

Assessment: Botulinum neurotoxin for the treatment of spasticity (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 adult and childhood spasticity.

Methods: A literature search was performed including MEDLINE and Current Contents for therapeutic articles relevant to BoNT and spasticity. 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: adult spasticity (14 Class I studies); spastic equinus and adductor spasticity in pediatric cerebral palsy (six Class I studies).

Recommendations: Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children (Level A). *Neurology*® 2008;70:1691-1698

GLOSSARY

BoNT = botulinum neurotoxin; **CP** = cerebral palsy; **FDA** = Food and Drug Administration; **SNAP** = synaptosomal-associated protein; **VAMP** = vesicle-associated membrane protein.

INTRODUCTION Pharmacology and immunology of botulinum toxin. Botulinum neurotoxin (BoNT) is a microbial protein that exists in seven serotypes, designated A through G. Although the individual serotypes are immunologically distinct, all members of the group possess similar subunit structures, act on the same target organs, and produce similar functional outcomes.^{1,2} Each molecule is typically released from bacteria as part of a noncovalent complex with other proteins. These auxiliary proteins do not play a role in the therapeutic actions of the toxin, but they may be involved in its undesirable effects.

BoNT is an enzyme that acts in the cytosol of nerve endings to cleave three polypeptides that govern exocytosis. Serotypes A and E cleave synaptosomal-associated protein (SNAP)-25, serotypes B, D, F, and G cleave vesicle-associated membrane protein (VAMP), and serotype C

cleaves both syntaxin and SNAP-25.^{3,4} The ability of BoNT to block acetylcholine release at neuromuscular junctions accounts for its therapeutic action to relieve dystonia, spasticity, and related disorders. The toxin has additional therapeutic benefits, not necessarily related to neuromuscular transmission. These include 1) blockade of acetylcholine release at autonomic nerve endings and 2) blockade of transmitter release at peripheral nerve endings that use mediators other than acetylcholine. In addition to peripheral effects of BoNT, indirect effects on the spinal cord and brain that result from changes in the normal balance of efferent and afferent signals may also occur. Both the direct and indirect actions of the toxin are largely or completely reversible.

Undesirable effects associated with administration of BoNT fall into three broad categories. First, diffusion of the toxin from the intended

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sites of action can lead to unwanted inhibition of transmission at neighboring nerve endings. Second, sustained blockade of transmission can produce effects similar to anatomic denervation, including muscle atrophy. The third undesirable effect is immunoresistance to BoNT.⁵ Resistance results from the development of circulating antibodies that bind to the heavy chain and prevent its association with nerve membranes, thus preventing internalization of the enzymatically active light chain. Auxiliary proteins in the toxin complex could act as adjuvants to stimulate the immune response to the toxin in keeping with the lower incidence of immunoresistance associated with the decreased proportion of nontoxin protein in clinical preparations.⁶

As of January 2008, two BoNT serotypes (A and B) are Food and Drug Administration (FDA) approved for clinical use in the United States. Botox[®] is approved for the treatment of strabismus, blepharospasm, cervical dystonia, axillary hyperhidrosis, and glabellar lines, and Myobloc[®] is approved for cervical dystonia. There are broader regulatory approvals in Europe, including focal adult spasticity. Other serotypes of BoNT are being evaluated in clinical trials. BoNT-A is marketed as Botox[®] (Allergan, Inc.), Dysport[®] (Ipsen Limited), a Chinese formulation, Hengli (Lanzhou Institute of Biologic Products), and Xeomin[®] (Merz Pharmaceuticals), while BoNT-B is marketed as Myobloc[®] (Solstice Neurosciences, Inc.), also called Neurobloc[®] in some countries. Within BoNT-A brands, there are differences in potency among Botox[®], Xeomin[®], and Dysport[®] that require differences in dosages.

Controversy surrounds the definition of BoNT potency. The standard unit of BoNT potency is derived from the mouse lethality assay, in which 1 mouse unit is defined as the amount of BoNT that kills 50% of mice when injected intraperitoneally (i.e., LD50). However, the assay methodology varies among manufacturers, making dose comparison difficult. Furthermore, it is difficult to extrapolate animal data to potency in humans, given the relative lack of head-to-head studies of different BoNT preparations. With these limitations, cross-study comparisons have resulted in relative dose equivalents of Botox[®]: Dysport[®]: Myobloc[®] of approximately 1:3–4:50–100. However, given the high range of intra- and interpatient variability, doses must be established for each BoNT preparation for individual patients.⁷ Both basic science and clinical studies indicate that BoNT-A has a longer duration of action than BoNT-B.⁸

DESCRIPTION OF THE ANALYTICAL PROCESS The literature search used MEDLINE and Current Contents for relevant, fully published, peer-reviewed articles up to April 2007 and was supplemented through manual searches by panel members. The search terms used were botulinum toxin and movement disorders, dystonia, tics, tremors, hemifacial spasm, blepharospasm, cerebral palsy, spasticity, autonomic, Frey's syndrome, sweating, hyperhidrosis, drooling, headache, back pain, pain, laryngeal disorders, dysphonia, and urologic disorders. The following criteria were used: 1) relevant to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) limited to human subjects; 3) limited to therapeutic studies. Abstracts, reviews, and meta-analyses were excluded.

The panel was comprised of specialists with experience in the therapeutic use of BoNT for the indications under consideration or with expertise in guideline methodology. Each article was reviewed by at least two panelists who did not participate in the trial reported. The articles were classified as Class I through IV using the AAN guideline process (see AAN classification of evidence for therapeutic intervention on the *Neurology*[®] Web site at www.neurology.org). Disagreements on article classification were resolved by discussion and consensus.

Since the different preparations of BoNT have different potencies and durations of action, and there are insufficient head-to-head comparison data to compare their clinical effects, 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. The current article reviews the use of BoNT for the following indications: adult spasticity and spasticity in pediatric cerebral palsy. Two companion articles review the use of BoNT for other conditions: one on headache, back pain, autonomic, and urologic disorders,⁹ and another on selected movement disorders, including blepharospasm, hemifacial spasm, cervical dystonia, focal limb dystonia, laryngeal dystonia, and tics and tremor.¹⁰ While brief mention is made of other treatments for the covered indications, discussion of detailed evidence supporting their efficacy is beyond the scope of this article.

ANALYSIS OF EVIDENCE Spasticity in adults. Spasticity results from diverse etiologies including stroke, trauma, multiple sclerosis, and neoplasm involving the CNS. Reduction in function is re-

lated to at least three factors: muscle weakness, soft tissue contracture, and muscle overactivity. BoNT in a spastic muscle should, in theory, affect each of these mechanisms of impairment as follows: 1) by reducing spastic co-contraction (inappropriate antagonistic co-activation during volitional command on an agonist); 2) by decreasing spastic dystonia (stretch-sensitive tonic muscle contraction, in the absence of volitional command) of the injected muscle; 3) by contributing to ease the stretch and lengthening of the injected muscle; and 4) by helping to increase antagonist torque.

Treatment options for spastic paresis include physical and occupational therapy, bracing/splinting, tizanidine, benzodiazepines, oral or intrathecal baclofen, tendon release, and rhizotomy. Most clinical trials of BoNT in the treatment of adult spasticity have emphasized changes in resistance to passive movement (i.e., muscle tone). While active (i.e., voluntary) functional improvement with BoNT is reported in case series and frequently observed in clinical practice, there is no consensus on appropriate outcome measures for active function. BoNT has been approved for adult and childhood spasticity by regulatory agencies in many European countries, but has not yet been approved for these indications in the United States by the FDA.

Upper extremity spasticity. There are 11 Class I efficacy trials in adult upper extremity spasticity, with 10 utilizing BoNT-A and one BoNT-B (table e-1 on the *Neurology*[®] Web site at www.neurology.org).¹¹⁻²¹ All but one used measurements of tone as the primary outcome measure. All demonstrated that BoNT is safe and reduced tone in a dose-dependent manner.^{14,15,17,20,22} Global satisfaction scores reported by subjects, family members, or clinicians showed benefits of BoNT. Recent open label trials suggest that benefits continue to occur after repeated injections.^{23,24} However, resistance to passive movement has not been shown to correlate with active function, defined as activities that the subject can voluntarily perform with the spastic limb. Although no Class I studies of BoNT in the spastic upper limb focused on active functional gains as a primary outcome measure, functional assessment measures have been used as secondary outcome measures.

Class I studies incorporating subjective assessments of daily function by the patient or caregiver have shown functional improvement following BoNT injection in the spastic upper limb.^{12,14,15,17} These reports usually emphasize passive func-

tion, such as tasks involving the nonaffected hand or dressing or hygiene performed by the caregiver. One Class I study found that BoNT produced significant improvement in the Disability Assessment Score, which combines reports of passive and active function.¹⁸ In this scale, the subject and the site investigator chose a target area of outcome assessment of personal hygiene, dressing, pain, or limb position and rated the area using a four-point scale ranging from no to severe disability. Although direct assessments of functional tasks by a clinician have the advantage of greater objectivity and permit selective testing of active function,^{14,15,17,21} significant gains were reported in only one Class I study measuring active functional testing in adult upper limb spasticity.²¹

Lower extremity spasticity. Three trials fulfilled criteria for Class I evidence^{17,25,26} (table e-2). Most studies focused on reduction in muscle tone with demonstrated efficacy, but only few measured changes in gait, particularly velocity. One placebo-controlled crossover protocol²² reported a nonsignificant 17% increase in walking speed after BoNT injection into calf muscles in spastic hemiparesis. Class I placebo-controlled studies have so far failed to demonstrate gains in walking speed.^{17,21} Reports suggest that protocols of low frequency electrical stimulation of injected muscles after injection enhance the blocking effect of BoNT,²⁷ and in particular improve the benefit on walking speed after calf muscle injection.²⁸ In a double-blind, placebo-controlled, crossover study, patients with multiple sclerosis and severe spasticity of thigh adductors receiving BoNT-A (400 U) in hip adductor muscles had functional gain, specifically easier nursing care, and better comfort when sitting in a wheelchair.²⁹

Most studies of BoNT in limb spasticity used electrophysiologic techniques to optimize muscle localization for injection, analogous to focal limb dystonia. The most common approaches involve electrical stimulation or EMG. While these techniques are intuitively attractive, there is a lack of controlled or comparative studies in spasticity proving their effectiveness over other injection techniques, such as needle localization with anatomic landmarks. Recommended doses of BoNT injection into specific muscles have been derived predominantly from expert consensus rather than dose-response studies.

Conclusions. BoNT is established as effective in the treatment of adult spasticity in the upper and lower limb in reducing muscle tone and improving passive function (14 Class I studies). While

Table Summary table for botulinum toxin in the treatment of spasticity

Disorder	Class	No. of subjects	Outcome measures	Adverse events	Conclusions	Recommendations*	Limitations
Adult spasticity	14 Class I	906	Tone (Ashworth), passive fx: range of motion, cleaning, hygiene, pain	Focal weakness, pain	Established safe and effective	A	Methodologic challenges in study design
			Active fx: Goal Attainment Scale, Frenchay; global disability (MD/pt)		Probably effective	B	Limited outcome measures to demonstrate efficacy in active functional gains
Childhood spasticity in cerebral palsy	6 Class I	376	Tone (Ashworth), passive fx: range of motion, active fx: gait/video/kinematic analysis; global disability (MD/pt)	Pain, weakness, falls, incontinence, dysphagia	Established safe and effective	A	Best evidence for equinus varus

*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; fx = function; MD = physician; pt = patient.

relatively few studies examined active function, recent data suggest that BoNT is probably effective in improving active function (one Class I study). There are inadequate data to determine if electrical stimulation or EMG techniques for optimal muscle localization improves outcome.

Recommendations

- BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (Level A), and should be considered to improve active function (Level B).
- There is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection (Level U).

Clinical context. There are no controlled studies comparing BoNT to other treatment modalities for spasticity. There is also a need to confirm efficacy for active function in controlled trials. This will require solving methodologic challenges of study design, including enrollment criteria that provide more homogeneous etiologies and degrees of severity of spastic paresis, and outcome measures adequate to demonstrate active motor function.

Spasticity due to cerebral palsy in children. Cerebral palsy (CP) is a disorder of movement and posture as a result of a CNS abnormality. Muscle hypertonia, coupled with growth of a child, can lead to fixed contractures, torsional deformities of long bones, and joint instability, which further impair the child's motor performance. Treatment options for childhood CP include physical and occupational therapy, splinting/casting, and surgical approaches, such as tendon release and selective dorsal rhizotomy. Early studies suggested that BoNT injections could be used as an alternative treatment for an equinus varus deformity and obviate the need for surgery prior to gait maturity. Since

that time, over 80 articles have been published discussing the use of BoNT-A in the management of CP.

Spastic equinus. Four Class I studies³⁰⁻³³ of BoNT injection into the gastrocnemius improved gait over 1 to 3 months (table e-3). The optimal dosage for different body weight and age range has not been established. One Class I³² and two Class II studies^{34,35} evaluated the efficacy of different doses. In all three studies, the highest dose was most effective (24 or 30 U/Kg Dysport[®], or 200 U Botox[®] regardless of weight). Several randomized single-blind studies compared the effect of ankle casting to BoNT injections in a small number of children.³⁶⁻⁴¹ Casting did not provide additional benefit (table e-3).

Hamstrings. Two small open-label studies (Class IV) found modest improvement in either gait kinematics or hamstring length with BoNT injection into the hamstrings.^{42,43}

Adductor spasticity. One Class I⁴⁴ study using BoNT injection into the adductors and medial hamstrings showed an average improvement in knee-to-knee distance of about 9 cm ($p < 0.002$) and decrease in adductor spasticity on modified Ashworth scale of 2 ($p < 0.001$). Another Class I study⁴⁵ evaluated the need for postoperative pain control in children undergoing adductor muscle lengthening. There was a 74% reduction in postoperative pain ($p < 0.003$) and 50% less analgesic use ($p < 0.005$) when comparing BoNT-treated children to the placebo group.

Upper extremity spasticity. Goals for injection of the upper limb include the relief of spastic posturing and improvement in upper limb function. Two small Class II studies and one Class III study⁴⁶⁻⁴⁸ addressing the use of BoNT in the upper extremity described modest improvement in tone and range of movements, without demonstration of significant functional gains.

Conclusions. BoNT injection of the gastrocnemius-soleus muscles is established as effective in the treatment of spastic equinus in patients with CP (four Class I studies). There is insufficient evidence to support or refute the benefit of additional casting to BoNT injection of the gastrocnemius-soleus muscles (inconsistent Class II and III studies) and the injection of BoNT into the hamstrings (only Class IV studies). In patients with adductor spasticity, BoNT injection is probably effective in improving adductor spasticity and range of motion (one Class I study), as well as postoperative pain in children undergoing adductor muscle lengthening surgery (one Class I study). In patients with upper extremity symptoms, BoNT injection is probably effective in improving spasticity and range of motion (two Class II studies and one Class III study).

Recommendations

- BoNT injection of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy (Level A).
- BoNT injection should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery (Level B).
- BoNT injection should be considered as a treatment option in children with upper extremity spasticity (Level B).

Clinical context. As in adult spasticity, there is lack of consensus on what constitutes meaningful functional gain following treatment for spasticity. While many clinicians, patients, and caregivers find the results of BoNT treatment for spasticity gratifying, the FDA has not approved BoNT for the treatment of spasticity in children.

Summary. The evidence supporting the use of BoNT in adult and childhood spasticity is summarized in the table.

RECOMMENDATIONS FOR FUTURE RESEARCH

- BoNT is now standard clinical practice for the treatment of many disorders of excess motor activity, including numerous forms of dystonia and spasticity. However, treatment response varies widely, within and among indications. Future studies should investigate factors that predict which patient subgroups have optimal response.
- Most patients would prefer not to have injections as frequently as currently required. Future directions will likely involve the development of other toxins, including those

that are less costly, more accessible to those in need, with a longer duration of action, and with delivery approaches other than injection.

- A major limitation in published clinical trials of BoNT is the lack of standardized rating tools for many clinical indications (e.g., spasticity, focal hand dystonia). Furthermore, there is often disagreement among investigators, clinicians, patients, family members, and regulatory agencies as to what constitutes functional improvement. Future studies would benefit from the development of validated scales applicable across the spectrum of tasks eliciting the abnormal movements and sensitive to changes with focal treatment such as BoNT.
- Further studies on injection methodology including the use of EMG guidance, ultrasonography, and electrical stimulation are needed to optimize treatment technique.
- Many trials in the use of BoNT have used rigid injection protocols with insufficient attention to the capacity for individualized choice of muscles and doses. Study designs that leave the choice of target muscles and doses to the investigators' discretion are more likely to reflect clinical practice and may affect reported efficacy.
- More research is needed in the choice of muscles used in BoNT injection. For spasticity, selection might be based on qualitative assessments of overactivity at rest and during attempts at active motion, as opposed to relying on a quantitative tone score that may not reflect disability during attempts at active movements.
- More research is needed to determine the optimal dose of BoNT for individual muscles, and the choice of the number and location of injection sites.
- More studies are needed to assess the safety and efficacy of repeated and long-term injections of BoNT, and to address the risk of development of secondary resistance to BoNT due to antibody formation.
- In children with cerebral palsy, controlled studies are needed to study the long-term effect of BoNT injections, especially in relation to the growth and maturity of the children and the necessity and timing of orthopedic surgery. Much work remains to be done to determine whether BoNT injection is a minor supporting intervention for children with cerebral palsy or a mainstream

standard therapy for the majority of children. For example, short- and long-term studies comparing the outcome of patients who receive BoNT therapy as part of the treatment program with the outcome of patients in those programs where BoNT is not part of the treatment regimen would be helpful.

- Further studies, including comparative head-to-head trials, are needed to establish whether one serotype or brand of BoNT is more effective than another, and to determine the dosing equivalency and relative antigenicity between serotypes and brands. It is not clear how such studies will be funded, which will likely require partnership among academic investigators, governmental agencies, and the pharmaceutical industry.

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

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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



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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 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

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eyes. Prior to BoNT, there were no effective medical or surgical treatments for this disorder. Blepharospasm was one of the first studied indications for BoNT treatment. The open label observations were felt to be so dramatic that there have been only a few attempts to perform properly controlled clinical trials. In 1989, Botox[®] received Food and Drug Administration (FDA) approval for blepharospasm, including benign essential blepharospasm or VII nerve disorders, in patients 12 years and older. Two efficacy trials fulfilled criteria for Class II (table e-1 on the *Neurology*[®] Web site at www.neurology.org).

One Class II trial was a double-blind comparison of injecting BoNT-A into one eyelid and saline into the other.³ Six patients received BoNT-A (Botox[®]) at a dose of 20 U/eye for the active treatment. Blinded rating of videotapes showed bilateral reduction in blepharospasm that was greater on the side injected with active toxin. The other Class II study was a double-blind, prospective, crossover trial of 11 patients using BoNT-A (Botox[®]) at 25 U/eye, supplementing up to 50 U/eye 1 month later if needed.⁴ Assessment by physician observation and rating of videotapes, using the Fahn scale and by patient subjective rating, showed significant efficacy lasting a mean of 2.5 months. Adverse effects were generally mild (blurred vision, tearing, ptosis, and ecchymosis).

One Class II and one Class III study compared two different brands of BoNT-A (Botox[®] and Dysport[®]). In the Class II study, there were 212 patients evaluated in a crossover design using a 4:1 dose ratio of Dysport[®] to Botox[®].⁵ The primary endpoint, duration of effect, was similar for the two products. The Class III study used a parallel design of 42 patients without blinded raters and also used a dose ratio of 4:1.⁶ Duration of action was again the primary endpoint, and this endpoint and others including number of booster doses needed, latency of effect, clinical efficacy, and adverse reactions were similar for the two products. A Class I study compared Xeomin[®] and Botox[®], using equivalent doses in 300 patients, with 256 patients completing the study. There was no difference in efficacy or adverse effects between the two formulations.⁷

Conclusions. For patients with blepharospasm, BoNT injection is probably effective with minimal side effects (two Class II studies). After dosage adjustment, Botox[®] and Xeomin[®] are probably equivalent (one Class I study), and Botox[®] and Dysport[®] are possibly equivalent (one Class II and one Class III study).

Recommendation. BoNT injection should be considered as a treatment option for blepharospasm (Level B).

Clinical context. The evidence supporting BoNT use in blepharospasm is suboptimal. The large magnitude of benefits 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.

Hemifacial spasm. Hemifacial spasm is characterized by a combination of unilateral clonic and tonic spasms of the muscles innervated by the facial nerve. Treatment options include oral pharmacologic therapies, including carbamazepine, baclofen, and benzodiazepine, and resulting in limited efficacy, and microvascular decompression of the facial nerve, a highly invasive procedure. Encompassed in the category of VII nerve disorders, hemifacial spasm is FDA approved. One efficacy trial of BoNT fulfilled criteria for Class II, and one for Class III (table e-2). The Class II study⁸ of 11 patients was a prospective, blinded trial with four arms: an arbitrary dose based on clinical experience of between 2.5 and 10 units of BoNT-A (Botox[®]), half the dose, double the dose, and saline placebo. Each subject cycled through the four treatment arms in a random order. Using a clinical scale to rate videotapes and a patient subjective scale, 84% had objective improvement with at least one of the active doses with a trend for better response with higher dose; only one patient improved on placebo. Seventy-nine percent reported subjective benefit lasting a mean of 2.8 months with active therapy. Weakness of the face, generally mild, was the most common adverse effect (97%). Other adverse effects included bruising, diplopia, ptosis, and headache.

A Class III study⁹ was a double-blind, prospective, parallel design study with only four patients per group using individualized therapy (dose range 2.5 to 40 units) with BoNT-A (Botox[®]) in the active arm. Ninety-three patients studied in an open label fashion were also reported. There was greater improvement on a clinical scale with BoNT than with a saline placebo. Benefit lasted a mean of 3.8 months. Side effects, present in 63% of patients, were generally mild and included dry eye, mouth droop, and ptosis.

One Class II study compared Botox[®] and Dysport[®] in a parallel design without placebo control or blinded raters.⁶ There was a dose ratio of 4:1 for Dysport[®] to Botox[®]. The primary endpoint (duration of action) and other endpoints (number of booster doses needed, latency of effect, clinical efficacy, and frequency of adverse reactions) were

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-naïve CD subjects. One study¹⁶ 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 with 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-naïve 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-naïve 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 tri-

hexyphenidyl 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 pain subscales and patient and physician global scales showed similar benefit. Adverse events were greater in the BoNT-B treated groups, 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.¹¹ 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 physician and patient global scores. 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 dystonia¹⁷ (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 trial¹⁸ 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 eval-

uation. 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

(one Class I and three Class II studies). While a few patients in one Class II study suggest that BoNT may be effective for lower extremity dystonia, the data are inadequate to provide a recommendation.

Recommendation. BoNT should be considered as a treatment option for focal upper extremity dystonia (Level B).

Clinical context. The treatment of focal limb dystonia with BoNT presents challenges, particularly in achieving sufficient neuromuscular blockade to alleviate dystonic movements without causing excessive muscle weakness. While many clinicians advocate EMG or nerve stimulation guidance to optimize needle localization for injection, further data are needed to establish this recommendation.

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 ABSD²⁷ 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 re-

sults 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 antidopaminergic 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).²⁹ 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).³⁰ 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.³² 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 pos-

tural 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 tremor³³ did not show a statistically significant benefit in BoNT-treated patients. There are two Class IV open-label studies in voice tremor^{34,35} 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

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

*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.

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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; and performs botulinum toxin injections. Dr.

Brashear 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 chemodeneration. Dr. Hallett holds financial interest in Amylin Pharmaceuticals, Eli Lilly, Genetech, 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 Satoris Inc., and has received research support from NIH, Pfizer, Inc., and NeurogesX, Inc.

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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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See pages 1691 and 1699

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. *Neurology*® 2008;70:1707-1714

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 spasticity¹ and movement disorders.² 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

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autonomic disorders arise from cholinergic overactivity, i.e., at the neuromuscular junction in overactive bladder or at the neurosecretory junction in hypersecretory disorders. An increasing number of studies, including placebo-controlled trials, demonstrate that BoNT may be a valuable agent to treat autonomic disorders associated with localized cholinergic overactivity. Its mode of action in pain, however, is less well understood. This article evaluates the current knowledge and evidence of BoNT in selected disorders of autonomic function and pain.

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.

ANALYSIS OF EVIDENCE **Hypersecretory disorders.** 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^{3,4} (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.³ 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.⁴ 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^{5,6} 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.⁵ 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.⁶ One Class III study⁷ 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 parotidectomy⁸⁻¹⁰ (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 II¹¹⁻¹⁴ studies were identified in the treatment of sialorrhea in Parkinson's disease (3 BoNT-A and 1 BoNT-B). One of the studies¹¹⁻¹⁴ 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.¹⁵ 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 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).¹⁶ 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.¹⁷ 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.¹⁸ 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),^{19,20} one Class II study,²¹ 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.¹⁹ 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.²⁰ 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

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.²¹ 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 offered as a treatment option for neurogenic detrusor overactivity (Level A).
- BoNT should be considered 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 hemorroidectomy, 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.²² 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 headache²³⁻³³ (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.²⁷⁻³² One study³³ 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^{23,24} and two Class II studies^{25,27} 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 study²⁴ 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 study²³ 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^{25,27} randomized patients to placebo or BoNT. The primary outcome in one study²⁷ was a change in the frequency of moderate to severe migraines per month. In the second study,²⁵ 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 study²⁷ 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,²⁵ 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.²⁸⁻³¹ CDH was explicitly defined in all articles. All studies included a large number of patients with transformed migraine. One study³⁰ evaluated a subgroup of patients with CDH who were not on prophylactic medication.²⁹ Three of the studies²⁸⁻³⁰ 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 study³¹ 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.²⁹⁻³¹ The placebo nonresponders were the primary population of interest for these studies. One of the studies²⁸ 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,²⁹ 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).³⁰ The largest study of patients with CDH,³¹ 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 4²⁸ and 6.²⁹ 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						
Disorder	Class	Outcome measures	Adverse events	Conclusions	Recommendations*	Limitations
Axillary hyperhidrosis	2 Class I	Gravimetry; responder rate; patient satisfaction	No difference between BoNT and placebo	Safe and effective	A	No head-to-head comparisons with other treatment options
Palmar hyperhidrosis	2 Class II	Gravimetry; ninhydrin test; VAS	Injection pain; mild hand muscle weakness	Probably effective	B	No head-to-head comparisons with other treatment options
Gustatory sweating	5 Class III	Area of sweating; ninhydrin test; self assessment	Injection pain	Possibly effective	C	No head-to-head comparisons with other treatment options
Drooling	4 Class II	Drooling scores; weight of dental roles; VAS	Dry mouth	Probably effective	B	No head-to-head comparisons with other treatment options
Detrusor overactivity	2 Class I and 1 Class II	Urodynamic measures; QOL; frequency of incontinence	Urinary retention	Safe and effective	A	No head-to-head comparisons with other treatment options
DSD in spinal cord injury	2 Class II	PRUV	None known	Probably effective	B	No head-to-head comparisons with other treatment options
Low back pain	1 Class II	VAS; Oswestry low back pain questionnaire	None known	Possibly effective	C	Diverse etiologies for low back pain
Episodic migraine	2 Class I and 2 Class II	Change in frequency per month; proportion with 50% decrease in frequency compared with baseline	Ptosis, local transient pain at the site of injection, bruising, diplopia	Probably ineffective	B	Suboptimal dose and muscle selection may account for treatment failures
Tension-type headache	2 Class I	VAS; area under the curve; proportion of severe headaches post treatment	Transient weakness of neck muscles, local skin tension, ptosis, flulike reaction	Probably ineffective	B	Suboptimal dose and muscle selection may account for treatment failures
Chronic daily headache	4 Class II	Change in headache-free days	Ptosis, transient weakness of neck, flulike reaction	Insufficient evidence	U	Suboptimal dose and muscle selection may account for treatment failures

*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 articles^{32,33} 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,^{25,33} whereas two studies^{32,33} 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 study³⁴ 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 article³² 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 holds 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 sup-

port 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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