Practice guideline update: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache


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ABBREVIATIONS

AAN: American Academy of Neurology
aboBoNT-A: abobotulinumtoxinA
AE: adverse events
BDI: Blepharospasm Disability Index
BoNT: botulinum neurotoxin
CD: cervical dystonia
CI: confidence interval
CM: chronic migraine
DAS: Disability Assessment Scale
EM: episodic migraine
FDA: US Food and Drug Administration
GDS: Guideline Development Subcommittee
incoBoNT-A: incobotulinumtoxinA
JRS: Jankovic Rating Score
MAS: modified Ashworth scale
onaBoNT-A: onabotulinumtoxinA
QOL: quality of life
RD: risk difference
rimaBoNT-B: rimabotulinumtoxinB
RMT: randomized, masked trials
SC: standard of care
TTH: tension-type headache
TZD: tizanidine
ABSTRACT

Objective: To update the 2008 American Academy of Neurology (AAN) guidelines addressing safety and efficacy of botulinum neurotoxin (BoNT) for treatment of blepharospasm, cervical dystonia (CD), headache, and adult spasticity.

Methods: We searched the literature for therapeutic articles relevant to BoNT for selected indications. We classified articles according to 2004 AAN criteria.

Results: **Blepharospasm.** OnabotulinumtoxinA (onaBoNT-A) (2 Class II studies) and incobotulinumtoxinA (incoBoNT-A) (1 Class I study) are probably effective, and abobotulinumtoxinA (aboBoNT-A) (1 Class II study) is possibly effective. **CD.** AboBoNT-A (2 Class I studies) and rimabotulinumtoxinB (rimaBoNT-B) (3 Class I studies) are established as effective. OnaBoNT-A (1 Class I study and 1 Class II study) and incoBoNT-A (1 Class I study) are probably effective. **Spasticity.** AboBoNT-A, incoBoNT-A, and onaBoNT-A are established as effective (multiple Class I studies), and rimaBoNT-B is probably effective (1 Class I study), for the reduction of muscle tone in adult upper-limb spasticity. AboBoNT-A and onaBoNT-A are established as effective (multiple Class I studies) for the reduction of tone in adult lower-limb spasticity. **Headache.** OnaBoNT-A is established as effective for increasing the number of headache-free days in chronic migraine (CM) (2 Class I studies) and is probably effective for improvement in health-related quality of life (1 Class I study). OnaBoNT-A is established as ineffective in the treatment of episodic migraine (EM) (3 Class I studies) and is probably ineffective for treating chronic tension–type headaches (2 Class I studies).

Recommendations: **Blepharospasm.** OnaBoNT-A and incoBoNT-A injections should be considered as treatment options (Level B), and aboBoNT-A may be considered (Level C). **CD.** AboBoNT-A and rimaBoNT-B should be offered (Level A), and onaBoNT-A and incoBoNT-A should be considered (Level B), as treatment options. **Spasticity.** AboBoNT-A, incoBoNT-A, and onaBoNT-A should be offered (Level A), and rimaBoNT-B should be considered (Level B), as treatment options for spasticity of the upper limbs. AboBoNT-A and onaBoNT-A should be offered as treatment options for spasticity of the lower limbs (Level A). **Headache.** OnaBoNT-A should be offered as a treatment option for CM, to increase the number of headache-free days (Level A), and should be considered to reduce headache impact on health-related QOL (Level B). OnaBoNT-A should not be offered as treatment for EM (Level A) or considered for chronic tension-type headaches (Level B).
INTRODUCTION

In 2008, the American Academy of Neurology (AAN) published guidelines on the therapeutic uses of botulinum neurotoxin (BoNT) in certain neurologic conditions. New research published since then on 4 BoNT indications—blepharospasm, cervical dystonia (CD), spasticity, and headache—prompted this update.

BoNT pharmacology and immunology are reviewed in the 2008 AAN guidelines. BoNT is commercially available in 2 serotypes, A and B. There are 4 US Food and Drug Administration (FDA)—approved preparations of BoNT: onabotulinumtoxinA (onaBoNT-A), abobotulinumtoxinA (aboBoNT-A), incobotulinumtoxinA (incoBoNT-A), and rimabotulinumtoxinB (rimaBoNT-B). The FDA-approved and other regulatory-approved indications do not necessarily correspond to those in the recommendations presented here.

There are important pharmacologic differences between BoNT preparations, including potency and duration of action. Therefore, unlike the approach taken in the previous guidelines, where BoNT was evaluated for safety and efficacy as a single class, in this update we assessed each formulation separately for each indication. As a result, the level of support for efficacy in the conclusions and recommendations may be lower for the individual BoNT formulations than it would be had BoNT been considered as a class. The recommendations reflect the confidence in the level of evidence, but because studies of comparative efficacy are few, the recommendations should not be construed to indicate that one drug is superior to another. Efficacy of BoNT is for symptomatic control, as there is no evidence for disease modification.

DESCRIPTION OF THE ANALYTIC PROCESS

The AAN’s Guideline Development Subcommittee (GDS) (appendices e-1 and e-2) assembled a panel of specialists either with extensive clinical and research experience in the use of BoNT for the indications discussed or with expertise in guideline methodology, following the processes described in the 2004 AAN guideline process manual. AAN staff and GDS leadership vetted each panel member for conflicts of interest and attempted to balance the author panel between those with and those without potential conflicts. Additionally, a nonconflicted panel member independently confirmed the risk of bias rating for each study.

We searched the EMBASE, Medline, and Science Citation Index databases to find relevant studies published from April 2007 (endpoint of the search performed for the prior guidelines) to August 2011. We updated the search in December 2014 and again in October 2015. The bibliographies of review articles also were searched to identify articles missed by the initial search strategy (see appendix e-3 for complete search strategy). Additionally, because studies comparing different BoNT formulations in the treatment of CD were not included in the 2008 guideline, we repeated the pre-2008 search to identify comparative trials.

To be eligible for inclusion, English-language articles had to compare outcomes between patients with blepharospasm, CD, adult spasticity, or headache receiving a preparation of BoNT that is commercially available in the United States with outcomes of a group of patients receiving an alternative therapy. Acceptable alternative therapies included placebo or another
treatment—including a different form of BoNT or a different technique for administering BoNT. At least 20 patients must have been enrolled in each study. In general, only randomized, masked trials (RMTs) were considered. When RMTs were not available to assess long-term outcomes or safety concerns, evidence from nonrandomized trials was used.

We identified 3,371 citations. A review of titles and abstracts identified 55 potentially relevant articles for blepharospasm, 100 for CD, 279 for spasticity, and 144 for headache. We reviewed the full text of these articles for meeting inclusion criteria. Of those articles, we extracted data from 23 articles on blepharospasm, 23 on CD, 86 on spasticity, and 28 on headache.

Each article was reviewed by at least 2 panelists who did not participate in or have a relevant conflict of interest with the reported trial. We classified each article for risk of bias (Class I, II, III, or IV) using the AAN classification scheme for therapeutic questions (appendix e-4). Disagreements about article selection and classification were resolved by consensus. We formulated recommendations on the basis of the conclusions; recommendations are tied directly to the evidence (appendix e-5). Table e-1 presents the conclusions and recommendations for efficacy of various BoNT formulations.

The serotype and formulation of BoNT used in specific studies are provided in the text and in evidence tables e-2 through e-6. In general, we do not describe studies with a higher risk of bias when we were able to obtain studies with a lower risk of bias.

ANALYSIS OF EVIDENCE

Blepharospasm

Blepharospasm is a dystonia that can cause disabling eyelid closure. The 2008 guideline concluded that BoNT as a class is probably safe and effective for treatment of blepharospasm on the basis of 2 Class II studies comparing onaBoNT-A with placebo, 1 Class II study comparing onaBoNT-A with aboBoNT-A, and 1 Class I study comparing onaBoNT-A with incoBoNT-A. Since the 2008 publication, 2 Class I RMTs and 2 Class II RMTs meeting inclusion criteria have been published (table e-2). We discuss these studies and 3 Class IV articles addressing long-term outcomes.

One Class I study randomized 109 patients in a 2-to-1 ratio to incoBoNT-A or placebo. At doses of up to 50 U/eye, incoBoNT-A was superior to placebo (difference in change in Jankovic Rating Score [JRS] at week 6, 1.0, 95% confidence interval [CI] 0.5 to 1.4). Benefit lasted a median of 10.6 weeks. A Class II RMT with 28% dropouts compared aboBoNT-A (40 U, 80 U, or 120 U) with placebo. Disability improved in a dose-related manner on active treatment as measured by the Blepharospasm Disability Index (BDI) (a validated and responsive measure of disability in patients with blepharospasm). Median change in the BDI after 80 U as compared with placebo was -3.0 (95% CI -4.0 to -1.0). Benefit lasted 12 weeks with 40 U and up to 16 weeks with 80 U or 120 U.

A second Class I RMT published since 2008 compared onaBoNT-A with incoBoNT-A (1:1 dosing). Doses of 25–40 U/eye were used. The study found comparable magnitude (change in
BDI -2.0, \( p = 0.148 \) and duration of benefit (13 weeks) between BoNT preparations. A second comparative Class II RMT used a split-face design. Forty-five patients were injected with the same dose of onaBoNT-A and incoBoNT-A, with injections to one eye with one drug and the other eye with the other drug (injected side randomly assigned). No differences were found in patient preference, BDI, JRS, or orbicularis oculi strength at any of the 5 study treatment sessions.\textsuperscript{e10}

Commonly reported adverse events (AEs) with BoNT injections included periorbital hematoma (25%), ptosis (range of risk differences [RDs] 13% to 54%), dry eyes (range of RDs 7.1% to 13%), and blurred vision (RD 42%). AEs were more common at higher doses.

Four Class IV observational studies reported long-term outcomes. Benefit from aboBoNT-A or onaBoNT-A was sustained for at least 15 years in 128 patients,\textsuperscript{e11} onaBoNT-A for 10 years in 83 patients,\textsuperscript{e12} and incoBoNT-A for 69 weeks in 82 patients.\textsuperscript{e13} In 288 patients arbitrarily assigned to toxin formulation, similar degrees of benefit were sustained for at least 10 years (onaBoNT-A), 15 years (aboBoNT-A), and 5 years (incoBoNT-A).\textsuperscript{e14}

No studies meeting inclusion criteria were found for rimabotulinumtoxin for treatment of blepharospasm.

**Conclusions**

OnaBoNT-A (2 Class II studies from 2008 guideline) and incoBoNT-A (1 Class I study) are probably safe and effective for treating blepharospasm, and aboBoNT-A (1 Class II study) is possibly effective. There is insufficient evidence to determine the efficacy of rimaBoNT-B.

IncoBoNT-A and onaBoNT-A (1 Class I comparative effectiveness study from the 2008 guideline and 2 more recent comparative effectiveness studies [1 Class I and 1 Class II]) are established as equivalent in efficacy for treating blepharospasm. AboBoNT-A and onaBoNT-A (1 Class II study from the 2008 guideline) are possibly equivalent for treating blepharospasm.

**Recommendations**

OnaBoNT-A and incoBoNT-A injections should be considered (Level B), and aboBoNT-A may be considered (Level C), as treatment options for blepharospasm.

**Clinical context**

BoNT is considered the first-line treatment of blepharospasm by most movement disorder specialists.\textsuperscript{e15} All three type A toxins appear to have similar efficacy and can continue to be efficacious over long periods.

**CD**

CD is characterized by involuntary contractions of neck and upper shoulder muscles, resulting in abnormal postures or movements (or both) of the neck, shoulder, and head.\textsuperscript{e16}
The 2008 guideline concluded that BoNT is established as safe and effective for CD treatment on the basis of 1 Class I trial of onaBoNT-A, 2 Class I trials of aboBoNT-A, and 3 Class I trials of rimaBoNT-B. Moreover, on the basis of a single Class I study comparing aboBoNT-A with trihexyphenidyl, the guideline concluded that BoNT is probably more efficacious and better tolerated than trihexyphenidyl.

Since the 2008 guideline publication, 2 placebo-controlled trials of BoNT (1 Class I, 1 Class II) that met inclusion criteria were published (see table e-3). In addition, 3 Class I studies comparing different formulations not discussed in the 2008 guideline were identified. These studies, and 3 Class IV studies describing long-term outcomes, are discussed here.

The first Class I study compared the efficacy and safety of incoBoNT-A (120 U, 240 U) with those of placebo for CD. IncoBoNT-A improved Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total scores from baseline to week 4 as compared with placebo (placebo = −2.2, 120 U = −9.9, and 240 U = −10.9, p < 0.001). Improvement also was seen in secondary variables, including the TWSTRS subscales for motor severity, disability, and pain, and the Patient Evaluation of Global Response scores. The most frequently reported AEs in the incoBoNT-A groups were dysphagia, neck pain, and muscular weakness, all determined to be generally mild.

Of the 233 patients who completed an open-label lead-in trial, 214 patients, who had benefit, were re-randomized to receive either 120 U or 240 U of incoBoNT-A (Class II). Both incoBoNT-A doses provided significant improvements in mean TWSTRS total scores, and in Severity, Disability, and Pain subscores, from each injection session to the respective 4-week follow-up visit (p<0.001 for TWSTRS total score and p<0.05 for all subscores). There was no significant difference in efficacy between the 2 studied doses, although the study was not powered to demonstrate such differences. The most frequently reported AE for all drug injection intervals during the extension period was dysphagia (23.4% in the 240 U–dose group and 10.7% in the 120 U–dose group).

Another Class II study (presented to the FDA in 1999) was published in 2012. Patients with CD were randomized to receive onaBoNT-A (the original Botox formulation containing 25 mg of neurotoxin complex protein per 100 U) or placebo. There was a 10-week open-label wash-in period followed by a 10-week double-blind treatment period. OnaBoNT-A produced greater improvements in the CD Severity Scale (-1.81 vs -0.31 points, p = 0.012) and Global Assessment Scale (61.7% vs 41.6% improved, p = 0.022). Rhinitis and treatment-related dysphagia were more frequent with onaBoNT-A.

Five studies compared different formulations of BoNT. The first 2 studies (Class I) randomized patients with CD to onaBoNT-A (150–250 U) or rimaBoNT-B (10,000 U). In the first study, participants were prior responders to BoNT-A and naïve to BoNT-B, whereas in the second study, participants were naïve to both preparations. Both studies noted similar durations of effect and no significant difference in improvement of TWSTRS scores at 4 weeks. Dysphagia occurred more frequently in the rimaBoNT-B group in both studies (48% vs 19% in the first study and 16% vs 14.5% in the second study).
The third Class I study\textsuperscript{23} compared the effect of onaBoNT-A 70 to 240 U with aboBoNT-A 240 to 720 U and observed no difference in the improvement of post-treatment Tsui scores at 4 weeks (mean difference 0.2, 95% CI -0.7 to 1.1, lower scores with aboBoNT-A). The authors also reported similar durations of effect and AEs in both groups. In a Class II 9-month randomized, double-blind, multicenter, noninferiority, 2-period crossover study with a 2.5:1 (aboBoNT-A:onaBoNT-A) protocol involving 103 patients with CD, 94 of whom completed the study, there were no statistically significant differences between aboBoNT-A and onaBoNT-A in mean changes in the Tsui scale (0.8 points favoring onaBoNT-A, 95% CI -0.1 to 1.7), TWSTRS, global impression, or frequency of AEs from baseline to 4 weeks after each injection.\textsuperscript{24} In another comparison study (Class II), 46 patients with CD were enrolled in a double-blind, randomized, crossover trial of onaBoNT-A vs aboBoNT-A in 1:3 dose conversion ratios.\textsuperscript{25} There was no significant difference between the 2 products at week 4, but at week 12 there was a significantly shorter duration and lower efficacy of onaBoNT-A assessed by reduction in TWSTRS total score, suggesting that the optimal conversion ratio between onaBoNT-A and aboBoNT-A is lower than 1:3.

Three long-term, prospective, open-label studies (Class IV) evaluated the clinical response over repeated injections. In 1 study of 333 patients with CD who had never been previously exposed to BoNT, injections with onaBoNT-A were administered for a median of 9 injection series (range 1–15).\textsuperscript{26} Mean dose per session was 187 (±76.5) U over a mean of 2.5 years (range: 3.2 months–4.2 years). Patients maintained benefit from injections over a 2-year period.

Another study followed an initial double-blind, placebo-controlled evaluation of aboBoNT-A with a long-term, open-label extension. The study showed a reduction in TWSTRS in the active treatment group as compared with placebo and continued benefit with active treatment over a mean of 52 weeks (4–94 weeks).\textsuperscript{27} The mean treatment interval was 15 to 17 weeks. Dysphagia was the most frequent AE (6%–17% of patients) and was unrelated to dose or treatment cycle. A third, observational, study involving 1,046 patients with CD who were naïve to BoNT (63.5%) or had not received toxin in ≥16 weeks, the mean dose of onaBoNT-A over 2,481 treatment sessions was 189.8 (± 87.1) U.\textsuperscript{28} The mean TWSTRS total score in participants who completed all assessments (n = 479) decreased from 39.2 at baseline to 27.1 at final visit (p < 0.0001). Although 26.2% of participants reported experiencing AEs (7% weakness, 6.4% dysphagia), the study provided Class IV evidence for the clinical efficacy and safety of onaBoNT-A in CD.

**Conclusions**

AboBoNT-A (2 Class I studies reviewed in the 2008 guideline) and rimaBoNT-B (3 Class I studies reviewed in the 2008 guideline) are established as safe and effective for the treatment of CD. OnaBoNT-A (1 Class I study reviewed in the 2008 guideline, and 1 more recent Class II study) and incoBoNT-A (1 more recent Class I study) are probably safe and effective for the treatment of CD.

RimaBoNT-B and onaBoNT-A (2 Class I comparative effectiveness studies) are established as equivalent in efficacy for treating CD. AboBoNT-A and onaBoNT-A (1 Class I study) are probably equivalent for treating CD.
Recommendations

AboBoNT-A and rimaBoNT-B should be offered (Level A), and onaBoNT-A and incoBoNT-A should be considered (Level B), as options for the treatment of CD.

Clinical context

BoNT is accepted as first-line treatment for CD. Although evidence levels may differ across BoNT formulations, all formulations have regulatory approval and are commonly used. There is an extensive clinical history of onaBoNT-A and incoBoNT-A use, but the lack of additional Class I studies led to only a Level B recommendation. Comparative trials indicate similar efficacy for rimaBoNT-B and onaBoNT-A, and for aboBoNT-A and onaBoNT-A, in the treatment of CD.

Spasticity in adults

Adult spasticity results from diverse etiologies, including stroke, trauma, and multiple sclerosis (MS). The 2008 guideline\(^1\) concludes that BoNT is established as effective in the treatment of adult spasticity in the upper extremity on the basis of 6 Class I studies of aboBoNT-A, 4 Class I studies of onaBoNT-A, and 1 Class I study of rimaBoNT-B. The guideline also concludes that BoNT is effective in treating lower-limb spasticity on the basis of 2 Class I studies of aboBoNT-A and 1 Class I study of onaBoNT-A. Studies demonstrated that BoNT is effective for reducing muscle tone and improving passive function (e.g., improved range of motion) and is probably effective for improving active function (1 Class I study of aboBoNT-A). Those recommendations do not address specific BoNT formulations.

Because a 2010 AAN guideline provides recommendations for BoNT treatment of spasticity in pediatric patient populations,\(^2\) this review discusses only adult spasticity.

Upper-extremity spasticity

Table e-4 lists the studies meeting inclusion criteria identified in the search.

AboBoNT-A. Four newer Class I trials\(^3\)\(^0\)\(^-\)\(^3\)\(^3\) investigating aboBoNT-A demonstrated significant reductions in upper-limb tone as measured by the modified Ashworth scale (MAS). These studies also measured functional outcomes. The first study\(^3\)\(^0\) demonstrated no significant difference in quality of life (QOL) but observed significantly greater global benefit in patients given BoNT. The second study\(^3\)\(^1\) observed no significant difference between groups for improved active arm function as measured by the Action Research Arm Test at 1 month (RD favoring the BoNT group 5.7%, 95% CI -3.5 to 14.6%). However, participants treated with aboBoNT-A showed improvement in upper-limb muscle function at 3 months as measured by the Motricity Index (mean change in index 3.5, 95% CI 0.1 to 6.8, greater number of points in the intervention group). The third study\(^3\)\(^2\) demonstrated no significant change in functional assessment scores. The fourth, a more recent study\(^3\)\(^3\) showed significant reduction in the MAS at week 4 in both the 500-U group (-1.2, \(p < 0.001\) vs placebo) and the 1,000-U group (-1.4, \(p <
0.001 vs placebo). The Physician Global Assessment Score was also significantly improved at week 4 in both active treatment groups. AboBoNT-A groups improved in response rate (>1 point) on the principal target functional domain of treatment of the Disability Assessment Scale (DAS), a measure of self-reported disability, at 4 weeks among participants treated with 1,000 U of aboBoNT-A, but not with 500 U or placebo (62% in 1,000 U, \( p = 0.0018 \) vs placebo; 50% in 500 U, \( p = 0.1279 \) vs placebo; and 39.2% in placebo). The higher-dose BoNT-A group also demonstrated improved active range of motion in the elbow, wrist, and fingers.

A fifth Class I study\(^6\) of patients with upper-limb spasticity focused on caregiver burden. This study found that 67% of caregivers of patients receiving aboBoNT-A reported a \( \geq 4 \)-point reduction on the carer burden scale as compared with 20% of caregivers of patients injected with saline (\( p = 0.001 \)).

Additional analyses of these aboBoNT-A trials have been published.\(^{6,6} \) One demonstrated significant improvements in the Goal Attainment Scale in patients receiving BoNT as compared with controls (\( z = 2.33 \) at 20 weeks favoring treatment group).\(^6\)

**OnaBoNT-A**

Three newer Class I trials\(^{37-39} \) and 1 Class II trial\(^40\) examined onaBoNT-A efficacy and safety in upper-limb spasticity.

All 4 studies demonstrated consistent efficacy in tone reduction in the upper limb.\(^{37-40} \) The DAS was measured in 2 studies.\(^{37,38} \) Improvement was observed only in patients choosing improved limb position\(^{37,40} \) and dressing\(^38\) as principal treatment goals. One of the Class I studies\(^39\) enrolled 21 patients and failed to demonstrate significant effects of BoNT on many functional outcomes, including pain. However, this study was underpowered to exclude potentially important differences. OnaBoNT-A was well tolerated, with no significant difference observed in the overall AE incidence between treatment and placebo groups.

Using goal attainment scaling scores as the primary endpoint measure, another Class I study (prospective, double-blind)\(^41\) randomized participants to one of two groups: onaBoNT-A plus “standard of care” (SC) or placebo plus SC. No difference was found between groups with respect to achievement of principal and secondary active functional goals. Significantly more patients achieved their secondary passive goal with onaBoNT-A plus SC vs placebo plus SC at week 24, but not at week 12 or week 52.

**IncoBoNT-A**

Two new Class I trials\(^42,43\) showed significant improvement in tone reduction with incoBoNT-A. In the first trial, incoBoNT-A produced a greater proportion of participants with \( \geq 1 \)-point improvement in the Ashworth scale score at 4 weeks (odds ratio 3.97, 95% CI 1.9 to 8.3). In the second study, participants treated with incoBoNT-A demonstrated larger reductions in Ashworth scale scores of muscle groups in the primary target clinical pattern (-0.9 with incoBoNT-A vs -0.5 with placebo, \( p < 0.001 \)) as well as a greater proportion with \( > 1 \)-point improvement (69.6%
vs 37.5%, respectively). Both studies also showed that incoBoNT-A produced greater response in all domains of the DAS and global assessment of benefit. The open-label extension study of the first trial\textsuperscript{42} showed persistence of benefit without detection of neutralizing antibodies.\textsuperscript{44}

**RimaBoNT-B**

In a newer Class I study,\textsuperscript{45} 24 patients were randomized to 1 of 2 doses of rimaBoNT-B or placebo and followed for 3 months. Patients randomized to either BoNT dose had improvement in the primary outcome measure, active elbow extension vs placebo (+8.3°, 95% CI 1.1° to 15.5°). There was no significant change as compared with placebo in upper-limb function as measured by the Modified Frenchay Scale.

**Conclusions**

AboBoNT-A, incoBoNT-A, and onaBoNT-A are established as safe and effective for the reduction of adult upper-limb spasticity and improvement of passive function (multiple Class I studies for all preparations). RimaBoNT-B is probably safe and effective for the reduction of adult upper-limb spasticity (1 Class I study).

Data are inadequate to determine the efficacy of aboBoNT-A, onaBoNT-A, incoBoNT-A, or rimaBoNT-B for improvement of active function associated with adult upper-limb spasticity (Class I studies, inconsistent results dependent on active functional outcome).

**Recommendations**

For focal manifestations of adult spasticity involving the upper limb, aboBoNT-A, incoBoNT-A, and onaBoNT-A should be offered (Level A), and rimaBoNT-B should be considered (Level B), as treatment options.

**Lower-extremity spasticity**

Table e-5 lists the characteristics of the studies identified by the updated literature search. One Class I study of aboBoNT-A\textsuperscript{46} in patients with MS observed reduced pain in both legs in patients randomized to aboBoNT-A (RD proportion of patients reporting decreased pain at 12 weeks 29.9%, 95% CI 10.9% to 46%). However, there was no significant difference in tone reduction.

Three Class I studies of onaBoNT-A in the treatment of adult lower-limb spasticity\textsuperscript{47–49} demonstrated significant reduction in tone. In regard to functional measures, 1 study failed to show significant gains in walking speed\textsuperscript{47} vs placebo but did observe improvement in the Clinicians Global Impression at weeks 4, 6, and 8 ($p = 0.016–0.048$).\textsuperscript{47} In another study,\textsuperscript{48} onaBoNT-A injections provided no benefit when compared with placebo in lower-limb sagittal kinematics in adults with cerebral palsy who were ambulatory. However, self-reported rating of muscle stiffness/spasticity significantly improved. In the third study,\textsuperscript{49} patients randomized to onaBoNT-A injections as compared with those randomized to placebo reported significant improvement in gait quality (31.5% vs 20.7%, $p = 0.02$).
The literature search did not identify studies meeting inclusion criteria addressing the efficacy of incoBoNT-A or rimaBoNT-B for adult lower-limb spasticity.

Conclusions

AboBoNT-A and onaBoNT-A are established as safe and effective for the reduction of adult lower-limb spasticity (multiple Class I studies). Data are inadequate to determine the efficacy of incoBoNT-A or rimaBoNT-B for treatment of adult lower-limb spasticity.

Data are inadequate to determine the efficacy of aboBoNT-A, onaBoNT-A, incoBoNT-A, or rimaBoNT-B for improvement of active function associated with adult lower-limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple Class I studies).

Recommendations

For focal manifestations of adult spasticity involving the lower limb that warrant treatment, onaBoNT-A and aboBoNT-A should be offered (Level A) as treatment options. There is insufficient evidence to support or refute a benefit of incoBoNTA or rimaBoNT-B for treatment of adult lower-limb spasticity.

Comparative studies

In a Class I study of 60 participants with adult upper-limb spasticity, onaBoNT-A was superior to tizanidine (TZD) for improving wrist and finger flexor tone (mean change in MAS score BoNT -1.32, TZD -0.22, p = 0.001), whereas TZD showed no benefit over placebo at 6 weeks. Notably, the high incidence of AEs with TZD limited dose titration (90.5% of patients receiving TZD experienced one or more AEs).e37

Conclusion

OnaBoNT-A is probably superior to TZD for reducing upper-extremity tone (1 Class I study) in adult spasticity.

Recommendation

OnaBoNT-A should be considered as a treatment option before TZD for treating adult upper-extremity spasticity (Level B).

Techniques to optimize response to BoNT

Three Class I studies comparing different BoNT injection techniques were identified in the updated search. In a Class I study, onaBoNT-A injections targeted into the endplate band of the biceps were superior to nontargeted injections at the same dose and dilution.e50 In this same study, when the same 160-U dose of BoNT was used, a low-potency (20 U/cc) injection with a
5-fold-higher volume was superior to a high-potency (100 U/cc) injection in clinical and electrophysiologic measures of spasticity.\textsuperscript{e50} Another Class I study demonstrated that a single motor point injection of onaBoNT-A 25 U/cc produced benefits as shown on the Ashworth scale, Tardieu catch angle, and root mean square surface electromyographic activity similar to those of 4 distributed injections of biceps brachii and brachioradialis muscles.\textsuperscript{e51} A Class I incoBoNT-A trial demonstrated the noninferiority of 20 U/mL vs 50 U/mL dilution 4 weeks postinjection on the DAS and Ashworth scale in patients with upper-limb spasticity of diverse etiologies.\textsuperscript{e52} A cautionary note with regard to the use of high-volume injections is highlighted by reports of spread of BoNT to the contralateral limb following high-dose, high-volume BoNT injections in upper-limb spasticity.\textsuperscript{e53}

A Class II study\textsuperscript{e54} randomized 49 patients with spastic equinus after stroke to 3 different techniques for guiding onaBoNT-A injections into the gastrocnemius muscle: manual needle placement, electrical stimulation, and ultrasonography. The study reported significant improvements in the MAS in the ultrasonography-guided group as compared with the other placement modalities (manual vs ultrasound effect size 0.46). However, no significant difference in the Tardieu spasticity scale was observed (manual vs ultrasound effect size 0.21).

Conclusions

Endplate targeting into proximal upper-extremity muscles is probably an effective strategy for enhancing tone reduction in adult spasticity (1 Class I study). In studies comparing varying BoNT-A dilution potency and injection volumes, onaBoNT-A is probably effective (high volume, low potency superior, 1 Class I study), whereas incoBoNT-A showed noninferiority of the 2 dilutions (1 Class I study).

There is insufficient evidence to support or refute the superiority of specific techniques for guiding BoNT injection placement in the treatment of spasticity (inconsistent outcomes from 1 Class II study).

Recommendations

Both high-volume, low-potency injections of onaBoNT-A and endplate targeting of onaBoNT-A into proximal upper-extremity muscles should be considered to enhance tone reduction in spasticity (Level B).

Clinical context

Although BoNT can reduce increased tone, the impact of BoNT injections on functional outcomes is mixed,\textsuperscript{e41} suggesting that potential functional gains are highly patient specific. In relation to upper-extremity spasticity, because of the lack of comparative trials, there is insufficient evidence to indicate that any one of the BoNT formulations is superior to the others. In relation to lower-extremity spasticity, there are fewer data overall, including no data dealing with comparative effectiveness.
Headache

Twenty-eight full-text studies were examined for treatment of chronic migraine (CM), episodic migraine (EM), tension-type headache (TTH), chronic daily headache, and other headache types. Eight met inclusion criteria and are summarized in table e-6.

Chronic migraine

CM refers to migraine attacks occurring 15 days or more monthly for at least 3 months, with attacks lasting 4 hours or more. EM refers to migraine with a lesser frequency of attack.

The 2008 guideline found inconsistent results from 4 Class II studies comparing onaBoNT-A with placebo, resulting in insufficient evidence to support or refute a benefit of BoNT for treatment of CM.\textsuperscript{e3}

Comparison of BoNT with placebo

Two Class I placebo-controlled studies\textsuperscript{e56,e57} published since the 2008 guideline met inclusion criteria. In one,\textsuperscript{e56} onaBoNT-A was ineffective for changes from baseline for total headache episodes (the primary endpoint). However, BoNT was effective for the secondary endpoint of change in frequency of total headache days/28 days (mean intergroup difference -1.4 days, 95% CI -2.4 to -0.40). In the second study,\textsuperscript{e57} onaBoNT-A was effective for reducing total headache days/28 days from baseline to weeks 21–24 post-treatment (the primary endpoint). Nine fewer headache days were seen in the BoNT-A group, with 6.7 in the placebo group ($p < 0.001$).

In both studies the placebo response was high. In addition, it is possible patients receiving onaBoNT-A became unmasked to treatment assignment due to weakness of facial muscles.

Several follow-up reports describing pooled analyses of both Class I studies have been published. One Class I follow-up report\textsuperscript{e58} described significant reduction in headache impact and improvement in health-related QOL after 24 weeks of double-blind treatment (proportion of patients with severe Headache Impact Test-6 scores 67.6% of patients given BoNT vs 78.2% of patients given placebo, $p <0.001$).

Two reports\textsuperscript{e59,e60} presented Class III pooled analyses regarding the 56-week open-label extension phases of both onaBoNT-A studies. Although all patients were treated with BoNT after the 24-week placebo-controlled phase, sustained differences were observed between patients initially randomized to onaBoNT-A as compared with those initially randomized to placebo (change in headache-day frequency at week 56: -11.7 in the onaBoNT-A/onaBoNT-A treated vs -10.3 in the placebo/onaBoNT-A treated -11/7, $p = 0.19$). However, this pooled analysis did not prespecify a method to control for type I error. After application of a Bonferonni correction, none of the differences was significant.

Comparison of BoNT with other headache preventive treatments

One Class III study\textsuperscript{e61} demonstrated similar efficacy for onaBoNT-A and topiramate in CM. No
other studies comparing oral preventive medications with BoNT injections met inclusion criteria. There also are no studies comparing different BoNT serotypes in headache. AEs of onaBoNT-A included neck pain and muscle weakness.

Conclusions

OnaBoNT-A is established as safe and effective for increasing the number of headache-free days in CM (2 Class I studies) and probably effective for improvement in health-related QOL (1 Class I study).

There is insufficient evidence to compare the effectiveness of BoNT with that of oral prophylactic topiramate. No Class I or II studies of other formulations of BoNT in CM have been published.

Recommendations

OnaBoNT-A should be offered as a treatment option to patients with CM to increase the number of headache-free days (Level A) and should be considered to reduce headache impact on health-related QOL (Level B).

Clinical context

Although the reduction of headache days with onaBoNT-A was statistically superior to placebo in 2 Class I studies, the magnitude of the difference is small (1.7 and 2.3).

Episodic migraine

The 2008 conclusion,\textsuperscript{63} based on 2 Class I and 2 Class II studies, indicates onaBoNT-A injection is probably ineffective for treatment of EM. One Class I study\textsuperscript{62} published since that guideline publication compared onaBoNT-A at doses of 75 U, 150 U, and 225 U with placebo, using 3 treatment cycles 3 months apart. OnaBoNT-A was ineffective for reducing migraine frequency from baseline to day 180.

Conclusion

OnaBoNT-A is ineffective for the treatment of EM (3 Class I studies, 2 from the 2008 report).

Recommendation

OnaBoNT-A should not be offered as a treatment for EM (Level A).

Tension-type headache

No new studies meeting inclusion criteria were found that would have changed the conclusion of the 2008 guideline.\textsuperscript{63} BoNT injection is probably ineffective for treating chronic TTH (2 Class I studies).
**Recommendation**

OnaBoNT-A should not be considered as a treatment for chronic TTH (Level B).

**RECOMMENDATIONS FOR FUTURE RESEARCH**

1. Treatment response varies widely within and between indications. Future studies should investigate factors that predict which patient subgroups have optimal responses.

2. A major limitation in published BoNT clinical trials is the lack of standardized rating tools for many clinical indications (e.g., spasticity, focal dystonia). Furthermore, there is often disagreement among investigators, clinicians, patients, family members, and regulatory agencies about what constitutes meaningful functional improvement. Future studies would benefit from the development of sensitive, validated scales applicable across the spectrum of clinical and functional criteria. Because efficacy of BoNT has been demonstrated, placebo-controlled trials using BoNT will be difficult to recruit and may no longer be considered ethical. Thus, well-designed comparative studies may be needed to determine relative efficacy and safety.

3. More research is needed in order to determine the optimal BoNT dose and dilution potency for individual muscles, the choice of number and location of injection sites, and the optimal technique for injection localization (e.g., surface anatomy, EMG guidance, electrical stimulation, ultrasonography).

4. For spasticity, there is a need to confirm efficacy for active function in controlled trials. This will require designing enrollment criteria that provide more homogeneity in etiologies and severity, and validated outcome measures sensitive enough to demonstrate change in active motor function.

5. Further research on the mechanism of action of BoNT in treating spasticity would inform optimal timing of treatment and whether disease modification is possible. For example, if BoNT has effects beyond paralysis of extrafusal muscle fibers (e.g., enhancing neuroplasticity), then one might consider earlier BoNT treatment in the course of cerebral injury.

6. The clinical importance of BoNT neutralizing antibodies and whether there are differences among formulations in this risk remains unclear. Furthermore, there is no consensus on the validity of assays to measure antibody formation. In 1 study, only 4 of 326 (1.2%) patients treated with onaBoNT-A had BoNT antibodies. Three of these patients became clinically nonresponsive to onaBoNT-A. In contrast, another study analyzed the long-term follow-up of 4 separate prospective clinical trials of rimaBoNT-B involving a total of 1,134 patients with CD. In this study, 33% to 44% of patients chronically treated developed BoNT-neutralizing antibodies. The development of antibodies in these patients did not alter the clinical response to rimaBoNT-B.
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CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.e4

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Appendix e-1: 2013–2015 Guideline Development Subcommittee (GDS) members

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Appendix e-2: Mission statement of GDS

The mission of the GDS is to prioritize, develop, and publish evidence-based guidelines related to the diagnosis, treatment, and prognosis of neurological disorders. The GDS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.
Appendix e-3: Complete search strategy

Initial search

The search terms used for blepharospasm were: blepharospasm, orbicular spasm, eyelid spasm, BSP, EB, hemifacial spasm, orofacial spasm, hemifacial myokymia, facial hemispasm, HFS, Meige Syndrome, meige, botulin, botox, BoNT, BtA, BTX. The search terms used for cervical dystonia were: botulin toxin, botulin, botox, BoNT, BtA, BTX, dystonia, cervical dystonia, dystonic disorder, torticollis, cervical dystonia, anterocollis, retrocollis, laterocollis, wryneck. The search terms used for headache were: botulinum toxin, botulin, botox, BoNT, BtA, headache, head ache, head pain, cranial pain, cephalgia, cephalalgia, hemicrania, Horton, SUNCT, migraine. The search terms used for spasticity were: botulinum toxin, botulin, botox, BtA, spasticity, muscle spasm, spastic.

Updated search

Therapy/Broad[filter] AND (("botulinum toxins"[MeSH Terms] OR ("botulinum"[All Fields] AND "toxins"[All Fields]) OR "botulinum toxins"[All Fields]) OR ("onabotulinumtoxinA"[Supplementary Concept] OR "onabotulinumtoxinA"[All Fields] OR "onabotulinumtoxinA" [All Fields]) OR ("abobotulinumtoxinA"[Supplementary Concept] OR "abobotulinumtoxinA"[All Fields] OR "abobotulinumtoxinA"[All Fields] OR "abobotulinumtoxinA"[All Fields] OR "botulinum toxins, type a"[MeSH Terms] OR "type a botulinum toxins"[All Fields]) OR ("incobotulinumtoxinA"[Supplementary Concept] OR "incobotulinumtoxinA"[All Fields] OR "incobotulinumtoxinA"[All Fields] OR "botulinum toxins, type a"[MeSH Terms] OR "type a botulinum toxins"[All Fields]) OR ("rimabotulinumtoxinB"[Supplementary Concept] OR "rimabotulinumtoxinB"[All Fields] OR "rimabotulinumtoxinB"[All Fields]) OR ("onabotulinumtoxinA"[Supplementary Concept] OR "onabotulinumtoxinA"[All Fields] OR "botulinum"[All Fields]) OR ("abobotulinumtoxinA"[Supplementary Concept] OR "abobotulinumtoxinA"[All Fields] OR "abobotulinumtoxinA"[All Fields] OR "dysport"[All Fields]) OR ("incobotulinumtoxinA"[Supplementary Concept] OR "incobotulinumtoxinA"[All Fields] OR "xeomin"[All Fields] OR ("rimabotulinumtoxinB"[Supplementary Concept] OR "rimabotulinumtoxinB"[All Fields] OR "myobloc"[All Fields]) OR ("rmabotulinumtoxinB"[Supplementary Concept] OR "rmabotulinumtoxinB"[All Fields] OR "neurobloc"[All Fields]))
Appendix e-4: Therapeutic classification of evidence scheme

Class I

A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation
b. primary outcome(s) clearly defined
c. exclusion/inclusion criteria clearly defined
d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
   1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
   2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
   3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
   4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II

A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV

Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.
**Objective outcome measurement**: an outcome measure that is unlikely to be affected by an observer’s (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).
Appendix e-5: Classification of recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an “A” recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).
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