SPECIAL ARTICLE

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

M. Naumann, MD
Y. So, MD, PhD
C.E. Argoff, MD
M.K. Childers, DO, PhD
D.D. Dykstra, MD, PhD
G.S. Gronseth, MD
B. Jabbari, MD
H.C. Kaufmann, MD
B. Schurch, MD
S.D. Silberstein, MD
D.M. Simpson, MD

Addresses correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Ave., St. Paul, MN 55116
guidelines@aan.com

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 spasticity[1] 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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See pages 1691 and 1699

From the Department of Neurology (M.N.), Klinikum Augsburg, Germany; Stanford University (Y.S.), CA; Department of Neurology (H.C.K.), New York University School of Medicine (C.E.A.), New York; Wake Forest University Health Sciences (M.K.C.), Winston-Salem, NC; Department of Physical Medicine and Rehabilitation (D.D.D.), University of Minnesota, Minneapolis; University of Kansas (G.S.G.), Kansas City; Department of Neurology (B.J.), Yale University School of Medicine, New Haven, CT; Balgrist University Hospital (B.S.), Zurich, Switzerland; Jefferson Headache Center (S.D.S.), Thomas Jefferson University Hospital, Philadelphia, PA; and Department of Neurology (D.M.S.), Mount Sinai Medical Center, New York, NY.

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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 study[7] 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[8-10] (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 II[11-14] studies were identified in the treatment of sialorrhea in Parkinson's disease (3 BoNT-A and 1 BoNT-B). One of the studies[11-14] 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 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.[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 headache[23-33] (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 study[33] 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 study[24] 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[23] 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 study[27] 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 study[27] 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 study[30] evaluated a subgroup of patients with CDH who were not on prophylactic medication.[29] Three of the studies[28-30] 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 study[31] 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 studies[28] 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 4[28] 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; Owestry 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% decease 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 study[32] 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 study[26] 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 study[34] 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 article[32] 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 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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REFERENCES

1. Simpson DM, Gracies J-M, Graham HK, et al. 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. Neurology 2008;70:1707–1714 .
2. Simpson DM, Blitzer A, Brashear A, et al. 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. Neurology 2008;70:1691–1698.
3. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ 2001;323:596–599.
4. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med 2001;344:488–493.
5. Lowe NJ, Yamauchi PS, Lask GP, Patnaik R, Iyer S. Efficacy and safety of botulinum toxin type a in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. Dermatol Surg 2002;28:822–827.
6. Schnider P, Binder M, Auff E, Kittler H, Berger T, Wolff K. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Br J Dermatol 1997;136:548–552.
7. Saadia D, Voustianiouk A, Wang AK, Kaufmann H. Botulinum toxin type A in primary palmar hyperhidrosis: randomized, single-blind, two-dose study. Neurology 2001;57:2095–2099.
8. Naumann M, Zellner M, Toyka KV, Reiners K. Treatment of gustatory sweating with botulinum toxin. Ann Neurol 1997;42:973–975.
9. Eckardt A, Kuettner C. Treatment of gustatory sweating (Frey's syndrome) with botulinum toxin A. Head Neck 2003;25:624–628.
10. Laccourreye O, Akl E, Gutierrez-Fonseca R, Garcia D, Brasnu D, Bonan B. Recurrent gustatory sweating (Frey syndrome) after intracutaneous injection of botulinum toxin type A: incidence, management, and outcome. Arch Otolaryngol Head Neck Surg 1999;125:283–286.

11. Mancini F, Zangaglia R, Cristina S, et al. Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Mov Disord 2003;18:685–688.
12. Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology 2004;62:37–40.
13. Lipp A, Trottenberg T, Schink T, Kupsch A, Arnold G. A randomized trial of botulinum toxin A for treatment of drooling. Neurology 2003;61:1279–1281.
14. Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG. Botulinum toxin type A for drooling in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord 2006;21:704–707.
15. Boroojerdi B, Ferbert A, Schwarz M, Herath H, Noth J. Botulinum toxin treatment of synkinesia and hyperlacrimation after facial palsy. J Neurol Neurosurg Psychiatry 1998;65:111–114.
16. Gallien P, Reymann JM, Amarenco G, Nicolas B, de Seze M, Bellissant E. Placebo controlled, randomised, double blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. J Neurol Neurosurg Psychiatry 2005;76:1670–1676.
17. Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. Arch Phys Med Rehabil 1990;71:24–26.
18. de Seze M, Petit H, Gallien P, et al. Botulinum a toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol 2002;42:56–62.
19. Schurch B, de Seze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol 2005;174:196–200.
20. Ghei M, Maraj BH, Miller R, et al. Effects of botulinum toxin B on refractory detrusor overactivity: a randomized, double-blind, placebo controlled, crossover trial. J Urol 2005;174:1873–1877; discussion 1877.
21. Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E, Porena M. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. J Urol 2004;172:240–243.
22. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology 2001;56:1290–1293.
23. Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. J Pain 2006;7:688–696.
24. Saper JR, Mathew NT, Loder EW, DeGryse R, VanDenburgh AM. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type A injection sites and doses in the prevention of episodic migraine. Pain 2008 (in press).
25. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 2004;24:838–843.
26. Schulte-Mattler WJ, Krack P. Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. Pain 2004;109:110–114.
27. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group [comment]. Headache 2000;40:445–450.
28. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia 2004;24:60–65.
29. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 2005;45:293–307.
30. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache 2005;45:315–324.
31. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2005;80:1126–1137.
32. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia 2004;24:675–680.
33. Relja M, Telarovic S. Botulinum toxin in tension-type headache. J Neurol 2004;251 suppl 1:I12–14.
34. Silberstein SD, Gobel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study [see comment]. Cephalalgia 2006;26:790–800.

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M. Naumann, Y. So, C. E. Argoff, et al.

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