ORIGINAL ARTICLE

Trial of Botulinum Toxin for Isolated or Essential Head Tremor

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ABSTRACT

BACKGROUND

Local injections of botulinum toxin type A have been used to treat essential head tremor but have not been extensively studied in randomized trials.

METHODS

In a multicenter, double-blind, randomized trial, we assigned, in a 1:1 ratio, adult patients with essential or isolated head tremor to receive botulinum toxin type A or placebo. Botulinum toxin or placebo was injected under electromyographic guidance into each splenius capitis muscle on the day of randomization (day 0) and during week 12. The primary outcome was improvement by at least 2 points on the Clinical Global Impression of Change (CGI) scale at week 6 after the second injection (week 18 after randomization). The CGI scale was used to record the patient's assessment of the degree of improvement or worsening of head tremor since baseline; scores range from 3 (very much improved) to −3 (very much worse). Secondary outcomes included changes in tremor characteristics from baseline to weeks 6, 12, and 24.

RESULTS

A total of 120 patients were enrolled; 3 patients were excluded during screening, and 117 patients were randomly assigned to receive botulinum toxin (62 patients) or placebo (55 patients) and were included in the intention-to-treat analysis. Twelve patients in the botulinum toxin group and 2 patients in the placebo group did not receive injections during week 12. The primary outcome — improvement by at least 2 points on the CGI scale at week 18 — was met by 31% of the patients in the botulinum toxin group as compared with 9% of those in the placebo group (relative risk, 3.37; 95% confidence interval, 1.35 to 8.42; P=0.009). Analyses of secondary outcomes at 6 and 12 weeks but not at 24 weeks were generally supportive of the primary-outcome analysis. Adverse events occurred in approximately half the patients in the botulinum toxin group and included head and neck pain, posterior cervical weakness, and dysphagia.

CONCLUSIONS

Injection of botulinum toxin into each splenius capitis muscle on day 0 and during week 12 was more effective than placebo in reducing the severity of isolated or essential head tremor at 18 weeks but not at 24 weeks, when the effects of injection might be expected to wane, and was associated with adverse events. (Funded by the French Ministry of Health; Btx-HT ClinicalTrials.gov number, NCT02555982.)

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*A list of investigators in the Btx-HT Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Essential tremor is one of the most common movement disorders in adults, with prevalences of approximately 1% in the general population and 4 to 5% among persons older than 65 years of age[1] and with adverse effects such as social isolation, phobia, depression, and interference with work.[2,3] Agents that are effective against essential limb tremor, such as beta-blockers, are usually less effective against head tremor.[4] Botulinum toxin type A, which has been effective to varying degrees in the treatment of essential limb tremor, prevents the release of acetylcholine in synapses, leading to a reduction in aberrant muscle movement. Botulinum toxin is widely used for the treatment of head tremor, but randomized trials assessing its effect are limited.[5-8] Results of two open-label trials,[6,7] as well as one randomized, controlled trial that enrolled only 10 patients,[5] had ambiguous results, but a meta-analysis of randomized, controlled trials suggested that botulinum toxin injection could reduce the severity of head tremor.[8] An evidence-based review commissioned by the Movement Disorder Society concluded that there was insufficient evidence for the use of any agent in the treatment of head tremor.[9] In this trial, we investigated the efficacy and safety of botulinum toxin injections in patients with essential or isolated head tremor.

Methods

Trial Oversight

This multicenter, double-blind, randomized, placebo-controlled trial was performed in 17 hospitals in the French NS-Park–F-CRIN Network (https://parkinson.network/en). Patients were recruited by their treating neurologists during clinical follow-up in the movement disorder department of each hospital. The University Hospital of Clermont-Ferrand sponsored the trial. The first and last authors were primarily responsible for writing the initial version of the manuscript; four authors designed the trial and made the decision to submit the manuscript for publication. Statistical analyses were performed independently at the Department of Biostatistics, University Hospital of Clermont-Ferrand. The authors vouch for the completeness and accuracy of the data, the adherence of the trial to the protocol (available with the full text of this article at NEJM.org), and the completeness of the reporting of adverse events. The funding sources had no role in the trial design, the collection of data, the analysis or interpretation of data, or the writing of the manuscript.

The protocol was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (www.spirit-statement.org). The protocol was approved by the relevant regional ethics committee in France (Comité de Protection des Personnes Sud-Est VI) and accorded with the International Council for Harmonisation Good Clinical Practice guidelines. There was no data and safety monitoring board. Before undergoing screening, all the patients provided written informed consent to participate in the trial.

Flasks containing onabotulinumtoxinA (Botox) were provided by Allergan. Allergan had no role in the trial, and there was no confidentiality agreement between the authors and Allergan.

Patients

Patients with essential head tremor or isolated head tremor, with or without associated limb tremor,[10] were eligible for enrollment. Head tremor at rest,[11,12] when lying down, or with static posture when sitting had to be severe enough to be troublesome, as defined by a score of 2 or higher on the Fahn–Tolosa–Marin Tremor Rating Scale (TRS; scores range from 0 to 4, with higher scores indicating tremor with a higher amplitude and a score of 2 indicating moderate tremor with an amplitude of 0.5 to <2.5 cm).

Patients with dystonic head tremor were excluded to the best of our ability. The presence of dystonic tremor was assessed by movement disorder specialists on the basis of a clinical examination and as a score of more than 1 on the dystonic component of the Tsui scale (item A, amplitude of the deviation in head movement).[13] Scores range from 1 to 9, with a score of more than 1 indicating a deviation in head movement that exceeded 15 degrees in more than 1 direction.

Patients with head tremor as a component of a cerebellar syndrome were also excluded from the trial. Patients with Parkinson's disease were not included (an early version of the protocol indicated that patients with Parkinson's disease would be approached for possible inclusion, but

the protocol has since been corrected). Patients who were previously treated with botulinum toxin were eligible for inclusion if the latest injections had been administered at least 4 months before randomization. Oral treatments for head tremor were allowed if the dose and frequency of administration had been stable during the month preceding enrollment and remained stable during the trial. Patients who had previously undergone surgery for deep-brain stimulation were eligible for inclusion if the surgery had been performed at least 6 months before enrollment; the stimulation variables had to remain stable during the month preceding enrollment and for the duration of the trial. A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix (available at NEJM .org) and the protocol.

TRIAL PROCEDURES

Patients were assigned, in a 1:1 ratio, to receive botulinum toxin or placebo according to a randomization list predetermined by the trial biostatistician with the use of permuted blocks. Randomization was stratified according to trial center, and botulinum toxin and placebo were assigned by means of an interactive response technology system administered by the pharmacy of the sponsoring center. On the day of injection, a nurse at each center was responsible for preparing the syringes containing botulinum toxin or placebo; syringes were sheathed in aluminum foil to hide their contents because the active agent may have a yellow color owing to the presence of albumin. Patients and investigators were unaware of the trial-group assignments. Additional information about randomization and masking is provided in the Supplementary Appendix.

Injections were administered on day 0 and during week 12. In flasks containing 200 IU of onabotulinumtoxinA in powder form, onabotulinumtoxinA was reconstituted with 4 ml of 0.9% sterile saline solution to achieve a concentration of 50 U per milliliter. On day 0, a 75-IU (1.5-ml) dose of botulinum toxin was injected into each splenius capitis muscle under electromyographic guidance. Spontaneous tonic electromyographic activity was used in combination with a clinical examination and palpation to select the injection site in the muscles. The choice of single or multiple injection sites in the splenius capitis muscles was made on the basis of electromyographic findings and the neurologist's judgment.[14] The dose of botulinum toxin injected during week 12 was either identical to the dose injected on day 0 (75 IU) or it was increased to 100 IU (2 ml) if the dose injected on day 0 was considered to be ineffective at the week 6 visit. These doses were chosen on the basis of available published data and after a consensus was reached among the movement disorder specialists.[5-7] In the placebo group, 0.9% sterile saline solution was injected.

Patients underwent a clinical assessment at baseline (day 0) and during weeks 6, 12, 18, and 24. Patients were followed up by telephone interview during weeks 2, 3, 13, and 14 for the assessment of adverse events.

OUTCOMES

The primary outcome was improvement by at least 2 points on the Clinical Global Impression of Change (CGI) scale[15] at week 6 after the second injection (week 18 after baseline). The CGI scale was used by the clinician to record the patient's assessment of the degree of improvement or worsening of head tremor since baseline. The scale ranges from 3 to −3, with a score of 3 defined as very much improved; 2, much improved; 1, minimally improved; 0, no change; −1, minimally worse; −2, much worse; and −3, very much worse. An injection was considered to be ineffective if the improvement on the CGI scale was less than 2 points as assessed by the patient.

Secondary outcomes included improvement by at least 2 points on the CGI scale during weeks 6, 12, and 24; functional effects of head tremor as assessed by the patient with the use of two self-administered questionnaires — the Quality of Life in Essential Tremor Questionnaire (QUEST) and the Essential Tremor Embarrassment Assessment (ETEA) — on day 0 and during weeks 6, 12, 18, and 24; the score on the head tremor severity scale and the score on the TRS on day 0 and during weeks 6, 12, 18, and 24; and quantitative analysis of head tremor. The QUEST is a 30-item scale with five domains (communication, work and finances, hobbies and leisure, physical, and psychosocial) that is used to assess the effects of tremor on quality of life.[16,17] Items in each domain are rated on a scale from 0 (never)

to 4 (always). The ETEA is a 14-item tool with two parts in which the patient provides a self-assessment of tremor-related embarrassment with respect to motor disability and psychosocial features. In part A, the patient provides a simple response to each item on the scale. Responses are scored as 0 (disagree with the statement) or 1 (agree with the statement), and overall scores range from 0 to 14. In part B, the patient provides a more nuanced response to each item. Responses are scored on a 6-point Likert scale ranging from 0 (disagree with the statement) to 5 (agree strongly with the statement), and overall scores range from 0 to 70.[17,18] Scores on the QUEST and the ETEA are expressed as a percentage of the total number of possible points and range from 0 to 100%, with higher scores indicating greater impairment.

Severity of head tremor was assessed on a 5-point scale ranging from 0 (none) to 4 (severe, incapacitating tremor). The TRS is used to assess tremor in multiple domains across three parts.[11,12] Items in each domain are rated on a 5-point scale, with a score of 0 defined as none and a score of 4 defined as severe. In part A, the examiner assesses the amplitude of tremor in specific anatomic locations while the patient is at rest, while the patient maintains a specified posture, and while the patient performs a specified action or intention; scores range from 0 to 84. In part B, the effect of tremor on writing, drawing, and pouring is assessed; scores range from 0 to 36. In part C, the effect of tremor on activities of daily living is assessed; scores range from 0 to 32. The sum of the scores on parts A, B, and C range from 0 to 152, with higher scores indicating greater impairment.

Quantitative analysis of head movements was performed in all the patients who were seen at the 16 participating centers equipped with a wireless inertial magnetic measurement unit (MTw Awinda, Xsens Technologies). Patients were assessed for 60 seconds while seated. Quantitative analysis of the tremor amplitude on each axis (x, y, and z) of the head and of the tremor frequency was performed with the use of methods described elsewhere.[19] We assessed recordings on day 0 and during week 18 that were free of technical issues, such as an unstable Wi-Fi connection that hindered the transfer of data or a broken device that could not collect data.

STATISTICAL ANALYSIS

Assuming that improvement by at least 2 points on the CGI scale at week 6 after the second injection (week 18) would occur in 10% of the patients,[5] we estimated that the enrollment of 57 patients in each trial group would provide the trial with 90% power to detect an absolute between-group difference of 25 percentage points in the incidence of a primary-outcome event (10% in the placebo group vs. 35% in the botulinum toxin group), at a two-sided type I error of 5%. The target sample in each trial group was increased to 60 patients to account for potential losses to follow-up.

We analyzed data in the intention-to-treat population, which included all the patients who underwent randomization. If a patient had missing data on the CGI scale during week 6, 12, 18, or 24, the patient's score on the CGI scale during that week was considered to have improved by less than 2 points. Therefore, patients who had missing data on the primary outcome because they discontinued the trial were considered to have had a score on the CGI scale that had improved by less than 2 points at week 18 and at all weeks after discontinuation. A worst-case approach was used for the analysis of missing data for the primary outcome; no response (improvement by <2 points on the CGI scale at week 18) was imputed for patients in the botulinum toxin group with missing data, and success (improvement by ≥2 points on the CGI scale at week 18) was imputed for patients in the placebo group with missing data. For each secondary outcome, we accounted for missing data using a post hoc multiple imputation procedure that was based on sex, age, previous receipt of botulinum toxin treatment, and the baseline value of the secondary outcome. For the QUEST, the ETEA, and the TRS, imputation was performed with the use of predictive mean matching; for the head tremor severity score, imputation was performed with the use of multinomial logistic regression. Ten complete data sets were imputed, and the results were combined across imputations. We also analyzed the per-protocol population, which included all the patients in the intention-to-treat population except those who discontinued the trial after having received the first injection.

We used an unadjusted chi-square test to compare the incidence of a primary-outcome

event in the botulinum toxin group with that in the placebo group. Other binary outcomes, such as the presence or absence of adverse events, were assessed with the use of unadjusted chi-square tests or unadjusted Fisher's exact tests as appropriate. The score for the severity of head tremor was treated as a categorical variable and was compared between the trial groups with the use of multinomial regression. Results for binary and categorical variables (improvement by at least 2 points on the CGI scale and head tremor severity score) are provided as absolute differences with 95% confidence intervals or as relative risks with 95% confidence intervals. Overall scores and subscores on the TRS, QUEST, and ETEA at weeks 6, 12, 18, and 24 are presented as medians with interquartile ranges and were compared between the trial groups with the use of analysis of covariance, with the baseline score or subscore as a covariate. Outcomes that did not appear to be normally distributed were log-transformed, and results are expressed as mean differences in the log-transformed values between the trial groups.

For secondary outcomes, we did not have a prespecified plan to adjust the widths of confidence intervals for multiplicity; thus, the differences between the trial groups cannot be used for hypothesis testing, and no statistical inferences can be made on the basis of these results. In the original statistical analysis plan, we prespecified a modified intention-to-treat analysis that included all the patients who underwent randomization except those with one or more

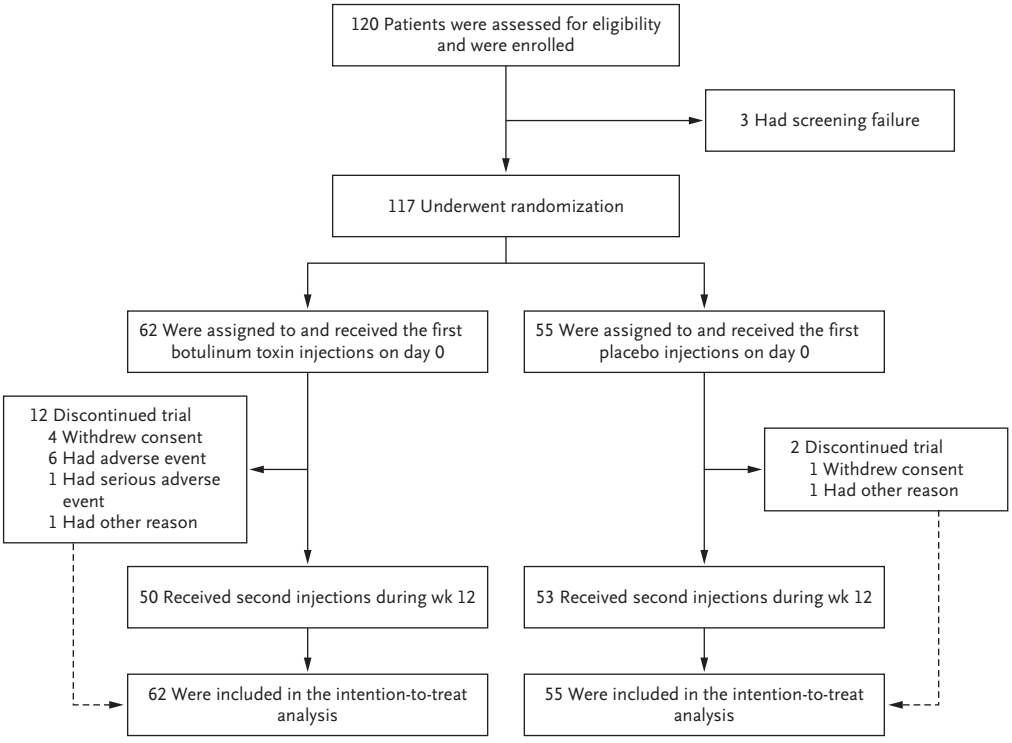

Figure 1. Screening, Randomization, and Follow-up.

Of the 12 patients in the botulinum toxin group who discontinued the trial, 4 patients withdrew consent because of lack of efficacy or for personal reasons (family issues or initiation of chemotherapy), 1 patient had a serious adverse event (severe dysphagia) after the first injection, 5 patients had adverse events (headache, muscle weakness, and dysphagia, alone or in combination) that were assessed by the investigator to be linked to the first injection, 1 patient had an adverse event (influenza) that was unrelated to the trial treatment, and 1 patient had a schedule conflict. Of the 2 patients in the placebo group who discontinued the trial, 1 patient withdrew consent because of a planned surgical intervention, and 1 patient was lost to follow-up.

Table 1. Characteristics at Baseline in the Intention-to-Treat Population.*

Characteristic	Botulinum Toxin Group (N=62)	Placebo Group (N=55)
Age — yr	64.7±10.4	66.0±11.2
Female sex — no. (%)	51 (82)	43 (78)
Race — no. (%)†		
White	55 (89)	54 (98)
Black	3 (5)	0
Asian	1 (2)	0
Other	1 (2)	0
Not reported	2 (3)	1 (2)
Associated limb tremor — no. (%)	50 (81)	42 (76)
Median disease duration (IQR) — yr	10 (3–21)	10 (6–26)
Severity score for head tremor — no. (%)		
1, mild	6 (10)	4 (7)
2, moderate	37 (60)	30 (55)
3, marked	17 (27)	18 (33)
4, severe	2 (3)	3 (5)
Median TRS score (IQR)‡		
Part A	8 (5–11)	8 (4–13)
Part A, head-tremor component§	3 (2–3)	3 (2–4)
Part B	9 (6–12)	9 (4–15)
Part C	4 (2–8)	7 (3–13)
Parts A, B, and C¶	22 (15–30)	24 (12–42)
Previous receipt of botulinum toxin treatment — no. (%)	5 (8)	10 (18)
Receiving oral treatment affecting head tremor — no. (%)‖		
Treatment known to improve tremor	28 (45)	23 (42)
Treatment known to worsen tremor	29 (47)	24 (44)
Previous surgery for deep-brain stimulation for essential tremor — no. (%)	0	2 (4)
Median QUEST score (IQR) — %**		
Communication	33 (8–50)	33 (17–58)
Work and finances††	0 (0–12.5)	0 (0–20)
Hobbies and leisure	29 (0–83)	67 (0–92)
Physical	28 (3–50)	17 (26–39)
Psychosocial	43 (25–60)	45 (30–68)
Overall	34 (14–46)	38 (23–58)
Median ETEA score (IQR) — %‡‡		
Part A	79 (57–93)	86 (64–100)
Part B	63 (39–75)	63 (45–78)

* Plus–minus values are mean ±SD. IQR denotes interquartile range.
† Race was determined by the investigator.
‡ The Fahn–Tolosa–Marin Tremor Rating Scale (TRS) is used to assess tremor according to anatomical location and severity (part A; scores range from 0 to 84), specific motor tasks and functioning (part B; scores range from 0 to 36), and functional disabilities (part C; scores range from 0 to 32). Higher scores indicate greater impairment.

Table 1. (Continued.)

§ The head-tremor component of part A of the TRS includes scores at rest and in the postural domain. Scores range from 0 to 8.
¶ The sum of the scores on parts A, B, and C of the TRS ranges from 0 to 152.
‖ Treatments known to improve tremor include propranolol, gabapentin, topiramate, primidone, and clonazepam. Treatments known to worsen tremor include escitalopram, venlafaxine, paroxetine, amitriptyline, mianserin, mirtazapine, levothyroxine, prednisolone, salbutamol, fluticasone, and beclomethasone.
** The Quality of Life in Essential Tremor Questionnaire (QUEST) is used to measure tremor-related quality of life. Scores are expressed as a percentage of the total number of possible points and range from 0 to 100%, with higher scores indicating greater impairment.
†† Data are for 52 patients in the botulinum toxin group and for 39 patients in the placebo group.
‡‡ The Essential Tremor Embarrassment Assessment (ETEA) is a 14-item tool in which the patient provides a self-assessment of tremor-related embarrassment with respect to motor disability and psychosocial features. Part A is a sum of the scores assigned to simple responses to each item; scores range from 0 to 14. Part B is a sum of the scores assigned to nuanced responses to each item; scores range from 0 to 70. Scores are expressed as a percentage of the total number of possible points and range from 0 to 100%.

major protocol violations. Because we had no patients with major protocol violations, we did not perform this analysis.

All the analyses were performed with the use of Stata software, version 15.0 (StataCorp). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between June 27, 2016, and March 24, 2021, a total of 120 patients were enrolled at 17 centers; 117 patients were randomly assigned to receive botulinum toxin (62 patients) or placebo (55 patients) and were included in the intention-to-treat analysis (Fig. 1). Because of findings during screening, 3 patients did not undergo randomization: 1 patient had head tremor that was too mild as assessed by the investigator, and 2 patients had cervical dystonia (Tsui scale score of >1). Overall, the two trial groups were similar with respect to characteristics at baseline (Table 1). The mean age of the patients was approximately 65 years, and 80% of the patients were women. The severity of head tremor was assessed as mild, moderate, marked, and severe in 7%, 60%, 30%, and 3% of women, respectively, and in 13%, 48%, 30%, and 9% of men. Associated limb tremor was present in 81% of the patients in the botulinum toxin group and in 76% of those in the placebo group. Two patients — both of whom were in the placebo group — had previously undergone surgery for deep-brain stimulation, and 8% of the patients in the botulinum toxin group and 18% of those in the placebo group had previously received botulinum toxin injections (Table 1). Approximately 3% of the total trial population was Black. The representativeness of the trial population with respect to the worldwide population of patients with head tremor is provided in Table S1 in the Supplementary Appendix.

Complete trial injections were received by 50 of the patients (81%) in the botulinum toxin group and by 53 of those (96%) in the placebo group. Thus, primary-outcome data were missing for 12 patients (19%) in the botulinum toxin group and for 2 (4%) in the placebo group. The per-protocol population included 50 patients in the botulinum toxin group and 53 in the placebo group.

OUTCOMES

Improvement by at least 2 points on the CGI scale at week 18 (primary outcome) occurred in 19 of 62 patients (31%) in the botulinum toxin group as compared with 5 of 55 patients (9%) in the placebo group (relative risk, 3.37; 95% confidence interval [CI], 1.35 to 8.42; P=0.009) (Table 2). These results were similar to those in the per-protocol analysis (Tables S2 and S3). We also observed similar results using the worst-case approach to address missing data at week 18, with a primary-outcome event occurring in 19 of 62 patients (31%) in the botulinum toxin group as compared with 7 of 55 patients (13%) in the placebo group (relative risk, 2.41; 95% CI, 1.10 to 5.29).

Improvements by at least 2 points on the CGI scale at other time points were assessed as secondary outcomes. The percentage of patients

Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population.*

Outcomes	Botulinum Toxin Group (N=62)	Placebo Group (N=55)	Treatment Effect (95% CI)
Primary outcome			
Improvement by ≥2 points on the CGI scale at wk 18 — no./total no. (%)†	19/50 (31)	5/53 (9)	3.37 (1.35 to 8.42)‡
Secondary outcomes§			
Improvement by ≥2 points on the CGI scale†			
At wk 6 — no./total no. (%)	27/60 (44)	4/54 (7)	5.99 (2.24 to 16.04)‡
At wk 12 — no./total no. (%)	18/55 (29)	5/54 (9)	3.19 (1.27 to 8.03)‡
At wk 24 — no./total no. (%)	14/48 (23)	7/52 (13)	1.77 (0.77 to 4.07)‡
Functional effects as assessed with the QUEST¶			
At wk 6			
Median score (IQR) — %	25 (12–40)	36 (20–58)	−0.24 (−0.50 to 0.01)‖
No. of patients with data	59	54	—
At wk 12			
Median score (IQR) — %	27 (13–42)	40 (25–59)	−0.25 (−0.45 to −0.05)‖
No. of patients with data	54	54	—
At wk 18			
Median score (IQR) — %	23 (12–38)	36 (17–58)	−0.31 (−0.62 to −0.01)‖
No. of patients with data	47	53	—
At wk 24			
Median score (IQR) — %	22 (10–36)	39 (14–59)	−0.19 (−0.46 to 0.07)‖
No. of patients with data	48	52	—
Functional effects as assessed with the ETEA**			
Part A			
At wk 6			
Median score (IQR) — %	75 (36–100)	79 (57–93)	−0.34 (−0.62 to −0.06)‖
No. of patients with data	59	54	—
At wk 12			
Median score (IQR) — %	85 (35–100)	86 (64–100)	−0.18 (−0.38 to 0.01)‖
No. of patients with data	55	54	—
At wk 18			
Median score (IQR) — %	71 (36–86)	79 (57–100)	−0.43 (−0.76 to −0.10)‖
No. of patients with data	48	53	—
At wk 24			
Median score (IQR) — %	75 (36–93)	79 (64–93)	−0.26 (−0.56 to 0.03)‖
No. of patients with data	48	52	—
Part B			
At wk 6			
Median score (IQR) — %	46 (21–70)	59 (39–84)	−0.38 (−0.65 to −0.10)‖
No. of patients with data	59	54	—
At wk 12			
Median score (IQR) — %	51 (27–75)	64 (36–86)	−0.21 (−0.40 to −0.01)‖

Table 2. (Continued.)

Outcomes	Botulinum Toxin Group (N=62)	Placebo Group (N=55)	Treatment Effect (95% CI)
No. of patients with data	55	54	—
At wk 18			
Median score (IQR) — %	42 (21–64)	59 (39–79)	–0.48 (–0.80 to –0.16)‖
No. of patients with data	48	53	—
At wk 24			
Median score (IQR) — %	50 (25–66)	55 (46–75)	–0.28 (–0.57 to 0.01)‖
No. of patients with data	48	52	—
Median TRS score (IQR)††			
At wk 6			
Part A, head-tremor component	2 (1–2)	3 (2–4)	–0.30 (–0.44 to –0.16)‖
Part C	3 (1–6)	7 (2–12)	–0.49 (–0.80 to –0.17)‖
Parts A, B, and C	16 (8–25)	24 (10–40)	–0.19 (–0.49 to 0.11)‖
No. of patients with data	58	53	—
At wk 12			
Part A, head-tremor component	2 (1–3)	3 (2–4)	–0.12 (–0.26 to 0.02)‖
Part C	3 (1–7)	5 (2–11)	–0.29 (–0.61 to 0.03)‖
Parts A, B, and C	18 (10–26)	22 (11–33)	–0.08 (–0.35 to 0.19)‖
No. of patients with data	54	55	—
At wk 18			
Part A, head-tremor component	2 (1–3)	2 (2–4)	–0.15 (–0.30 to –0.01)‖
Part C	3 (1–8)	6 (2–11)	–0.38 (–0.72 to –0.05)‖
Parts A, B, and C	17 (9–25)	22 (10–41)	–0.16 (–0.46 to 0.15)‖
No. of patients with data	47	53	—
At wk 24			
Part A, head-tremor component	2 (1–3)	2 (2–3)	–0.11 (–0.24 to 0.02)‖
Part C	3 (0–8)	7 (3–10)	–0.44 (–0.79 to –0.08)‖
Parts A, B, and C	15 (8–21)	21 (10–35)	–0.30 (–0.57 to –0.04)‖
No. of patients with data	47	52	—

* A worst-case approach was used for the analysis of missing data for the primary outcome; no response (improvement by <2 points on the CGI scale at week 18) was imputed for patients in the botulinum toxin group with missing data, and success (improvement by ≥2 points on the CGI scale at week 18) was imputed for patients in the placebo group with missing data. A post hoc multiple imputation approach was used to account for missing scores on the QUEST, the ETEA, and the TRS.

† The CGI scale was used by the clinician to record the patient's assessment of the degree of improvement or worsening of head tremor since baseline. Scores range from 3 (very much improved) to –3 (very much worse).

‡ The treatment effect is the relative risk with 95% confidence interval for the event in the botulinum toxin group as compared with the placebo group.

§ Confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

¶ Scores on the QUEST range from 0 to 100%, with higher scores indicating greater impairment.

‖ The treatment effect is the mean difference with 95% confidence interval between the log-transformed measure in the placebo group and the log-transformed measure in the botulinum toxin group.

** Scores on part A of the ETEA range from 0 to 14, and scores on part B range from 0 to 70. Scores are expressed as a percentage of the total number of possible points and range from 0 to 100%.

†† Scores on the head-tremor component of part A of the TRS range from 0 to 8; scores on part C, 0 to 32; and the sum of the scores on parts A, B, and C, 0 to 152. Higher scores indicate greater impairment.

with improvement by at least 2 points was 44% in the botulinum toxin group and 7% in the placebo group at week 6 (relative risk, 5.99; 95% CI, 2.24 to 16.04); 29% and 9%, respectively, at week 12 (relative risk, 3.19; 95% CI, 1.27 to 8.03); and 23% and 13% at week 24 (relative risk, 1.77; 95% CI, 0.77 to 4.07) (Table 2).

In the botulinum toxin group, 27 of 50 patients received the same dose of botulinum toxin (75 IU) at baseline and at week 12, whereas 23 patients received a higher dose (100 IU) at week 12. A primary-outcome event occurred in 56% of the patients who received the 75-IU dose at week 12 and in 17% of those who received the 100-IU dose at week 12. In the placebo group, 9 of 53 patients received the same dose (volume of placebo) at baseline and week 12, whereas 44 patients received an increased dose at week 12.

The QUEST was used to assess the functional affects of head tremor. The median QUEST score at week 18 was 23 (interquartile range, 12 to 38) in the botulinum toxin group and 36 (interquartile range, 17 to 58) in the placebo group (mean difference of the log-transformed values, −0.31; 95% CI, −0.62 to −0.01) (Table 2 and Table S4).

We used the ETEA to assess the degree of social embarrassment associated with head tremor as reported by the patients. At week 18, the median score was 71 (interquartile range, 36 to 86) in the botulinum toxin group and 79 (interquartile range, 57 to 100) in the placebo group (mean difference of the log-transformed values, −0.43; 95% CI, −0.76 to −0.10) on part A of the ETEA (a qualitative assessment of embarrassment scored according to a binary response to 14 statements) and was 42 (interquartile range, 21 to 64) and 59 (interquartile range, 39 to 79), respectively (mean difference of the log-transformed values, −0.48; 95% CI, −0.80 to −0.16), on part B (a quantitative assessment of embarrassment scored according to a graded response to 14 statements) (Table 2).

Severity scores for head tremor (assessed on a scale ranging from 0 to 4) are provided in Tables S3 and S4. Scores on the TRS with respect to the amplitude of head tremor and the effects of head tremor on activities of daily living are provided in Table 2. Results of quantitative assessment of head tremor were available from a convenience sample of 87 patients (43 patients in the botulinum toxin group and 44 patients in the placebo group) and are provided in Table S5. The change (reduction) in amplitude in all three spatial axes between day 0 and day 18 was generally greater in the botulinum toxin group than in the placebo group, and the change in the tremor frequency between these time points was similar in the two trial groups.

SAFETY

In the botulinum toxin group, adverse events occurred in a higher percentage of patients (47%) than in the placebo group (16%) ($P<0.001$) and included headache or neck pain (in 34% of the patients), posterior cervical weakness (in 15%), dysphagia (in 16%), cervical stiffness (in 10%), and pain at the injection sites (in 8%) (Table 3). Most of these events were considered by the investigators to be transient and mild in severity, with no need for therapeutic intervention. Two adverse events (in one patient each in the botulinum toxin group) were considered to be serious and resulted in hospitalization. Severe dysphagia developed in one patient, and the patient discontinued the trial. The other patient described a general feeling of weakness, difficulty in finding words, and dizziness but did not discontinue the trial treatment. No serious adverse events occurred in the placebo group. The incidences and types of adverse events were similar among the patients who received 75 or 100 IU of botulinum toxin at week 12 (Table S6).

DISCUSSION

In this multicenter, double-blind, placebo-controlled, randomized trial performed in France, patients with essential or isolated head tremor were injected with botulinum toxin or placebo in each splenius capitis muscle on day 0 and during week 12. The percentage of patients with improvement in head tremor, prespecified as improvement by at least 2 points on the CGI scale at week 18 (primary outcome), was higher in the botulinum toxin group than in the placebo group. Analyses of secondary outcomes were generally supportive of this finding with respect to reductions in subjective and objective measures of head tremor severity, functional affects, and social embarrassment. Our trial had stringent requirements for enrollment, outcome assessment, and injection technique, and approxi-

mately 40% and 30% of the patients in the botulinum toxin group at weeks 6 and 18, respectively, had improvement by at least 2 points on the CGI scale. These differences between the trial groups were generally sustained at other time points but not at 24 weeks, a time at which the effect of botulinum toxin injection has typically waned.[20]

Although the efficacy of various pharmacologic and surgical treatments has been shown in patients with limb tremor, limited data are available on the treatment of essential head tremor.[1,8] Improved subjective clinical ratings and accelerometric findings 2 to 3 weeks after the injection of botulinum toxin into the splenius capitis muscles were shown in 14 patients who had had head tremor without dystonia.[6] In another trial, a global improvement in the severity and functional effects of head tremor after botulinum toxin injections in the splenius capitis or sternocleidomastoid muscles was observed in 42 patients (67%) who had disabling head tremors of various types (dystonic or essential), with a mean duration of maximum improvement of 10.5 weeks.[7]

Most previous trials were open-label and were not placebo-controlled. One double-blind, placebo-controlled trial assessed the effects of botulinum toxin injections in each sternocleidomastoid muscle and splenius capitis muscle in 10 patients with essential head tremor,[5] but the trial did not show significant improvement in the botulinum toxin group as compared with the placebo group, possibly because of the small number of patients. Unlike our trial, previous trials included patients with heterogeneous subtypes of head tremor, injection of various doses into various muscles, and inconsistent timing of postinjection assessments.

Almost half the patients in the botulinum toxin group in our trial had adverse events, including local pain, neck weakness, and dysphagia, which was similar to previous findings.[6] Although most of the adverse events were transient and mild in severity as assessed by the investigators, some were disabling and led to hospitalization; adverse events were not independently adjudicated.

The strengths of our trial include the large sample size as compared with previous trials, as well as the standardized injection protocol. The trial had limitations. First, the loss of some of the patients to follow-up may have biased the analyses, especially because the percentage of patients who discontinued the trial after the first injection was greater in the botulinum toxin group than in the placebo group. Second, we did not control for all the variables that may have influenced clinical global improvement, such as external psychological factors (e.g., stress or anxiety related to familial or professional situations, which are known to increase the amplitude of tremor). However, the use of oral treatments and the variables for deep-brain stimulation for tremor had to remain stable during the trial. The trial-group assignments may have been partially unmasked because a subset of the patients received a higher botulinum toxin dose in the second injection, owing to a lack of efficacy of the dose in the first injection, and because physicians had access to electromyographic information while they administered the injections. Finally, our findings may not be generalizable to populations that were not included in the trial, such as patients with dystonic head tremor and patients with head tremor associated with cerebellar syndrome and other neurologic conditions, and the trial population had limited racial diversity.

In patients with isolated or essential head tremor, electromyographically guided injection of botulinum toxin into each splenius capitis muscle at day 0 and during week 12 led to greater clinical improvement than placebo at 18

Table 3. Adverse Events in the Safety Analysis Population.*

Event	Botulinum Toxin Group (N=62)	Placebo Group (N=55)	P Value
	no. of patients (%)		
Headache or neck pain	21 (34)	9 (16)	0.03
Cervical stiffness	6 (10)	1 (2)	0.12
Posterior cervical weakness	9 (15)	0	0.003
Dysphagia	10 (16)	0	0.002
Pain at injection sites	5 (8)	0	0.06
Any adverse event	29 (47)	9 (16)	<0.001

* The safety analysis population included all the patients who received at least one injection of botulinum toxin or placebo. P values were calculated with the use of the chi-square test.

weeks but not at 24 weeks and was associated with adverse events.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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