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Treatment of cervical dystonia with Botox (onabotulinumtoxinA)

Development, insights, and impact

Joseph Jankovic, MD[a,*], Joseph Tsui, MBBS[b], Mitchell F. Brin, MD[c,d]

Abstract

Cervical dystonia (CD), the most common focal dystonia encountered in neurologic practice, is a chronic disorder in which the muscles of the neck involuntarily contract and cause abnormal postures and movements of the head, neck, and shoulders. Treatment of CD prior to botulinum toxin was unsatisfactory, as existing therapies often did not improve symptoms. The use of botulinum toxin for CD grew out of its success in treating blepharospasm, another type of focal dystonia. On the basis of results from a double-blind, placebo-controlled trial, onabotulinumtoxinA was approved in 2000 in the US for the treatment of CD in adults in order to alleviate abnormal head position and neck pain. A subsequent large observational trial further demonstrated the effectiveness of onabotulinumtoxinA for CD, showing improvements in various rating scales, physician-reported measures, and profound positive effects on patient quality of life, including in amelioration of pain and improvements in work productivity. In addition, onabotulinumtoxinA treatment also reduced the complications of CD, as patients no longer develop contractures (permanent muscle and tendon shortening from prolonged untreated dystonia), which markedly limited the range of neck motion. The onset of onabotulinumtoxinA treatment also accompanied advances in understanding the functional anatomy of neck muscles, basal ganglia physiology, and video and other recording technology. Following the success of onabotulinumtoxinA in the treatment of CD, its use has been expanded into numerous other therapeutic indications, and these advances stimulated educational and training programs by various neurologic and other medical societies.

Abbreviations: CD = cervical dystonia, CD PROBE = **C**ervical **D**ystonia **P**atient **R**egistry for **O**bservation of Ona**b**otulinumtoxinA **E**fficacy, CDSS = Cervical Dystonia Severity Scale, EMG = electromyography, TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

Keywords: botulinum toxin, neuromuscular agents, spasmodic torticollis

1. Overview of cervical dystonia

Cervical dystonia (CD), also known as spasmodic torticollis, is a chronic neurological disorder characterized by involuntary sustained or intermittent contractions of the neck muscles, which results in abnormal movements and/or postures of the head, neck, and shoulders.[1] The abnormal postures include torticollis (rotation), laterocollis (lateral tilt), retrocollis (extension), anterocollis (neck flexion), or a combination of these, but other subtypes of CD have also been described.[2,3] Patients may use sensory tricks (also called alleviating maneuvers or gestes antagonistes), such as touching their head on the lateral chin with their fingers or leaning against a support, to temporarily restore their head position.[4–6]

Onset of CD is typically in the fourth to fifth decade of life, and women outnumber men.[7] Usually considered idiopathic or genetic in its origin, it may be secondary to conditions such as brain and neck injury or toxicities from certain drugs, particularly the antipsychotic drugs (also known as neuroleptics) that act by blocking dopamine receptors.[1]

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CD is the most common form of focal dystonia encountered in movement disorder clinics, and its prevalence has been estimated at 28–183 cases per million.[7,8] The disorder confers many adverse effects on quality of life. Pain is common prior to treatment, with nearly 90% of patients in a large observational trial reporting pain related to CD at baseline, with 71% rating their pain as moderate or severe.[9] Pain in CD is also associated with many negative effects on employment.[10] Studies have found that 19–39% of patients stopped working due to CD, and of those employed, 58–69% reported decreased work productivity due to CD.[10,11]

The following historical narrative was compiled based on review of the literature and interviews with the authors, and the quoted portions reflect the personal observations and reflections of the individuals who were interviewed. In some instances, this article describes uses for which Allergan has not sought and/or received regulatory approval in individual countries and are mentioned for historical context or background only.

2. Unmet need for treatment of CD

Prior to the emergence of botulinum toxin for CD in the early 1980s, the existing treatments included pharmacotherapy with anticholinergic, antidopaminergic, dopaminergic, serotonergic, or gamma-aminobutyric acid-mimetic agents, but none of these showed consistent efficacy.[12–14] Baclofen was effective for some patients but had mostly been studied in other forms of dystonia, and benzodiazepines were mainly used only for mild CD.[15] For patients with more widespread and severe dystonia, such as adults with severe segmental, hemi-, or generalized dystonia[16] or predominantly axial truncal dystonia,[17] Marsden and colleagues reported favorable results of a combined treatment in which tetrabenazine, pimozide, and an anticholinergic were sequentially introduced.[16] However, this treatment regimen was not widely adopted, nor commonly used in CD.

Figure 1. Dr. Joseph Jankovic receiving the Clinical Lifetime Achievement Award from the International Neurotoxin Association at the International Conference of TOXINS: Basic Science and Clinical Aspects of Botulinum and Other Neurotoxins in January 2019 in Copenhagen, Denmark. Photo provided by Dr. Joseph Jankovic.

*Dr Jankovic (*Fig. 1*), who joined the faculty at Baylor College of Medicine in 1977 following his residency at Columbia University, where he also trained in movement disorders with Stanley Fahn: The treatment of cervical dystonia before Botox was very challenging because there were no effective treatments. The medications that we used at the time such as the anticholinergic drugs, including trihexyphenidyl, were associated with a variety of side effects: cognitive changes, dry mouth, urinary problems; and yet they were not terribly effective specifically for cervical dystonia... The other drugs that were used at that time were baclofen and benzodiazepines. Again, these drugs were not terribly effective and many have associated side effects, but that's all we had.*

Surgical procedures for CD, such as myectomy, rhizotomy, and thalamotomy, were usually reserved for severe cases and often resulted in disabling complications.[15]

Dr. Tsui, who was a fellow with Donald Calne at the University of British Columbia in the early 1980s and is now a professor at that institution: [Thalamotomy] produced severe dysphagia in some patients, and the neurosurgeon [with whom I worked] at that time swore that he would never do it again.

However, a few surgical interventions, particularly ramisectomy, were reported to be successful in relieving CD symptoms when performed by skilled surgeons.[18]

Dr. Brin, who was a resident, fellow, and on the faculty at Columbia University over the course of the 1980s, then was at Mount Sinai School of Medicine in the 1990s, and is now chief scientific officer of Botox and neurotoxins at Allergan, an AbbVie company: *In skilled hands, minimalistic surgical procedures resulted in favorable outcomes for many patients. The surgeon with whom I collaborated, Claude Bertrand, taught me about functional anatomy as we were discussing potential candidates, and reflected that some patients were actually not candidates for surgery and sent some of them to me for onabotulinumtoxinA.*

Because phenol had been used to treat patients with spasticity, a few investigators attempted phenol injection to treat CD.[19,20] However, these studies involved very few patients and one reported that 4 patients experienced dysesthesia of the transverse cutaneous nerve of the neck.[20]

As CD progressed without effective treatment, many patients developed contractures, or permanent shortenings of cervical muscles and tendons, limiting neck range of motion. Prior to botulinum toxin, physical therapy was often used to attempt to ameliorate the muscle contractions to prevent the development of contractures. A variety of devices and braces, including magnets (Fig. 2), were also used to take advantage of sensory tricks a patient might use for correction of head position and to help patients maintain a straight position of their head. Unfortunately, these devices were uncomfortable and not very useful.

Dr. Tsui: Most of those devices are very individualized and most of the time they don't work for most other people. Braces have been developed at our center, but some patients develop abrasions because they rub against the braces constantly, so that none of these work universally.

3. Botulinum toxin A and its early use as a treatment for CD

Following intramuscular injection, botulinum toxin binds to motor nerve terminals, where it prevents acetylcholine release by cleaving proteins needed for vesicular neurotransmitter release, which leads to decreased muscle contraction (see Chapter 2 of this supplement for a full description of the mechanism of action).[21,22] The first clinical use of botulinum toxin was reported in the early 1980s by Dr. Alan Scott, an ophthalmologist at the Smith-Kettlewell Eye Research Institute who sought an injectable agent that could weaken extraocular muscles for

his patients with strabismus (crossed eyes).[23,24] After demonstrating the utility of botulinum toxin (called Oculinum at that time) in strabismus, Dr. Scott and others began treating patients for blepharospasm, another type of focal dystonia involving involuntary contraction of the eyelid muscles.[25–27] The use of botulinum toxin for CD grew out of its success in treating blepharospasm.

Dr. Jankovic: I started to communicate with Alan Scott in the early 1980s. When his paper came out on strabismus, I remember writing to him.... Eventually I went to Smith-Kettlewell in the early 1980s, and we injected several patients that had blepharospasm. That's when we started to talk about other indications, including cervical dystonia.... We started to inject in 1981 and the first patient I can remember was a patient who had cranial cervical dystonia; she had horrible blepharospasm and oromandibular dystonia, but she also had dynamic cervical dystonia with lateral oscillation, tremor, of the head.

4. Development of onabotulinumtoxinA for CD

Although botulinum toxin is now the treatment of choice for CD,[28] the idea of injecting patients with a potent toxin was initially met with incredulity and resistance.

Dr. Jankovic: I still remember submitting my first IRB [Institutional Review Board] protocol, and the chairman of the Baylor IRB happened to be a good friend of mine. I remember that within 24 hours after I submitted the protocol, he called me and the first thing that came out of his mouth was, "Joe, you want to do WHAT?" He just couldn't believe that I was actually going to inject botulinum toxin. So, we had this very long discussion about the protocol, and I tried to explain to him that there was enough animal and even human data about its safety at the time to move forward. The IRB eventually approved the project but insisted that we have a "blue code" team present just in case. The protocol was designed as a double-blind, placebo-controlled study of efficacy and safety in patients with cranial-cervical dystonia. We got a grant from the [Benign Essential] Blepharospasm Research Foundation, which was the first grant they awarded. I still remember it was $25,000. It was a small study, but it got published,[29] and the data were used to support Alan Scott's application for approval of botulinum toxin in the treatment of blepharospasm and other facial spasms, which was eventually granted by the food and drug administration in 1989. After that, we kept using botulinum toxin in an open-label fashion in a variety of movement disorders, trying to gain more experience with dosages and which muscles to inject for different indications.

An important question in the early days of botulinum toxin treatment of CD was how to measure the effect of treatment. Dr. Tsui developed an eponymous scale ("Tsui scale") that measures the amplitude and duration of sustained movements as well as the severity and duration of unsustained head movements.[30]

Dr. Tsui: The development of a scale was very difficult. When I first arrived [at the University of British Columbia], we tried to develop objective scales. We attempted to use our hands to assess patients and EMG and so on, but those were not successful because once we put anything on the patient's head, the sensory risk stimulus would change the position of the head. So, we were sure that we had to use a scale without any apparatus. That is, we had to observe the patient's position, and that's why we developed a scale which was relatively simple to score.... The other obstacle was the difficulty to do double-blind studies on patients because once you perform injections, the muscles would undergo atrophy, and then the examining doctors and the patients might both know whether it was an active substance or a placebo. So that's why I developed a scheme of videotaping patients before and after injections at regular intervals and then using a scale to give it to 2 separate observers, who were completely blind to the order of the videotapes, to score the patients on the tapes.

Good correlation was seen with both observers in the use of the Tsui scale, thus validating it, as did the publication of the first double-blind study of botulinum toxin that exclusively included patients with CD.[31,32]

Dr. Tsui: The data were presented at a meeting on dystonia at Lake Louise [see Fig. 3*]. Stanley Fahn, Donald Calne, David Marsden, and all the big names in movement disorders were there. I presented [data on the double-blind study of botulinum toxin for CD] right after Stanley Fahn. He had listed the treatments for cervical dystonia, and botulinum toxin was number 6 on the list. After I presented, based on my data and considering the benefit/risk compared to other therapies, I suggested that he might want to move botulinum toxin to number 1.*

The authors continued to use botulinum toxin under their research protocols in the 1980s, which helped to establish the injection protocol, and followed patients over a long term.[33–35] Allergan subsequently developed the CD indication for onabotulinumtoxinA.

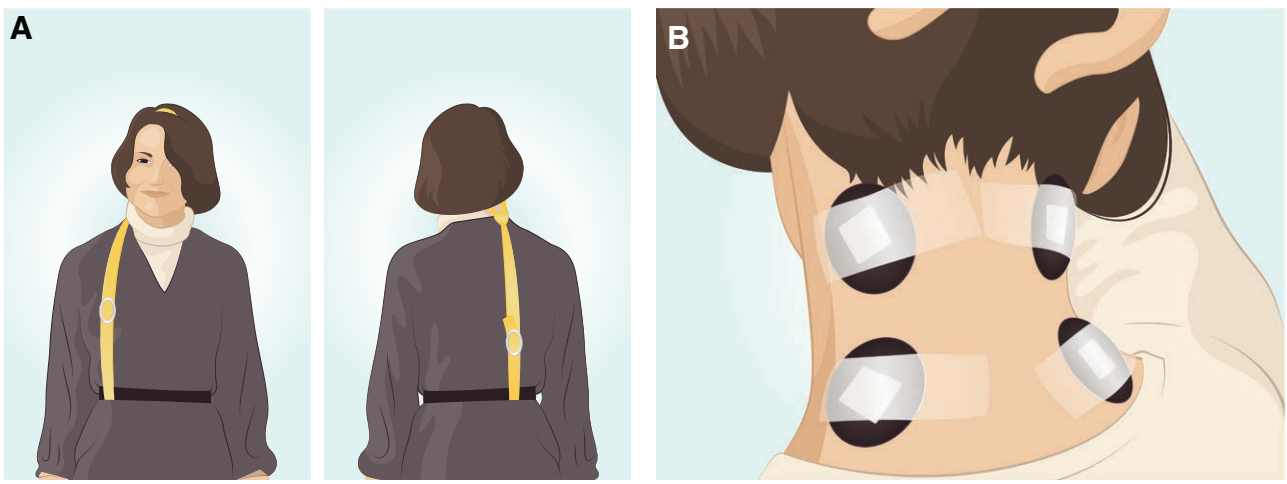

Figure 2. Devices used prior to the availability of onabotulinumtoxinA to ameliorate head position in cervical dystonia. (A) Illustration of a patient with cervical dystonia using a strap to provide a sensory trick. (B) Patient using magnets for their cervical dystonia. Both are based on actual patient photographs.

Figure 3. Canadian Conference on Neurodegenerative Diseases at Lake Louise, Banff National Park, Alberta, Canada in 1987. From left to right: Dr. Stanley Fahn, Dr. David Marsden, Dr. Joseph Tsui, Dr. Donald Calne, and Dr. Alan Crossman. Photo provided by Dr. Joseph Tsui.

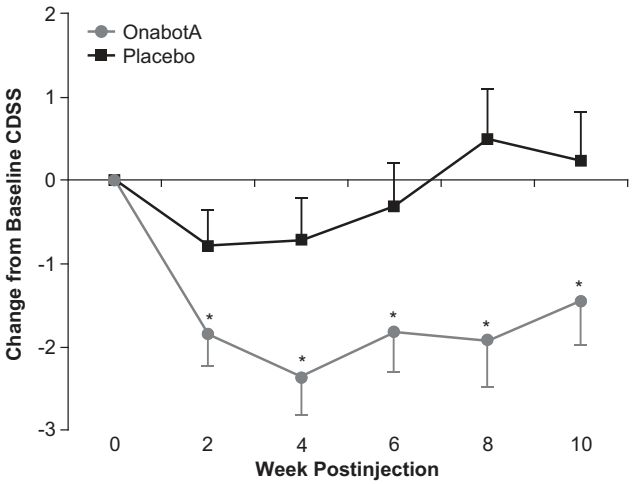

Figure 4. Change from baseline in Cervical Dystonia Severity Scale (CDSS) in patients treated with onabotulinumtoxinA or placebo during the double-blind period of the registrational trial for onabotulinumtoxinA for the treatment of cervical dystonia. Decreases in the CDSS indicate less head deviation from a neutral position. This figure is reprinted with permission from Charles D, Brashear A, Hauser RA, Li HI, Boo LM, Brin MF. Efficacy, tolerability, and immunogenicity of onabotulinumtoxinA in a randomized, double-blind, placebo-controlled trial for cervical dystonia. *Clin Neuropharmacol.* 2012;35(5):208–214. https://journals.lww.com/clinicalneuropharm/. *P <.05. OnabotA, onabotulinumtoxinA.

5. Efficacy and safety highlights

OnabotulinumtoxinA was approved in the US in 2000 for the treatment of CD to decrease the severity of neck pain and abnormal head position in adult patients.[21] At the time, there was no precedent for approving a therapy for CD. The food and drug administration desired a rating scale that reflected only the motor component of CD for use in the registration trials, and so Allergan developed the Cervical Dystonia Severity Scale (CDSS) for that purpose. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[36] was used in most other studies as the primary outcome measure.

The registrational trial, conducted from 1995 to 1997, included patients with a documented history of onabotulinumtoxinA treatment. After a 10-week open-label period, patients were randomized to onabotulinumtoxinA (n=88) or placebo (n=82) for the 10-week double-blind period.[37] Significant improvements were seen at the primary timepoint of week 6 in the double-blind period for onabotulinumtoxinA compared with placebo in the CDSS (P=.012; Fig. 4) and in the physician global assessment scale (P=.022).

To assess the effects of onabotulinumtoxinA in a real-world, clinical setting, Allergan initiated the Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE), a prospective, observational, multicenter registry in which patients could receive up to 3 treatments of onabotulinumtoxinA.[38] Patients were either naïve to botulinum toxin, new to the physician's practice, and/or if in a botulinum toxin clinical trial, had not received treatment for ≥16 weeks. Over 1000 patients enrolled, and significant improvements from baseline were observed in several clinician- and patient-reported measures (Fig. 5), confirming the effectiveness of onabotulinumtoxinA.[39] In particular, a significantly higher proportion of patients reported improvement in their CD as measured on the Patient Global Impression of Change at the final visit compared with the first phone interview (92% vs 83%; P<.0001). Significant improvements from baseline were observed in all 8 subscales of the Cervical Dystonia Impact Profile-58, a quality of life questionnaire, at all timepoints (P<.0001). The majority of patients experienced pain relief following onabotulinumtoxinA treatments, and all pain scales showed significant improvements from baseline.[40] Following onabotulinumtoxinA treatment, significantly fewer patients reported decreased work productivity or missed work due to CD, with the number of missed work days per month decreasing from 5 to 1.[10]

OnabotulinumtoxinA has shown a similar duration of effect across trials. Most patients who showed a positive response in the registrational trial returned to their baseline status about 3–4 months after treatment.[21] Consistent with this, a meta-analysis of trials of onabotulinumtoxinA treatment of CD found a mean duration of effect of 13.2–13.5 weeks[41] and in CD PROBE, the mean time between onabotulinumtoxinA treatments was 14.6–15.1 weeks.[39] The meta-analysis also established a dose effect (Fig. 6) in that the mean durations of effect were significantly longer in studies with a mean dose ≥180U compared with <180U onabotulinumtoxinA (15.3–15.5 vs 12.2–12.5 weeks; P<.01).[41] Notably, doses of onabotulinumtoxinA are not interchangeable with those of other botulinum toxin A products.[21,42]

In additional studies, consistent benefit of repeated treatment has been observed. The CD PROBE study showed robust improvements in a variety of physician- and patient-reported outcome measures over 3 onabotulinumtoxinA treatments.[39] In a longer-term retrospective review of patients with dystonia (57% of whom had CD) who received ≥1 treatment with botulinum toxin (95% of which was onabotulinumtoxinA) for at least 10 years, global response effects were sustained over time.[43]

Because repeat onabotulinumtoxinA treatments are needed for patients with this chronic condition, there is the potential for the development of antibodies to onabotulinumtoxinA over time, sometimes leading to a lack of response to treatment.[44] However, immunogenicity rates for onabotulinumtoxinA are low,[45] with neutralizing antibodies found in 1.2% of patients with CD in an observational study after a median of 9 (range 1-15) treatments over a mean of 2.5 years (range 0.26–4.2 years)[46] and in 0% of patients in a retrospective review after a mean of 4 (±2.8) treatments over 14.5 (±12.7) months.[47]

OnabotulinumtoxinA is generally well tolerated. The most frequent adverse events following onabotulinumtoxinA treatment for CD as noted in the product information are dysphagia, upper respiratory tract infection, neck pain, and headache;[21] region-specific information regarding safety and efficacy can be found in local labeling.

6. Impact of treatment with onabotulinumtoxinA on patients with CD and the broader biomedical community

OnabotulinumtoxinA meaningfully impacted the treatment of CD and, through long-term treatment, the course of the disorder.[48,49]

Dr. Brin: Following the introduction of Botox, people realized that it had a more favorable risk-benefit profile and gradually moved away from therapies such as surgery and phenol, which have the potential for permanent adverse events. Phenol treatments have been generally discontinued and surgery is reserved for patients who are not candidates for botulinum toxin injections.

Dr. Jankovic: Botox not only has dramatically changed the quality of life of patients with CD but has favorably altered the natural history of the condition by preventing the development of contractures.

The availability of onabotulinumtoxinA resulted in more CD patients seeking treatment.

Dr. Tsui: Since there was no effective treatment available for CD before the introduction of Botox, patients generally did not seek medical advice since they were frequently given wrong diagnoses, mostly pertaining to those with psychogenic origin. The incidence of CD was extremely low during those days because of lack of awareness. Since the approval of Botox in the treatment of CD, the reported incidence increased significantly because more patients are learning about an effective treatment for the condition. This also led to increased awareness of dystonia in the medical field and in the general public. Patients were no longer hiding away. Local chapters of patient support groups related to CD were established in many cities across North America, and they helped to promote the awareness of this condition significantly. They hold regular meetings and invite experts in the field to give talks. A couple of them expanded to a national level. The improvement in awareness also involved physician education, so that diagnosis can be made very early. Previously, the average time taken for a patient with CD to be referred to a proper specialist for treatment in British Columbia took an average of 7 years, going through multiple doctors. With increased awareness, patients are referred to our center within months.

Along with its impact on patients, the use of onabotulinumtoxinA for CD resulted in advancements for the biomedical community. Neurologists learned more about functional anatomy of the neck and the specific muscles affected in CD. Prior to that, neurologists had not often treated muscles of the neck, but the neck is a complicated area to treat owing to the number of muscles, which are positioned at different angles.

Dr. Brin: The development of a therapeutic for CD brought patients into research centers where they were invited into other basic and fundamental pathophysiological research studies. For example, at Columbia with our colleagues at Harvard, we were focusing on human genetics and identifying the mode of inheritance and linkage analyses to locate genes for dystonia (ie, how families would have decreased penetrance and varied clinical phenomenology). Similarly, at other centers, Tolosa and Kaji were focused on electrophysiology, as was Mark Hallett at the national institutes of health.

In addition, there was a convergence of technological, organizational, and medical developments at the time botulinum toxin was initially tested in CD.

Dr. Brin: Movement disorders as a field was coming of age. There was the society in Europe. Stan [Fahn] and Joe [Jankovic] were 2 of the founding members of the Movement Disorder Society

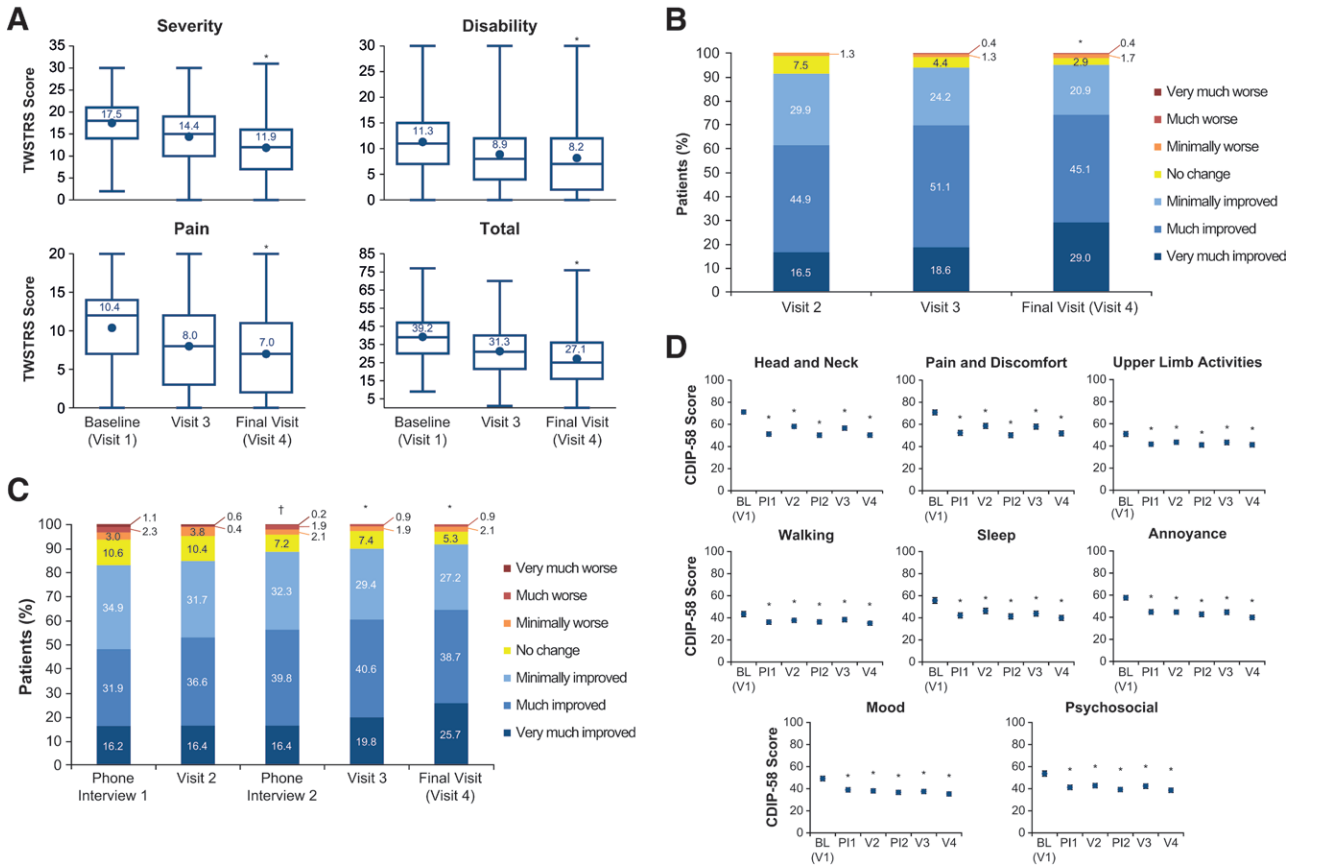

Figure 5. Physician- and patient-reported outcomes from CD PROBE for patients with complete data for each assessment. (A) Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), (B) Clinical Global Impression of Change, (C) Patient Global Impression of Change, and (D) Cervical Dystonia Impact Profile-58 (CDIP-58). Patients were treated with onabotulinumtoxinA at visits 1, 2, and 3. Reprinted from *J Neurol Sci,* Vol 349, Jankovic J, Adler CH, Charles D, Comella C, Stacy M, Schwartz M, Manack Adams A, Brin MF, Primary results from the Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE), Pages 84–93, Copyright (2015), with permission from Elsevier. *P <.0001 vs baseline, †P <0.01 vs baseline. BL, baseline; PI, phone interview; V, visit.

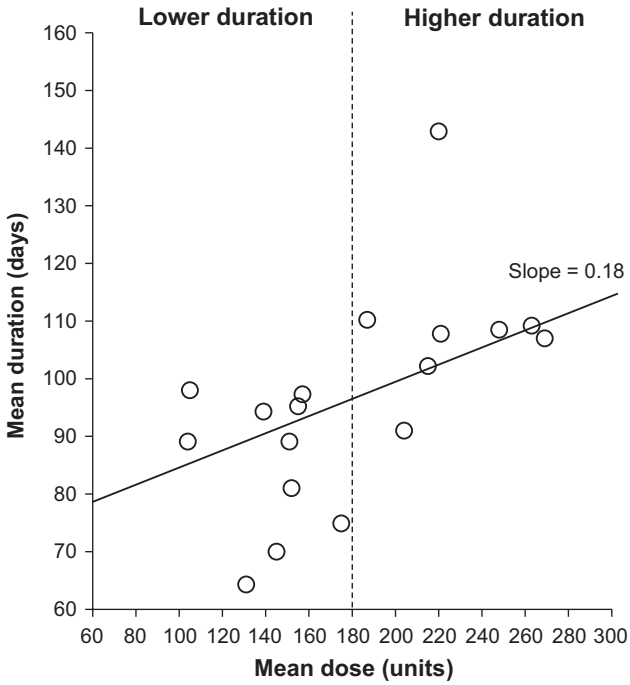

Figure 6. Regression line of mean dose of onabotulinumtoxinA by mean duration of effect. Reprinted by permission from Springer Nature Customer Service Center GmbH: Springer Nature *BMC Neurol.* Systematic review and meta-analysis of the duration of clinical effect of onabotulinumtoxinA in cervical dystonia, Marsh WA, Monroe DM, Brin MF, Gallagher CJ, 2014.

Figure 7. Founders and presidents of the Movement Disorder Society (now the International Parkinson and Movement Disorder Society), with years of presidency indicated. From left to right: Dr. Eduardo Tolosa, Dr. Stanley Fahn, Dr. Andrew Lees, Dr. Joseph Jankovic, and Dr. C. David Marsden. Photo provided by Dr. Joseph Jankovic.

in the US [see Fig. 7*]. There was a big emphasis on videotape analyses. The* Movement Disorders *journal became the first journal to use video, so there was a broader context here. The rating scales, use of video, and use of blinded observers were all being developed, and I think that the studies being conducted in the academic world with neurotoxin accelerated that whole process.*

Although onabotulinumtoxinA was initially approved for blepharospasm and strabismus, it soon became the treatment of choice for a variety of other focal dystonias, movement disorders, and numerous other neurological and non-neurological disorders[50] (see other articles in this supplement). Expanded use of onabotulinumtoxinA rested on its ability to produce a controlled amount of weakness in selected muscles combined with a favorable safety profile. Allergan has pursued clinical development of some of these therapeutic areas; please see the Botox prescribing information[21] for a list of approved indications.

Figure 8. This picture, showing (from left to right) Dr. Mitchell Brin (Columbia University), Dr. Joseph Jankovic (Baylor College of Medicine), Dr. Roger Aoki (Allergan), and Dr. Lester Kaplan (Allergan), was taken at the Pan-Asia Botulinum Toxin Experts Meeting in Kyoto, Japan, July 1994. Photo provided by Dr. Joseph Jankovic.

*Dr. Jankovic: I feel privileged to play a key role in the development of botulinum toxin as an effective and safe therapeutic. I am grateful to my academic and industry collaborators, including Drs. Brin and Aoki at Allergan [*Fig. 8*], for their support in this journey. There is no drug currently on the market that has more therapeutic applications than botulinum toxin. As a result, Botox has become one of the most recognizable brand names in the world.*[51,52]

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Author contributions

Conceptualization: Mitchell F. Brin.
Funding acquisition: Mitchell F. Brin.
Supervision: Mitchell F. Brin
Writing – review & editing: Joseph Jankovic, Joseph Tsui, Mitchell F. Brin.

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