET showed that BoNT injections did not provide a functional improvement, even though the tremor amplitude was significantly lower.<sup>5-7</sup> This limited benefit was explained by the occurrence of side effects (reversible hand weakness) and by a slight improvement in kinetic tremor. Moreover, only a small number of muscles were treated in these pioneering studies, and the BoNT dose levels were fixed. In an open-label study of 20 patients with ET, Pacchetti et al.<sup>8</sup> reported an improvement on the Bain and Findley Activities of Daily Living scale<sup>9</sup> and a reduction in a tremor severity score<sup>10</sup> 1 month and then 3 months after the injection. The effect on QoL was not evaluated. Several recent studies have suggested that the choice of the target muscles and the dose of BoNT can be based on a kinematic analysis (i.e., a multisensor technique capable of characterizing tremor at various joints)<sup>11-14</sup> or a combined clinical/electrophysiological approach.<sup>15</sup> All of these studies demonstrated a reduction in the tremor amplitude; however, the effect on functional abilities was either not assessed or gave conflicting results. Finally, Niemann and Jankovic<sup>16</sup> did not report on QoL and ADL in their retrospective evaluation of a large cohort of patients with hand tremor (due to various etiologies) receiving long-term BoNT-A treatment.

The use of BoNT to treat upper limb tremor in patients with PD has been assessed in a few studies.<sup>12,17-19</sup> A benefit was seen for tremor severity. However, the results for functional achievement (when assessed) were more debatable; for example, QoL did not change significantly.<sup>12</sup> Even fewer studies have assessed etiologies of upper limb tremor other than PD and ET. Vielotte et al.<sup>20</sup> retrospectively explored the effect of BoNT injections on cerebellar tremor. An improvement was noted, but it did not achieve statistical significance. In another retrospective study, Kim et al.<sup>21</sup> assessed a group of 21 patients with proximal upper limb tremor (due to dystonia, in most cases). Of the patients, 63% reported a functional benefit, and 68% received long-term treatment.

The objective of the present study of a cohort of patients with upper limb tremor (due to various etiologies) was to assess the effectiveness of repeated BoNT type A injections on ADL and QoL.

## Methods

The study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki, and it was registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*; reference: DEC16-241). Written, informed consent was obtained from all the study participants.

We retrospectively examined the medical records of consecutive patients treated with BoNT type A injections for upper limb tremor (due to various etiologies) in the Movement Disorders Department at Lille University Medical Center between January 2016 and June 2018. Each patient's tremor was classified according to the most recent consensus statement from the International Parkinson and Movement Disorders Society.<sup>22</sup> The following data were collected with regard to QoL and ADL: the Quality of Life for Essential Tremor (QUEST)<sup>23</sup> and the Essential Tremor Embarrassment Assessment (ETEA)<sup>24</sup> on the

day of the last injection and 1 month after the last injection (via a phone call). The QUEST is a specific measure of tremor-related QoL, with good acceptability; it was designed to assess ET but has also been used in PD.<sup>1</sup> The ETEA explores tremor-related embarrassment in various ADL and takes account of both motor disability and psychosocial features. We also noted basic demographic characteristics (gender and date of birth). To characterize the tremor, we noted the etiology, the age at onset, the affected body sites (fingers, hand, forearm and/or arm), the tremor mode (flexion-extension, pronosupination, abduction-adduction, and internal-external rotation), and any previous medical treatments. With regard to the treatment, we recorded the patient's age at the first BoNT injection and the last injection, total number of cycles, muscles injected, drugs used, dose of the first injection, dose of the last injection, patient-rated Clinical Global Impression-Improvement (CGI-I) score,<sup>25</sup> side effects (if any) 1 month after the last injection (via a phone call), and the reason for discontinuing treatment (if applicable). The BoNT dose was calculated in onabotulinumtoxin A units, since the latter drug was used for the great majority of the injections. If another toxin was injected, the following ratios were used: incobotulinumtoxin A: onabotulinumtoxin A 1:1 or abobotulinumtoxin A: onabotulinumtoxin A 3:1. The choice of the target muscles was mainly based on a clinical examination, although Electromyography (EMG) was sometimes used to select one of several muscles with similar actions (e.g., the pronator teres vs. the pronator quadratus). All the injections were performed using ultrasound guidance (Sonosite Edge, Sonosite Inc., Bothell, WA) by the same physician (AK).

## Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows software (version 22.0; IBM Corp., Armonk, NY), with the exception of the Shapiro-Wilk test (using statistical tools for high-throughput data analysis; [www.sthda.com/french/rsthda/shapiro-wilk.php](http://www.sthda.com/french/rsthda/shapiro-wilk.php)), the chi-squared test, and Fisher's exact test (using the BiostaTGV website at [biostatgv.sentiweb.fr](http://biostatgv.sentiweb.fr)). The threshold for statistical significance was set to  $p < 0.05$ . For quantitative variables, the Shapiro-Wilk test was used to study the normality of the data distribution, and intergroup comparisons were performed using Student's *t*-test or the Mann-Whitney U test. For qualitative data, intergroup comparisons were performed using the chi-squared test or Fisher's exact test (depending on the sample size). Correlations between data sets were assessed by calculation of Pearson's correlation coefficient. All quantitative data were quoted as the mean  $\pm$  standard deviation (median; range).

## Results

We assessed the medical records of 50 patients, whose demographic and clinical data are summarized in Table 1. The etiologies of the tremor were as follows: ET (n = 24), Holmes tremor (HT) (n = 11, all due to a focal cerebral lesion), primary writing tremor (n = 5), idiopathic dystonic tremor (n = 5), intention tremor (IT) (n = 4, all due to a focal cerebellar lesion), and PD (n = 1). In patients with a focal cerebral

**Table 1. Demographic and Clinical Data**

Group/etiology	Gender	Age at onset*	Main tremor modes					
			Thumb F-E	Hand F-E	Forearm F-E	Forearm P-S	Arm Ab-Ad	Arm I-E rot
All patients treated with BoNT (n = 50)	32 men 18 women	43.26 ± 19.49 46 (10–84)	5	37	16	37	20	10
Patients interviewed by phone (n = 38)	25 men 13 women	42.30 ± 18.16 45 (10–82)	5	28	7	31	12	6
Essential tremor (n = 21)	10 men 11 women	45.20 ± 19.47 50 (10–82)	1	17	3	19	6	1
Holmes tremor** (n = 8)	6 men 2 women	46.50 ± 17.17 30.5 (18–62)	1	5	4	5	4	4
Others (PWT = 4; IDT = 4; PD = 1)	9 men	41.00 ± 16.42 41 (15–66)	3	6	0	7	2	1

Abbreviations: Ab-Ad, abduction-adduction; BoNT, botulinum neurotoxin; F-E, flexion-extension I-E rot, internal-external rotation; IDT, idiopathic, dystonic tremor; IT, intention tremor; PD, Parkinson's disease; P-S, pronosupination; PWT, primary writing tremor.  
 \*Age at onset was unclear in one patient with ET (some time in childhood); \*\*Holmes tremor resulted from focal, cerebral lesions (thalamic, ischemic stroke: n = 5; thalamic hematoma: n = 2; thalamic teratoma: n = 1).  
 All data are quoted as the mean ± standard deviation and the median (range).

**Table 2. Botulinum Neurotoxin Injections**

Age at first injection (years)	Dose of the first injection (Ona units per limb)	Number of cycles	Last injection			
			Age (years)	Dose (Ona units per limb)	BoNT type	Side effects
56.66 ± 16.46 64 (18–87)	63.74 ± 14.53 67.5 (20–88)	12.45 ± 12.74 8.5 (1–57)	63.74 ± 14.53 67.5 (20–88)	136.24 ± 97.58 90 (45–390)	Ona: 33 Inco: 4 Abo: 1	7 patients (weakness in all cases)

Abbreviations: Abo, abobotulinumtoxin A; BoNT, botulinum neurotoxin; Inco, incobotulinumtoxin A; Ona, onabotulinumtoxin A.  
 All data are quoted as the mean ± standard deviation and the median (range).

lesion, the tremor (HT or IT) had started within days to months (maximum: 1 year) of the diagnosis. A family history of tremor was noted in eight patients with ET (33.3%). The *per os* medications tried unsuccessfully prior to the BoNT injections are indicated in Supplementary Table 1. During the 30-month study period, 11 patients were lost to follow-up (injections not effective: n = 5; deceased: n = 3; side effects: n = 1; another disease: n = 1; unknown: n = 1), and one patient could not be contacted by phone.

The data presented below came from the 38 patients in whom the effects of BoNT injections on ADL (according to the ETEA) and QoL (according to the QUEST) had been evaluated in a follow-up phone call. The 38 patients' demographic and clinical data are also summarized in Table 1. The characteristics of the BoNT injections are summarized in Table 2. Some comparisons between the two main subgroups of patients (ET and HT) are summarized in Table 3. The ETEA and QUEST scores before and after the BoNT injection, and the patient-rated CGI-I score 1 month after the injections, are summarized in Table 4. At baseline, the ETEA score (but not the QUEST score)

indicated that the tremor was less severe in the ET subgroup than in the HT subgroup ( $p = .045$ ). The ETEA and QUEST scores 1 month after the injections evidenced a significant improvement in the group of 38 patients and in the ET and HT subgroups. The patient-rated CGI-I score 1 month after the injections was 0 (i.e., not assessed) in 1 patient (2.6%), 1 (very much improved) in 10 patients (26.3%), 2 (much improved) in 15 patients (39.5%), 3 (minimally improved) in 9 patients (23.7%), and 4 (no change) in 3 patients (7.9%).

No correlation was found between tremor severity (according to the ETEA or QUEST score at the time of the last injection) and age or disease duration (for all patients or for the ET and HT subgroups). Neither the CGI-I score, the improvement in the ETEA score, or the improvement in the QUEST score 1 month after the injection was correlated with age or disease duration. The CGI-I score 1 month after the injections was not correlated with the improvement in the ETEA or QUEST score. The improvements in the ETEA and QUEST scores 1 month after the injections were correlated (Pearson's correlation coefficient;  $r = 0.54$ ;  $p < 10^{-6}$ ).

**Table 3. A Comparison of the Two Main Subgroups of Patients**

Group	Age at disease onset (years)	Age at the first BoNT injection (years)	Age at the time of post-treatment evaluation (years)	Number of tremor modes treated (per limb)	BoNT dose (Abo units per limb)
Essential tremor	45.20 ± 19.47 50.5 (13–82)	67.38 ± 68.14 67.0 (48–87)	70.67 ± 8.38 70.0 (49–88)	1.90 ± 0.71 2.0 (1–4)	95.43 ± 54.07 85.0 (12–220)
Holmes tremor	36.50 ± 17.17 30.5 (18–62)	40.38 ± 19.26 37.0 (21–69)	49.38 ± 17.59 49.0 (20–74)	2.88 ± 1.55 3.0 (1–5)	216.13 ± 127.93 212.5 (54–390)
<i>t</i> -value ( <i>p</i> ) in Student's <i>t</i> -test	1.17 (NS)	5.39 ( <i>p</i> < 10 <sup>-3</sup> )	8.24 ( <i>p</i> = .01)	-1.73 (NS)	-2.60 ( <i>p</i> = .03)

Abbreviations: Abo, abobotulinumtoxin A; BoNT, botulinum neurotoxin; NS, not significant.  
All descriptive data are quoted as the mean ± standard deviation and the median (range).

**Table 4. Results for the Patients Interviewed by Phone**

Etiology	ETEA score at baseline	ETEA score after BoNT injections	<i>t</i> -value ( <i>p</i> ) in student's <i>t</i> -Test	QUEST score at baseline	QUEST score after BoNT injections	<i>t</i> -value ( <i>p</i> ) in student's <i>t</i> -test	CGI-I patient score after BoNT injections
All patients interviewed by phone (n = 38)	35.84 ± 14.26 36 (12–66)	25.39 ± 14.40 27 (2–58)	7.69 (<0.001)	41.76 ± 18.71 46 (4–84)	28.39 ± 18.55 29 (1–74)	8.76 (<0.001)	2.08 ± 0.97 2 (0–4)
Essential tremor (n = 21)	40.76 ± 14.37 38 (17–66)	30.33 ± 14.92 33 (3–58)	5.03 (<0.001)	47.00 ± 18.09 49 (18–84)	32.24 ± 20.19 31 (4–74)	6.22 (<0.001)	2.24 ± 1.04 2 (0–4)
Holmes tremor (n = 8)	28.63 ± 12.13 32 (13–42)	21.00 ± 11.31 21 (9–39)	4.49 (.003)	42.63 ± 15.32 47 (15–61)	30.00 ± 14.09 29 (10–55)	3.7 (.008)	2.13 ± 0.99 2 (0–3)
Other tremors (n = 9)	30.78 ± 12.32 28 (12–52)	17.78 ± 11.89 13 (2–33)	4.92 (.001)	28.78 ± 18.27 21 (4–54)	18.00 ± 15.34 11 (1–42)	7.53 (<0.001)	1.67 ± 0.71 2 (1–3)

Abbreviations: BoNT, botulinum neurotoxin; CGI-I, Clinical Global Impression-Improvement; ETEA, Essential Tremor Embarrassment Assessment; QUEST, Quality of Life in Essential Tremor.  
All descriptive data are quoted as the mean ± standard deviation and the median (range).

The doses injected into the target muscles are summarized in Supplementary Table 2. The finger muscles were very rarely targeted, and the frequencies were similar in the two main indications (ET: 4.6% of the patients; HT: 4.0% of the patients; this difference was not significant in Fisher's exact test). The muscles for hand flexion-extension and pronosupination were frequently treated and were more frequently targeted in patients with ET (in 74.4% of cases) than in patients with HT (in 44.2% of cases; *p* < 10<sup>-5</sup> in a chi-squared test). The most proximal muscles (for flexion-extension of the forearm, and arm movements) were more frequently targeted in the HT subgroup (in 42.0% of cases) than in the ET subgroup (in 16.4% of cases; *p* < 10<sup>-8</sup> in a chi-squared test).

Weakness after the last injection was reported by seven patients (18.4%); this impairment variously affected the shoulder (n = 1), forearm flexion-extension (n = 1), pronosupination (n = 1), hand flexion-extension (n = 3), and finger (n = 1).

**Discussion**

The results of this study demonstrated an improvement in ADL (according to the ETEA) and QoL (according to the QUEST) 1 month

after BoNT injections in a group of patients with upper limb tremor. Improvements were also observed in ET and HT subgroups. Although patients with other types of tremor experienced an overall improvement, the small sample size prevented us from determining whether this difference was statistically significant. These results for ADL and QoL corresponded closely to levels of patient satisfaction; most patients felt much or very much improved, according to the CGI-I. In most previous studies of tremor and BoNT treatments, patients were evaluated after a single injection; in contrast, our patients had received 12.5 cycles, on average. We suspect that repeated injections may be more effective than a single injection. Indeed, repeated injections enable the physician to adapt the BoNT regimen and the number of target muscles.

Various drug classes have been used to treat patients with ET, including anticonvulsants, beta-adrenergic receptor antagonists, and GABAergic agents.<sup>26</sup> However, propranolol and primidone – the two main oral medications used in this condition – have shown limited functional benefit<sup>27</sup> or failed to reduce tremor in 30% of the patients.<sup>26</sup> After the failure of several lines of oral medication, neurosurgery and BoNT injections are ranked equally by today's guidelines.<sup>2,3</sup> Neurosurgery mainly targets the ventralis intermedialis nucleus (VIM) of the thalamus,

even though other targets (such as the subthalamic nucleus) have been proposed. Several surgical techniques can be used, and these may be lesional (focused ultrasound and gamma-knife thalamotomy) or nonlesional (high-frequency deep brain stimulation).<sup>28,29</sup> The good results obtained here and in other studies prompted us to consider the role of BoNT treatment in the overall therapeutic strategy. The first question relates to the role of BoNT in ET, with regard to oral medication. Prescription of BoNT injections as a first-line treatment is problematic for three main reasons. First, access to this treatment is currently quite limited (at least in France) because very few BoNT injectors are suitable for treating limb muscles, whereas the prevalence of ET is elevated.<sup>30</sup> Second, the treatment of all target muscles in all patients is not realistic. Third, there is no evidence to show that BoNT is more effective than oral medications. Another question concerns the role of BoNT with regard to lesional neurosurgery and deep brain stimulation. Although the latter are highly effective treatments for tremor, we consider that BoNT injections should be tried first. In fact, deep brain stimulation is associated with a risk of both short-term (cerebral hemorrhage or infection) and long-term side effects, and technical problems.<sup>31</sup> In one study, bilateral thalamotomy was associated with a higher risk of side effects than unilateral thalamotomy.<sup>32</sup> Moreover, severe adverse events (such as radionecrosis) are possible. Treatment with BoNT has a good short- and long-term safety profile,<sup>16</sup> and the side effects are always transient.

Oral medications (such as dopaminergic agents, anticholinergics, and antiepileptic drugs) are not highly effective for HT. For example, L-dopa does not always improve the rest component of HT.<sup>33</sup> Although stereotactic thalamic lesional surgery sometimes gives good results in HT, the outcome can also be disappointing.<sup>34</sup> Thalamic VIM deep brain stimulation seems to be more efficacious, but there is concern about the recurrence of tremor.<sup>35</sup> It has been suggested that dual stimulation has been proposed to improve the result.<sup>34,35</sup> The zona incerta<sup>36</sup> or the globus pallidus internal nucleus<sup>35</sup> can be targeted when the thalamus has been damaged. To the best of our knowledge, BoNT's efficacy on upper limb tremor has never been specifically studied in patients with HT. This may be due to the rarity of this disorder. In addition to being diffuse, HT is often of high amplitude. Hence, one would not expect BoNT to be of value, especially in terms of QoL and ADL. In fact, the degree of improvement was very clear and was similar to that observed in ET (Table 4). The set of target muscles differed somewhat, with more frequent injections in the shoulder girdle (Table 1). Moreover, the mean BoNT dose in the HT subgroup was higher than in the ET subgroup (216.13 and 95.43 onabotulinumtoxin A units, respectively).

Even though some encouraging results have been published,<sup>12,17–19</sup> the value of BoNT injections in Parkinsonian tremor is still subject to debate. In view of the effectiveness of oral medications and surgery, BoNT is rarely indicated in PD patients. Only one patient with PD was included in the present study, and the results were satisfactory. In line with the literature data, we also observed good outcomes in patients with primary writing tremor<sup>37</sup> or idiopathic dystonic tremor.<sup>16,21</sup> In patients with primary writing tremor, the rapid initiation of BoNT injections makes sense because the patients' response to oral medications is usually poor. Botulinum neurotoxin is the recommended

first-line therapy for focal dystonia. However, in the field of dystonic tremor, the value of BoNT has mainly been demonstrated for the relief of cervical dystonia.<sup>38</sup>

Even though our study was not designed to determine the best injection strategy or which patients are the best candidates for BoNT treatment, we feel able to put forward a number of hypotheses. Although the injection regimen differed markedly from one patient to another, some muscles were frequently injected (see Supplementary Table 2). The muscles for pronosupination and hand flexion-extension were treated in more than 90 and 75% of cases, respectively. The extensors were treated somewhat less frequently than the flexors, and received lower doses. Proximal (arm and shoulder) muscles were less commonly injected, although further studies are needed to determine whether distal tremor responds better than proximal tremor. In most of the literature studies, finger muscles were not injected. This might have been due to technical difficulties or due to the fear of inducing motor impairments. If we now focus on the potential "best responders," the absence of a correlation with the observed improvement in the QUEST, ETEA, or CGI-I scores indicates that a positive result can be observed whatever the patient's age or disease duration.

Although the absence of correlation between tremor severity and age or disease duration is somewhat surprising, there are three possible explanations. First, the disease did not progress in some patients (e.g., stroke patients). Second, the BoNT dose increased between the first and last injections. Finally, the small sample size may have biased the result.

With regard to safety, 18.4% of the patients (with various etiologies) reported weakness of the upper arm 1 month after the injections. In view of the subjective nature of the evaluation (a phone interview), it is not possible to say whether a motor impairment was present. However, there are relatively few different types of side effect after a BoNT injection. All muscle groups were affected, albeit with different frequencies: impaired hand flexion-extension was most common, but the muscles responsible for this movement were also those most commonly treated. In the literature, the frequency of this side effect ranges from 15 to 92%, and the severity varies.<sup>5–8,11,14,15,21</sup> The relatively low percentage of our patients reporting weakness (relative to the literature data) might be linked to the progressive adaptation of the BoNT dose.

The present study had several limitations. First, the retrospective design means that our results must be confirmed by a prospective, double-blind, placebo-controlled, randomized clinical study. For example, it is possible that the open study design favored positive results. Second, patients with unsatisfactory results (i.e., those who chose not to continue BoNT treatment) were underrepresented in our cohort. However, among the 50 patients treated over a 30-month period, only six (12%) asked to discontinue BoNT injections due to lack of efficacy ( $n = 5$ ) or for disabling side effects ( $n = 1$ ) (Table 3). Third, the small number of patients (especially in the HT group and for the other rare forms of tremor) constitutes a study limitation. More robust conclusions could be obtained by studying a larger sample after, for example, multicenter recruitment. It would also have been interesting to determine whether the positive impact on QoL and ADL correlated with an objective decrease in tremor (with a clinical or a kinematic analysis) and whether

the improvement persisted after several months. In the future, a long-term evaluation (e.g., 8 and 12 weeks after the injections, and over three cycles of injections) would be of value because repeated injections may be more effective than a single injection. Furthermore, it would be of value to implement a customized protocol, as already emphasized by other groups.<sup>8,11,12,14,15,17–19</sup>

Further studies are necessary to (1) confirm the efficacy of BoNT in patients with various etiologies of upper limb tremor and (2) address the following questions: Which patients are the best responders? Does the treatment response depend on, for example, disease etiology, tremor topography, or patient expectations? And do certain muscles (proximal vs. distal) and types of tremor (rest tremor, postural tremor, action tremor, etc.) respond better to BoNT?

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