Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review)

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

ABSTRACT

Objective: To perform an evidence-based review of the safety and efficacy of botulinum neurotoxin (BoNT) in the treatment of movement disorders.

Methods: A literature search was performed including MEDLINE and Current Contents for therapeutic articles relevant to BoNT and selected movement disorders. Authors reviewed, abstracted, and classified articles based on American Academy of Neurology criteria (Class I–IV).

Results: The highest quality literature available for the respective indications was as follows: blepharospasm (two Class II studies); hemifacial spasm (one Class II and one Class III study); cervical dystonia (seven Class I studies); focal upper extremity dystonia (one Class I and three Class II studies); focal lower extremity dystonia (one Class II study); laryngeal dystonia (one Class I study); motor tics (one Class II study); and upper extremity essential tremor (two Class II studies).

Recommendations: Botulinum neurotoxin should be offered as a treatment option for the treatment of cervical dystonia (Level A), may be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia, and upper extremity essential tremor (Level B), and may be considered for hemifacial spasm, focal lower limb dystonia, and motor tics (Level C). While clinicians’ practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data. *Neurology*® 2008;70:1699-1706

GLOSSARY

ABSD = abductor type of spasmodic dysphonia; ADSD = adductor type of spasmodic dysphonia; BoNT = botulinum neurotoxin; CD = cervical dystonia; FDA = Food and Drug Administration.

INTRODUCTION

Botulinum neurotoxin (BoNT) has emerged as an effective treatment for numerous movement disorders associated with muscle overactivity. Two companion articles provide reviews of the pharmacology and immunology of BoNT, and an evidence-based review of its use in spasticity,1 autonomic disorders, and pain.2 This article evaluates the current knowledge and evidence of BoNT in selected movement disorders.

DESCRIPTION OF THE ANALYTICAL PROCESS

The literature search strategy, panel formation, and literature analytic process are described in the companion article on BoNT in the treatment of spasticity.1 Since the different preparations of BoNT have different potencies and durations of action, the serotype and brand of BoNT used in specific studies are provided in the evidence tables, but the text distinguishes their effects only when the data are sufficient to do so, or when referring to specific dosages.

Blepharospasm. Blepharospasm is a focal dystonia characterized by involuntary contraction of orbicularis oculi, causing involuntary closure of the...
Neurology
similar for the two products. Benefit lasted 2.6–3.0 months.

Conclusions. BoNT is possibly effective with minimal side effects for the treatment of hemifacial spasm (one Class II and one Class III study). Botox® and Dysport®, after dosage adjustment, are possibly equivalent in efficacy (one Class II study).

Recommendation. BoNT injection may be considered as a treatment option for hemifacial spasm (Level C).

Clinical context. The evidence supporting BoNT use in hemifacial spasm is suboptimal. The large magnitude of effects in the initial open label studies likely has discouraged efforts to study BoNT in properly controlled clinical trials. No studies have compared BoNT with the other major treatment alternatives, including oral pharmacologic and surgical therapy.

Cervical dystonia. Cervical dystonia (CD) is a focal dystonia causing involuntary activation of the muscles of the neck and shoulders resulting in abnormal, sustained, and painful posturing of the head, neck, and shoulders. There are limited data assessing oral medications for cervical dystonia. Recent surgical studies, including deep brain stimulation, show promise. Out of approximately 80 studies of BoNT in the treatment of CD, 14 controlled studies were identified, including seven Class I studies (four with BoNT-A, three with BoNT-B) (table e-3).10-16 Botox® and Myobloc® are FDA approved for use in CD.

Three Class I studies enrolled BoNT-naive CD subjects. One study13 evaluated 55 subjects over 12 weeks. Subjects were stratified by primary type of torticollis and randomized to BoNT-A or placebo. Maximal benefit occurred at 6 weeks following injection, the BoNT-B group had more improvement in functional capacity, head turning, pain, and subjective assessment. Adverse events included dysphagia, neck weakness, and fatigue.

A second Class I study compared low, intermediate, and high doses of BoNT-A to placebo in 75 BoNT-naive CD subjects with rotational torticollis.12 At 1 month, the intermediate- and high-dose groups demonstrated improvement compared to placebo ($p < 0.05$). Subjective improvement occurred in 45–50% and was significant at 1 and 2 months for the high-dose group, and at 2 months for the intermediate-dose group. More adverse events occurred with higher doses, including neck weakness, voice changes, and dysphagia.

A third Class I study in BoNT-naive subjects compared BoNT-A and trihexyphenidyl (mean dose 16.25 mg; range 4–24 mg) at 3 months following treatment.15 BoNT-A was superior to trihexyphenidyl for TWSTRS disability (2 points), Tsui scale (5 points), and general health perception (6 points). Although there was greater improvement in TWSTRS pain score with BoNT (2 points), this did not reach statistical significance. The total TWSTRS and TWSTRS severity scores were not given for either group. The trihexyphenidyl group had more adverse events (76 events vs 31 for BoNT-A, $p < 0.0001$).

Four Class I studies enrolled subjects with previous response to BoNT. Three studies assessed safety and efficacy of BoNT-B,10,11,14 and one assessed safety and efficacy of BoNT-A.13 One of these studies randomized 109 subjects with CD to placebo, medium dose, or high dose of BoNT-B.10 There was an improvement in total TWSTRS scores at 1 month for both treatment groups compared to placebo (medium dose $p = 0.01$; high dose $p = 0.01$), with return to baseline by 3 months. The TWSTRS severity and TWSTRS disability and patient and physician global scales showed similar benefit. Adverse events were greater in the BoNT-B treated group with dry mouth and pain occurring in a dose-dependent way. All adverse events were mild.

A similar study assessed the effect of BoNT-B compared to placebo in 77 patients with CD who developed resistance to BoNT-A.13 At 1 month following injection, the BoNT-B group had more improvement in total TWSTRS score (21% vs 4% in placebo, $p = 0.0001$). Treatment with BoNT-B improved the TWSTRS severity, disability, and pain subscales and patient and physician global scales. Dry mouth occurred in 3% of placebo subjects and 44% of the BoNT-B group. A study evaluated BoNT-A compared to placebo in 80 subjects with CD previously treated with BoNT-A.13 This study showed improvement in TWSTRS total score and each of the subscales of the TWSTRS for severity, disability, and pain at 1 month with only blurred vision and neck weakness occurring more frequently than placebo.

Conclusion. BoNT is established as safe and effective for the treatment of CD (seven Class I studies).

Recommendations

- BoNT injection should be offered as a treatment option to patients with cervical dystonia (Level A).
- BoNT is probably more efficacious and better tolerated in patients with CD than treatment with trihexyphenidyl (Level B).

Clinical context. BoNT has longstanding and widespread use in the treatment of CD, a condition without effective alternative medical therapies. There are no data to compare BoNT with surgical
treatment of CD. The role of electromyography has not been established for cervical dystonia.

Focal limb dystonia. Most studies of BoNT in focal limb dystonia deal with the upper extremity. Although no controlled trials of BoNT exist for lower limb dystonia, some larger studies do include these patients. The term “focal hand dystonia” is used here to encompass writer’s cramp, other occupational hand dystonia, and nontask-specific hand dystonia. The pattern of limb dystonia varies widely among patients. There are no effective alternative medical or well-established surgical therapies for focal limb dystonia. The use of BoNT to treat limb dystonia requires thoughtful technique including customization of doses and muscle selection.

There is Class I and Class II evidence for focal limb dystonia (table e-4). The Class I trial randomized 40 patients with writer’s cramp in a double-blind design to BoNT or an equivalent volume of saline placebo. Injected muscles were chosen based on clinical examination. Participants with inadequate or no response were offered a second injection 1 month later. The primary outcome measure was the subject’s stated desire to continue injection. Seventy percent of those randomized to BoNT wished to continue treatment compared to 32% of those receiving placebo (p = 0.03). Significant improvement was also found in BoNT-injected subjects compared to those receiving placebo in secondary outcome measures including a visual analog scale, symptoms severity scale, writer’s cramp rating scale, and assessment of writing speed, but not in the functional status scale. Temporary weakness and pain at the injection site were the only adverse events reported.

One Class II trial was a prospective, double-blind, crossover study of 17 patients with several forms of limb dystonia, including lower extremity (3 patients) and secondary dystonia (4 patients). Subjects received a series of four injections in random order, one with a dose of BoNT that the investigators judged to be “optimal,” one at half the optimal dose, one at double the dose, and one with saline placebo. Using a patient subjective scale, 82% of patients receiving BoNT had benefit compared to 6% (one patient) who received placebo. Using physician rating of videotapes, 59% improved with active treatment and 38% with placebo (not significant). There was no dose-response relationship for benefit, and there was a large degree of interobserver variability. The authors attributed the lack of significance in physician ratings to an inadequate outcome evaluation. The main side effect was focal weakness that followed 53% of BoNT injections and was more likely at the higher doses. Weakness occurred with 13% of placebo injections. Other adverse effects included muscle stiffness, pain, and malaise.

Another Class II study used a placebo-controlled, double-blind, crossover design in 20 patients with writer’s cramp.19 Muscle selection was guided by clinical examination; dose of BoNT-A was based on investigator experience. Outcome assessments included evaluation of writing speed, accuracy, writing samples, and patients’ subjective report. There was significant improvement with BoNT therapy in the objective measures, but not in patients’ own assessments. Focal weakness was the only adverse effect and was severe enough to worsen pen control in one patient. The authors noted that this study evaluated only the first active treatment session that a patient received, so that the benefit obtained was likely not optimal.

Another Class II trial was a double-blind, placebo-controlled, crossover in 10 patients with focal hand dystonia.20 Muscles and BoNT-A doses were selected and optimized during a period of open treatment preceding the controlled study. Patient subjective rating and observer rating of videotapes during activities applicable to individual dystonia were the outcome measures. Eight patients had improved subjective rating and six had improved videotape rating with BoNT compared with placebo. Weakness was present in the injected muscles in 80% of subjects with active treatment.

Three Class II studies evaluated technical issues of BoNT administration (table e-4). In one study, a blinded, randomized, crossover design was used to compare continuous muscle activation to immobilization immediately after BoNT injection.21 Blinded evaluation of handgrip strength and writing revealed a significant increase in focal weakness with continuous muscle activity, but no subjective or objective improvement in writing. In another Class II study, patients were randomized to one of two muscle localization techniques: EMG recording or electrical stimulation.22 Injections guided by either technique were equally effective in producing weakness in the target muscle. The accuracy of muscle localization with and without EMG was evaluated in a third trial.23 Only 37% of needle placements based on surface anatomy were localized in the targeted muscle.

Conclusions. BoNT is probably effective for the treatment of focal upper extremity limb dystonia.
Laryngeal dystonia. Laryngeal dystonia (spasmodic dysphonia) generally presents as adductor type (ADSD) and less frequently as abductor type of spasmodic dysphonia (ABSD). ADSD is characterized by a “strain-strangle” voice, while ABSD produces a breathy and hypophonic voice. There are no effective alternative medical or surgical therapies for spasmodic dysphonia. There is one Class I study of BoNT24 (n = 13) of patients with ADSD. This double-blind, randomized, parallel group study compared seven patients receiving BoNT with six receiving saline. Outcome measures included instrumental quantitative measures of voice function and patient ratings. Significant benefit was found in the BoNT-injected group (p = 0.01) (table e-5). One Class III study found that the addition of voice therapy following BoNT in ADSD prolonged benefit from BoNT treatment.25 Another found that voice rest 30 minutes after BoNT injection prolonged the benefit of BoNT.26 One Class III study of 15 patients with ABSD did not find a significant difference using either percutaneous or endoscopic injection technique.

Conclusions. BoNT is probably effective for the treatment of ADSD (one Class I study). There is insufficient evidence to support a conclusion of effectiveness for BoNT in ABSD.

Recommendations

- BoNT should be considered as a treatment option for adductor spasmodic dysphonia (Level B).
- There is insufficient evidence to support or refute the use of BoNT in abductor spasmodic dysphonia (Level U).

Clinical context. The evidence supporting BoNT use in laryngeal disorders is suboptimal. While most clinicians utilize EMG targeting for laryngeal injections, the utility of this technique is not established in comparative trials. Dramatic results in the initial open label studies and the lack of other effective therapy likely have discouraged efforts to study BoNT in larger and more properly controlled clinical trials.

Tics. Typically associated with Tourette syndrome, tics are relatively brief, intermittent movements (motor tics) or sounds (vocal or phonic tics), usually preceded by a premonitory sensation.28 While antiparkinsonian drugs (neuroleptics) are often effective in treating troublesome multifocal tics, these drugs often produce undesirable side effects, particularly in patients with focal tics, such as blinking, blepharospasm, head jerking, neck twisting, and loud vocalizations, including coprolalia. Although confined to a limited anatomic distribution, such focal tics may be a source of embarrassment and may result in functional blindness, local discomfort, and social isolation.

In initial open label Class IV studies, injections of BoNT in the muscles involved in the motor and phonic tics was associated with a moderate to marked reduction in the intensity and frequency of the tics and nearly complete abolishment of the premonitory sensation. In a Class IV study of 35 patients treated in 115 sessions for troublesome or disabling tics, the mean peak effect response was 2.8 (range 0 = no effect; 4 = marked improvement in both severity and function). The mean duration of benefit was 3.4 months (up to 10.5). Latency to onset of benefit was 3.8 days (up to 10). Twenty-one of 25 patients (84%) with notable premonitory sensory symptoms derived marked relief of these symptoms from BoNT (mean benefit: 70.6%).

In a Class II study of 18 patients with simple motor tics, there was a 39% reduction in the number of tics per minute within 2 weeks after injection with BoNT, as compared to a 6% increase in the placebo group (p < 0.004, table e-6). In addition, there was a 0.46 reduction in “urge scores” with BoNT compared to a 0.49 increase in the placebo group (p = 0.02). This study lacked the power to show significant differences in other measured variables, such as severity score, tic suppression, pain, and patient global impression. The full effect of BoNT may not have been appreciated at 2 weeks. The study employed a single treatment session protocol that does not reflect the clinical practice of evaluating patients after several adjustments in doses and sites of injections. Furthermore, since subjects “did not rate themselves as significantly compromised by their treated tics,” it is likely that their symptoms were relatively mild at baseline.

Conclusions. BoNT is possibly effective for the treatment of motor tics (one Class II study).
There are insufficient data to determine the effectiveness of BoNT in phonic tics (one Class IV study).

**Recommendation.** BoNT may be considered as a treatment option for motor tics (Level C).

**Clinical context.** There are no data to compare the efficacy of BoNT and neuroleptics in the treatment of tic disorders.

**Tremor.** Tremor, an oscillatory movement produced by alternating or synchronous contractions of antagonistic muscles, is the most common movement disorder. While propranolol and primidone usually ameliorate mild or moderate essential tremor, pharmacotherapy is usually not sufficient to control a high-amplitude tremor that impairs activities of daily living. In such cases of disabling tremor, local injection of BoNT may be used before considering more aggressive intervention such as thalamic deep brain stimulation.

A Class II placebo-controlled study evaluated 25 patients with hand tremor of 2 (moderate) to 4 (severe) on the tremor severity rating scale31 (table e-7). Subjects were randomized to receive either 50 units of BoNT-A (Botox®) or placebo injections into the wrist flexors and extensors of the dominant limb. If patients failed to respond to the initial injection, they were eligible to receive another injection of 100 units 4 weeks later.

Rest, postural, and kinetic tremor were evaluated at 2- to 4-week intervals over a 16-week study period, using tremor severity rating scales, accelerometry, and assessments of improvement and disability. There was significant improvement on the tremor severity rating scale 4 weeks after injection in patients treated with BoNT as compared to placebo, and this effect was maintained for the duration of the study. Four weeks after injection, 75% of BoNT-treated patients vs 27% of placebo-treated patients (p < 0.05) reported mild to moderate improvement. Functional rating scales did not improve although trends were observed for some items. Postural accelerometry measurements showed a 30% reduction in amplitude in 9 of 12 BoNT-treated subjects and in 1 of 9 placebo-treated subjects (p < 0.05). Although all patients treated with BoNT reported some degree of finger weakness, no severe, irreversible, or unexpected adverse events occurred.

There were similar results in another Class II multicenter, double-blind, controlled trial that utilized a similar protocol and involved 133 patients with essential tremor. The patients were randomized to receive 50 or 100 U of Botox® into wrist flexors and extensors and were followed for 4 months. The study showed significant improvement in postural tremor, but only minimal improvement in kinetic tremor and functional assessments.

The study design of both Class II studies limits their applicability to clinical practice. Both used a rigid treatment protocol that employed a fixed BoNT dose and a predetermined set of muscles. In practice, dosages and injected muscles are often individually chosen on the basis of tremor pattern.

An underpowered Class II study of 10 patients with head tremor did not show a statistically significant benefit in BoNT-treated patients. There are two Class IV open-label studies in voice tremor that showed modest improvement from baseline in objective acoustic and subjective measures after unilateral or bilateral BoNT injection.

**Conclusions.** BoNT injection of forearm muscles is probably effective in reducing the tremor amplitude in patients with essential hand tremor (two Class II studies). The benefits must be considered in conjunction with the common adverse effect of muscle weakness associated with BoNT injection. Existing data are insufficient to draw a conclusion on the use of BoNT in the treatment of head and voice tremor.

**Recommendation.** BoNT should be considered as a treatment option for essential hand tremor in those patients who fail treatment with oral agents (Level B).

**Clinical context.** Oral agents and deep brain stimulation are alternative treatments for essential tremor. There are presently no data comparing the efficacy of BoNT to these treatment modalities. By reducing or eliminating BoNT injection into wrist extensors, the complications of finger and hand weakness may be reduced. However, no controlled data employing the new methodology are available.

**Summary.** The evidence supporting the use of BoNT in movement disorders is summarized in the table.

**RECOMMENDATIONS FOR FUTURE RESEARCH**

- Many of the recommendations for future research provided in the companion article on BoNT for spasticity are also pertinent to movement disorders. Additional recommendations follow.
- Further placebo-controlled trials are needed to evaluate the efficacy and safety of BoNT for several movement disorders, particularly blepharospasm, hemifacial spasm, lower limb dystonia, phonic tics, and head and voice tremor.
- To the extent that issues of feasibility and ethics make such studies unlikely, other
### Table
Summary table for botulinum toxin in the treatment of movement disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Class</th>
<th>No. of subjects</th>
<th>Outcome measures</th>
<th>Adverse events</th>
<th>Conclusions</th>
<th>Recommendations*</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>2 Class II</td>
<td>17</td>
<td>Subjective, Fahn scale</td>
<td>Dry eye, tearing, ptosis, diplopia, lid edema, ecchymosis</td>
<td>Probably effective</td>
<td>B</td>
<td>Lack of controlled studies due to dramatic efficacy</td>
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<tr>
<td>Hemifacial spasm</td>
<td>1 Class II</td>
<td>19</td>
<td>Clinical, video, subjective</td>
<td>Weakness, bruising, diplopia, ptosis, dry eye</td>
<td>Possibly effective</td>
<td>C</td>
<td>Lack of controlled studies due to dramatic efficacy; surgery major alternate Rx</td>
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<tr>
<td>Cervical dystonia</td>
<td>7 Class I</td>
<td>584</td>
<td>TWSTRS, Tsui, disability</td>
<td>Dysphagia, neck weakness, dry mouth, pain</td>
<td>Established safe and effective</td>
<td>A</td>
<td>No effective alternate Rx</td>
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<tr>
<td>Focal limb dystonia (UE)</td>
<td>3 Class II</td>
<td>47</td>
<td>Video, handwriting accuracy/speed</td>
<td>Focal weakness, pain</td>
<td>Probably effective</td>
<td>B</td>
<td>No effective alternate Rx</td>
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<tr>
<td>Focal limb dystonia (LE)</td>
<td>1 Class II</td>
<td>3</td>
<td>Video, subjective</td>
<td>Focal weakness, pain</td>
<td>Data inadequate</td>
<td>None</td>
<td>No effective alternate Rx</td>
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<tr>
<td>Laryngeal dystonia</td>
<td>1 Class I</td>
<td>13</td>
<td>Quant voice fx, patient ratings</td>
<td>Breathing, bleeding</td>
<td>Adductor SD: probably effective; abductor SD: inadequate data</td>
<td>B</td>
<td>No effective alternate Rx</td>
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<tr>
<td>Motor tics</td>
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<td>18</td>
<td>Tic frequency, urge scores, global disability</td>
<td>Focal weakness</td>
<td>Possibly effective</td>
<td>C</td>
<td>No comparative data with oral agents</td>
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<tr>
<td>Essential tremor (UE)</td>
<td>2 Class II</td>
<td>158</td>
<td>Tremor rating, subjective (MD/pt); SIP</td>
<td>Focal weakness</td>
<td>Probably effective</td>
<td>B</td>
<td>No comparative data with oral agents</td>
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</table>

*Classification of recommendations is available on the Neurology® Web site at www.neurology.org. A – Should be offered; B – should be considered; C – may be considered; UE – upper extremity; LE – lower extremity; Rx – prescription; SD – spasmodic dysphonia; MD – physician; pt – patient; SIP – Sickness Impact Profile.

strategies should be considered to prove the efficacy of these treatments in the current era of evidence-based medicine.

**DISCLAIMER** This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

**ACKNOWLEDGMENT**
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**DISCLOSURE**
The authors report the following conflicts: Dr. Simpson has received speaker honoraria and research support from Allergan, Merz, and Solstice, Inc., and performs botulinum toxin injections. Dr. Blitzer has received speaker honoraria from Allergan, Solstice, and Merz; research support from Allergan, Ipsen, Merz, and Ovation; performs botulinum toxin injections and has received payment for expert testimony. Dr. Comella has received speaker honoraria from Jazz Pharmaceutical, Merz Pharmaceutical, and UCB Pharmaceutical; research support from Allergan, Dystonia Study Group, and Solstice; and performs botulinum toxin injections. Dr. Dubinsky has received speaker honoraria from Allergan and research support from Allergan, MERZ INC., and Solstice Neurosciences. Dr. Dubinsky holds financial interest in Abbott Laboratories (spouse), performs botulinum toxin injections, and presents annual courses at AANEM on chemodenervation. Dr. Hallevi holds financial interest in Amylin Pharmaceuticals, Eli Lilly, Genentech, Genzyme, HealthSouth Corp., Medtronic, Pfizer, St. Jude Medical, Triad Hospitals, United Healthcare, and Valeant Pharmaceuticals International and performs botulinum toxin injections. Dr. Jankovic has received speaker honoraria from Allergan and Merz Pharmaceutical, research support from Allergan, Ipsen, and Merz Pharmaceutical, and performs botulinum toxin injections. Dr. Karp performs botulinum toxin injections. Dr. Ludlow holds financial interest in Fidelity Biotechnology (family member). Dr. Miyasaki has received research support from Boehringer Ingelheim, Huntington Study Group, NIH, Solvay, Solstice, and Teva. Dr. Naumann has received speaker honoraria from Ipsen and Allergan and performs botulinum toxin injections. Dr. So holds financial interest in Satori Inc., and has received research support from NIH, Pfizer, Inc., and NeurogesX Inc.

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Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review) [RETIRED]: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

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