Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review)

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

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ABSTRACT

Objective: To perform an evidence-based review of the safety and efficacy of botulinum neurotoxin (BoNT) in the treatment of autonomic and urologic disorders and low back and head pain.

Methods: A literature search was performed including MEDLINE and Current Contents for therapeutic articles relevant to BoNT and the selected indications. Authors reviewed, abstracted, and classified articles based on the quality of the study (Class I–IV). Conclusions and recommendations were developed based on the highest level of evidence and put into current clinical context.

Results: The highest quality literature available for the respective indications was as follows: axillary hyperhidrosis (two Class I studies); palmar hyperhidrosis (two Class II studies); drooling (four Class II studies); gustatory sweating (five Class III studies); neurogenic detrusor overactivity (two Class I studies); sphincter detrusor dyssynergia in spinal cord injury (two Class II studies); chronic low back pain (one Class II study); episodic migraine (two Class I and two Class II studies); chronic daily headache (four Class II studies); and chronic tension-type headache (two Class I studies).

Recommendations: Botulinum neurotoxin (BoNT) should be offered as a treatment option for the treatment of axillary hyperhidrosis and detrusor overactivity (Level A), should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B), and may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B). There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of BoNT in chronic daily headache (mainly transformed migraine) (Level U). While clinicians’ practice may suggest stronger recommendations in some of these indications, evidence-based conclusions are limited by the availability of data.

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GLOSSARY

BoNT = botulinum neurotoxin; CDH = chronic daily headache; DSD = detrusor sphincter dyssynergia; LBP = low back pain; MS = multiple sclerosis; NNT = number needed to treat; OLBPQ = Oswestry Low Back Pain Questionnaire; VAS = visual analog scale.

INTRODUCTION

Since its introduction about 25 years ago, botulinum neurotoxin (BoNT) has become the most effective treatment for numerous movement disorders associated with increased muscle tone. Two companion articles provide a review of the pharmacology and immunology of BoNT, and an evidence-based review of its use in spasticity and movement disorders. In addition to its activity at cholinergic motor endings, acetylcholine is also an important neurotransmitter in the parasympathetic, and to some degree, in the sympathetic autonomic nervous system. Several
Primary focal hyperhidrosis is a chronic idiopathic disorder of excessive sweating which most often affects the axillae, palms, soles, and forehead. Treatment options include topical or systemic pharmacologic therapy, iontophoresis, or surgical procedures. Drooling may be a disabling problem in parkinsonian syndromes, amyotrophic lateral sclerosis, and cerebral palsy. In these disorders, drooling is primarily due to decreased swallowing rather than increased salivary production and may be amenable to pharmacologic treatment or local radiation and surgery in severe cases.

**Axillary hyperhidrosis.** Two Class I studies and several Class II studies were identified in axillary hyperhidrosis (table e-1) on the Neurology® Web site at www.neurology.org. In a randomized, placebo-controlled, double-blind study of 320 subjects with axillary hyperhidrosis, 242 patients received BoNT and 78 received saline placebo intradermally. Patients receiving BoNT had a higher response rate (more than 50% reduction of sweat production compared to baseline sweating) at all time points than those receiving placebo (82% to 95% vs 20% to 37%; p < 0.001). There was a similar pattern in the decrease of sweat production, and improvement in quality of life. Treatment-related adverse events were reported by 27 patients (11%) receiving BoNT and 4 (5%) receiving placebo, but this difference was not significant (p = 0.13). The mean duration of therapeutic effect was 31 weeks.

In another Class I study of 145 patients with axillary hyperhidrosis, BoNT was injected into one axilla and placebo was injected into the other in a randomized, double-blind manner. At week 2, sweat production was reduced in the axilla that had received BoNT as compared with the placebo-injected side (p < 0.001). Injections were well tolerated.

**Palmar hyperhidrosis.** Two Class II and several Class III studies were identified in the use of BoNT in palmar hyperhidrosis (table e-1). In one randomized, placebo-controlled, double-blind Class II study in 19 patients with palmar hyperhidrosis, sweating was significantly reduced by BoNT as compared with placebo based on gravimetric measurements. There was no resulting muscle weakness. Another Class II study in 11 patients with palmar hyperhidrosis also showed reduction of palmar sweating compared with placebo (p < 0.001) using a digitized ninhydrin test. One Class III study evaluated the effect of BoNT on hand muscle strength. No grip weakness resulted in any patients, whereas pinch strength was reduced 2 weeks after the injection. Pinch strength returned to baseline levels 2 months after treatment.

**Gustatory sweating.** Five Class III studies were identified on the use of BoNT in gustatory sweating after parotidectomy (selection in table e-1). Intradermal injections of BoNT resulted in a significant and consistent reduction of the area of sweating without significant side effects.

**Drooling in neurodegenerative diseases and hyperlacrimation.** Four Class II studies were identified in the treatment of sialorrhea in Parkinson’s disease (3 BoNT-A and 1 BoNT-B). One of the studies also included 12 patients with ALS (table e-1). BoNT significantly reduced the amount of saliva production after injection of the parotid/submandibular glands. Adverse events were reported as mild. Only Class IV studies were identified in the use of BoNT in hyperlacrimation. These consistently showed a reduction of tearing after injections of BoNT into the lacrimal glands.

**Conclusions.** BoNT is established as safe and effective for the treatment of axillary hyperhidrosis (two Class I studies), is probably safe and effective for palmar hyperhidrosis (two Class II studies) and in drooling in patients with PD (four Class II studies), and is possibly effective for gustatory sweating (five Class III studies). There is insufficient evidence to support the effectiveness 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.
of BoNT in hyperlacrimation (Class IV studies).

**Recommendations**

- BoNT should be offered as a treatment option to patients with axillary hyperhidrosis (Level A).
- BoNT should be considered as a treatment option for palmar hyperhidrosis and drooling (Level B).
- BoNT may be considered for gustatory sweating (Level C).

**Clinical context.** While there are no head-to-head comparisons of BoNT with other treatment options in hyperhidrosis or drooling, many clinicians offer BoNT to patients with axillary hyperhidrosis unresponsive to topical treatment and to patients with palmar hyperhidrosis as an alternative to iontophoresis or sympathectomy. In neurodegenerative disorders, particularly amyotrophic lateral sclerosis, BoNT should be used with caution as dysphagia or worsening weakness may occur. Although the evidence for BoNT in gustatory sweating is suboptimal, there is no effective alternative treatment.

**Neuro-urologic disorders.** Patients with neurogenic bladder suffer from detrusor overactivity (detrusor hyperreflexia), which may be combined with detrusor sphincter dyssynergia (DSD; uncoordinated voiding). Both conditions cause high intravesical pressure and can lead to upper urinary tract damage. Treatment for both DSD and detrusor overactivity include pharmacologic therapy, catheterization, and surgery. Currently available pharmacologic treatments are often insufficient or not well tolerated.

**Detrusor sphincter dyssynergia.** There is one Class I and two Class II studies of BoNT in DSD (table e-2). In the Class I study, the effects of BoNT vs placebo were studied on DSD in 86 patients with multiple sclerosis (MS). The study employed a single transperineal injection of Botox® 100 units in 4 mL normal saline, or placebo, into the striated sphincter with EMG guidance. The primary endpoint was post-void residual volume at 30 days. Secondary endpoints included voiding and urodynamic variables. A single injection of BoNT did not decrease post-voiding residual volume in this group of patients with MS. These findings differ from those in patients with spinal cord injury (discussed below) and may be due to lower detrusor pressures in patients with MS.

A small Class II study in five patients with high spinal cord injury found BoNT to be superior to placebo for DSD. Measurements of urethral pressure profile, post-voiding residual urine volume, and bladder pressure during voiding all decreased in treated patients while no changes from baseline were observed in the placebo group. The duration of the toxin effect averaged 2 months. There was mild generalized weakness lasting 2 to 3 weeks in three patients after BoNT injections. Another small Class II study compared the effects of lidocaine (as control) to BoNT in 13 patients with spinal cord disease including traumatic injury, MS, and congenital malformations. Measurement of post-void residual urine volume, maximum urethral pressure, maximum detrusor pressure, and micturition diary satisfaction score demonstrated the superiority of BoNT to placebo. No significant side effects were reported in this study.

**Neurogenic detrusor overactivity.** BoNT decreased neurogenic detrusor overactivity in two Class I studies (one BoNT-A and one BoNT-B), one Class II study, and several Class III studies (table e-2). In one Class I study, 59 patients with spinal cord injury and MS were enrolled in a single treatment, randomized, placebo-controlled, 6-month safety and efficacy study. Patients received either BoNT-A or placebo. Injections were given into the detrusor muscle, avoiding the bladder base and trigone. Injection volume was 30 mL and 30 sites were injected. A single administration into the detrusor muscle was well tolerated and more effective than placebo in reducing the frequency of incontinence episodes, enhancing bladder function, and improving quality of life.

In another Class I study, the use of BoNT was studied for refractory neurogenic and non-neurogenic detrusor overactivity. Twenty patients, 18 to 80 years old, with detrusor overactivity unresponsive to oral antimuscarinic agents, participated in the study. Subjects were injected with either placebo or BoNT-B. After 6 weeks, treatments were crossed over. The primary outcome was the paired difference in change in average voided volumes. Secondary outcome measures included frequency, incontinence episodes, and paired differences in quality of life, as measured by the King’s Health Questionnaire. There were significant paired differences in the change in average voided volume, urinary frequency, and episodes of incontinence between active treatment and placebo. There were also differences in the change in quality of life affecting five domains of the King’s Health Questionnaire. This study is limited in that the study population was comprised of a mixed population of patients, with diverse etiologies of detrusor dysfunction.
overactivity (neurogenic and non-neurogenic). This limits the generalizability of the findings. The absence of a sustained washout period before the crossover might have biased the findings, and the low dose of BoNT-B used may have affected the duration of the results.

In another study, BoNT injection was compared to resiniferatoxin instillation (inhibits bladder C-fiber afferent nerves) into the bladder in 25 patients with spinal cord lesions with neurogenic detrusor overactivity. There was a significant decrease in catheterization and incontinence episodes for both treatments at 6, 12, and 18 months of follow-up. However, the BoNT injections provided superior clinical and urodynamic benefits as compared to intravesical resiniferatoxin. There were no significant side effects with either treatment.

Conclusions. BoNT is established as safe and effective for the treatment of neurogenic detrusor overactivity in adults (two Class I studies, one Class II study). Data on the use of BoNT for DSD are conflicting. BoNT is probably safe and effective for the treatment of DSD in patients with spinal cord injury (two Class II studies). However, on the basis of one Class I study, BoNT does not provide significant benefit for the treatment of DSD in patients with MS.

Recommendations
- BoNT should be considered as a treatment option for neurogenic detrusor overactivity (Level A).
- BoNT should be offered as a treatment option for DSD in patients with spinal cord injury (Level B).

Clinical context. Although the use of BoNT for the treatment of neuro-urologic disorders is encouraging, there are limited head-to-head comparisons of treatment options in DSD. Head-to-head comparisons of detrusor overactivity need to be done.

Low back pain. Low back pain (LBP) is a major public health problem. Approximately 10% of acute LBP syndromes develop into chronic LBP. An analgesic effect for BoNT has been suggested in a variety of painful conditions, including rectalgia (anismus), pain associated with hemorrhoidectomy, mastectomy, cystitis, prostatitis, and after radical neck dissection.

There is one Class II study of BoNT for the treatment of chronic LBP (table e-3). BoNT was compared to saline placebo in 31 adult patients with chronic and predominantly unilateral LBP of 6 months or greater duration. The pathology was mixed and included chronic disk disease, prior lumbar spine surgery, and nonspecific degenerative spine disease. BoNT or saline was injected into paraspinal muscles unilaterally at five sites between L1-S1 levels. The level of pain and functional impairment were evaluated at baseline and 3 and 8 weeks after treatment with visual analog scale (VAS) and the Oswestry Low Back Pain Questionnaire (OLBPQ). At 8 weeks, 60% of patients who had received BoNT demonstrated pain relief (50% or more decrease in VAS score) in contrast to 12.5% of the patients in the saline group (p = 0.01, NNT = 2.1). There was functional improvement in OLBPQ in 66.7% of the patients on BoNT and 18.8% of the saline group (p = 0.01, NNT = 2.1). BoNT also improved function (i.e., sitting, standing, and sleeping, quantified at six steps [0–6] for each subset). There were no significant adverse effects.

Conclusions. BoNT is possibly effective for the treatment of chronic predominantly unilateral LBP (one Class II study).

Recommendation. BoNT may be considered as a treatment option of patients with chronic predominantly unilateral LBP (Level C).

Clinical context. The evaluation and treatment of LBP is complicated by its diverse potential causes. In most clinical settings, it is difficult to diagnose the precise origin of pain. This creates challenges in study design, particularly in the selection of homogeneous subject populations.

Headache. Episodic migraine is a headache that is typically throbbing and often unilateral, usually accompanied by photophobia, phonophobia, nausea, or vomiting. The presence of focal neurologic symptoms defines migraine with aura. Episodic tension-type headache may be defined as a constant tight or pressing sensation, usually bilateral, that is typically not associated with photophobia, phonophobia, nausea, or vomiting. Chronic daily headache (CDH) is a headache that occurs more than 15 days out of a month, and it may be a migraine (chronic or transformed migraine) or tension-type headache (chronic tension-type headache). Pharmacologic agents are the mainstay for acute and prophylactic treatment of most forms of headache.

There are 11 randomized, placebo-controlled studies of BoNT in patients with headache (table e-4). Six studies were graded Class II because of a lack of description of allocation concealment or because the studies lost more than 20% of patients to follow-up. One study was a randomized crossover trial. This article did not adequately describe the methodology of the study. For example, it was unclear when patients
were crossed over and if there was a washout period. Because of these limitations, this study was graded Class III.

Episodic migraine. There are two Class I studies and two Class II studies of BoNT in patients with episodic migraine. Enrolled patients had two to eight episodic migraines per month. All the studies used a fixed-site injection strategy (i.e., sites of injection were selected a priori irrespective of the location of pain in an individual patient).

One Class I study compared BoNT-A to placebo in 232 patients with moderate to severe episodic migraine (four to eight episodes per month). Up to a total of 25 U were injected into the frontal, temporal, glabellar, or all three regions. The study was powered to detect a difference of two headaches per month between groups. There were reductions from baseline in migraine frequency, maximum severity, and duration, but there was no significant difference between BoNT and placebo groups at 1 to 3 months after injection. Another Class I study was comprised of three sequential investigations of 418 patients with re-randomization at each stage and doses ranging from 7.5 to 50 U. All patients had a history of four to eight moderate to severe migraines per month. BoNT-A and placebo produced a comparable decrease from baseline in migraine frequency at each timepoint between 1 and 4 months after injection, and there were no consistent, statistically significant, between-group differences.

The two Class II studies randomized patients to placebo or BoNT. The primary outcome in one study was a change in the frequency of moderate to severe migraines per month. In the second study, the primary outcome was the proportion of patients with 50% or more decrease in the frequency of headaches as compared with baseline. For the primary outcome measures, neither study demonstrated significant benefit of BoNT. One study showed a significant reduction in the proportion of patients experiencing a decrease of two or more headaches per month. The rate difference between the placebo-treated and the BoNT-treated patients was 19.5% (95% CI, 0.8 to 35.8). Thus, the number needed to treat (NNT) to result in one additional patient to have a decrease of two or more headaches per month is five. In the second study, which enrolled 60 patients, the rate difference between patients treated with placebo and BoNT experiencing 50% or more reduction in headache frequency was 5%, favoring the BoNT-treated group. However, this difference was not significant. The 95% CIs were large, extending from −19.2% to 29.5%. Thus, a clinically meaningful difference could not be excluded.

Conclusions. Based on published Class I and Class II studies, BoNT injection is probably ineffective in the treatment of episodic migraine (Level B).

Chronic daily headache. There are four Class II studies of BoNT in CDH. CDH was explicitly defined in all articles. All studies included a large number of patients with transformed migraine. One study evaluated a subgroup of patients with CDH who were not on prophylactic medication. Three of the studies used a follow-the-pain strategy for BoNT injections (i.e., the treating physician modified the sites of injection based on the location of pain in an individual patient). One study used a fixed-site strategy. Follow-up duration varied from 3 to 11 months. Loss to follow-up varied from 1.7% to 27%.

The primary outcome measure for all CDH studies was the mean change in headache-free days per month. Three of the studies used a run-in period in which all patients were treated with placebo to identify placebo nonresponders. The placebo nonresponders were the primary population of interest for these studies. One of the studies demonstrated a significant benefit of BoNT based on the primary outcome measure. This study showed a mean increase in the number of headache-free days per month of 11 days in the BoNT-treated population as compared to 8 days in the placebo group. Although no significant benefit was observed for the overall cohort in another study, the subgroup of patients with CDH not on prophylactic medications had a significant mean increase in headache-free days per month in the BoNT vs placebo group (10 days vs 6.7 days, respectively). The largest study of patients with CDH, enrolling 702 patients, showed no significant difference between BoNT-treated patients and placebo.

We calculated the difference in the proportion of patients attaining at least a 50% reduction in CDH for the BoNT-treated and placebo-treated patients (not the primary outcome for any of the CDH studies). Two studies demonstrated a significant benefit for BoNT relative to this outcome with NNTs of 4 and 6. The largest study showed no significant benefit of BoNT in reducing headache frequency compared to placebo.

Conclusions. Based on inconsistent results from four Class II studies, there is insufficient evidence to support or refute a benefit of BoNT for the treatment of chronic daily headache (Level U).
Table  Botulinum neurotoxin (BoNT) for autonomic disorders and pain

<table>
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<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Auxillary hyperhidrosis</td>
<td>2 I</td>
<td>Gravimetry; responder rate; patient satisfaction</td>
<td>No difference between BoNT and placebo</td>
<td>Safe and effective</td>
<td>A</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Palmar hyperhidrosis</td>
<td>2 II</td>
<td>Gravimetry; ninhydrin test; VAS</td>
<td>Injection pain; mild hand muscle weakness</td>
<td>Probably effective</td>
<td>B</td>
<td>No head-to-head comparisons with other treatment options</td>
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<tr>
<td>Gustatory sweating</td>
<td>5 III</td>
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<td>Injection pain</td>
<td>Possibly effective</td>
<td>C</td>
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<td>None known</td>
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<td>VAS; Owestry low back pain questionnaire</td>
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<td>Episodic migraine</td>
<td>2 I</td>
<td>Change in frequency per month; proportion with 50% decrease in frequency compared with baseline</td>
<td>Ptsis, local transient pain at the site of injection, bruising, diplopia</td>
<td>Probable ineffective</td>
<td>B</td>
<td>Suboptimal dose and muscle selection may account for treatment failures</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>2 II</td>
<td>VAS; area under the curve; proportion of severe headaches post treatment</td>
<td>Transient weakness of neck muscles, local skin tension, ptsis, , flulike reaction</td>
<td>Probably ineffective</td>
<td>B</td>
<td>Suboptimal dose and muscle selection may account for treatment failures</td>
</tr>
<tr>
<td>Chronic daily headache</td>
<td>4 II</td>
<td>Change in headache-free days</td>
<td>Ptsis, transient weakness of neck, flulike reaction</td>
<td>Insufficient evidence</td>
<td>U</td>
<td>Suboptimal dose and muscle selection may account for treatment failures</td>
</tr>
</tbody>
</table>

*Classification of recommendations is available on the Neurology® Web site at www.neurology.org.

VAS = visual analog scale; QOL = quality of life; DSD = detrusor sphincter dyssynergia; PRUV = post void residual urine volume.

**Chronic tension-type headache.** Four studies described outcomes in patients with chronic tension-type headaches randomized to BoNT or placebo injections. Two of these studies were Class I,26,32 one Class II,31 and one Class III.33 The definition of chronic tension-type headache was explicit in three of the articles.26,32,33 One study32 excluded patients with a history of migraine. Two articles32,33 allowed patients with migraine only if they had a history of less than one migraine per month.

A fixed-sites injection strategy was employed in two studies,26,33 whereas two studies32,33 used a follow-the-pain injection approach. The primary outcome measure in the Class I study26 was the area under the headache curve in the subjects’ headache diary. For the 6-week period starting 5 weeks postinjection, there was no significant difference, when compared to a baseline 6-week period, between the BoNT and placebo groups. A post hoc statistical analysis showed that this study was sufficiently powered to detect a difference in reduction of headache frequency of one headache per week. Thus, a clinically meaningful effect of BoNT was excluded. The other Class I study33 used as primary outcome the mean change from baseline in number of headache-free days from day 30 to 60 after injection. Both BoNT and placebo groups improved after injection, but BoNT was not more beneficial. A power analysis was not provided. A benefit could be demonstrated only in a secondary outcome measure, the number of patients with >50% decrease in headache days at day 90, in three of the five dosing schemes. A Class II article35 used the mean difference in intensity of headache measured by a VAS pre- and post-treatment. This study, which enrolled 30 patients, showed no significant difference in the severity of pain. As a secondary outcome, this study also recorded the percentage of patients obtaining a >45% reduction in headache severity. There was no significant benefit of BoNT, although this study was insufficiently powered to exclude a clinically important difference.

**Conclusions.** Based on the results of two Class I studies, at least one of which was adequately powered, BoNT injection is probably ineffective for patients with chronic tension-type headaches (Level B).

**Adverse events.** Adverse events reported from each study are listed in table e-4. The most common side effect, which occurred in 2.5% to 25% of patients, and seen almost exclusively in the BoNT group, was transient and mild muscle weakness. The studies reported no serious adverse events.

**Recommendation.** BoNT injections should not be considered in patients with episodic migraine and chronic tension-type headaches (Level B).
Clinical context. It is possible that underdosing and suboptimal muscle selection may account for some of the reported failures in studies of BoNT in headache.

Summary. The evidence supporting the use of BoNT in autonomic disorders and pain is summarized in the table.

RECOMMENDATIONS FOR FUTURE RESEARCH

• Many of the recommendations for future research provided in the companion article on BoNT for motor disorders are also pertinent to nonmotor indications. Additional recommendations follow.
• Larger placebo-controlled trials are needed to evaluate the efficacy and safety of BoNT for several hypersecretory disorders (palmar hyperhidrosis, drooling), neuro-urologic indications, and pain. Double-blind, placebo-controlled, randomized studies are needed to determine the effect of BoNT in different subsets of headache. Additionally, head-to-head studies of BoNT vs and combined with other proven effective therapies should be undertaken.

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.

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DISCLOSURE The authors report the following conflicts: Dr. Naumann has received speaker honoraria from Ipsen and Allergan and performs botulinum toxin injections. Dr. So has financial interest in Satoris Inc., and has received research support from NIH, Pfizer, Inc., and NeurogesX, Inc. Dr. Argoff performs botulinum toxin injections. Dr. Childers has received speaker honoraria and research support from Allergan and performs botulinum toxin injections. Dr. Dykstra has received speaker honoraria from Allergan and Solstice, research support from Allergan, and performs botulinum toxin injections. Dr. Gronseth has received speaker honoraria from Pfizer, GlaxoSmithKline, Boehringer Ingelheim, and Ortho-McNeil. Dr. Jabbari has received research support from Allergan and performs botulinum toxin injections. Dr. Kaufmann has received speaker honoraria from Chelsea Therapeutics, research support from NIH, payment for expert testimony, and performs autonomic testing. Dr. Schurch has received speaker honoraria from Pfizer, Astellas, and Allergan; research support from Allergan, IFP, NCCR, and SNF; and performs autonomic testing and botulinum toxin injections. Dr. Silberstein has received speaker honoraria from GlaxoSmithKline, Allergan, AstraZeneca, Endo, Medtronic, Merck, & J&J, Pfizer, Pozen, and Valeant Pharmaceuticals International; research support from Allergan, and performs botulinum toxin injections. Dr. Simpson has received speaker honoraria and research support from Allergan, Merz, and Solstice, Inc., and performs botulinum toxin injections.

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