

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

Report of the Guideline Development Subcommittee of the American Academy of Neurology



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## ABSTRACT

**Objective:** To update the 2008 American Academy of Neurology (AAN) guidelines regarding botulinum neurotoxin for blepharospasm, cervical dystonia (CD), headache, and adult spasticity.

**Methods:** We searched the literature for relevant articles and classified them using 2004 AAN criteria.

**Results and recommendations:** Blepharospasm: OnabotulinumtoxinA (onaBoNT-A) and incobotulinumtoxinA (incoBoNT-A) are probably effective and should be considered (Level B). AbobotulinumtoxinA (aboBoNT-A) is possibly effective and may be considered (Level C). CD: AboBoNT-A and rimabotulinumtoxinB (rimaBoNT-B) are established as effective and should be offered (Level A), and onaBoNT-A and incoBoNT-A are probably effective and should be considered (Level B). Adult spasticity: AboBoNT-A, incoBoNT-A, and onaBoNT-A are established as effective and should be offered (Level A), and rimaBoNT-B is probably effective and should be considered (Level B), for upper limb spasticity. AboBoNT-A and onaBoNT-A are established as effective and should be offered (Level A) for lower-limb spasticity. Headache: OnaBoNT-A is established as effective and should be offered to increase headache-free days (Level A) and is probably effective and should be considered to improve health-related quality of life (Level B) in chronic migraine. OnaBoNT-A is established as ineffective and should not be offered for episodic migraine (Level A) and is probably ineffective for chronic tension-type headaches (Level B). *Neurology*® 2016;86:1818-1826

## GLOSSARY

**AAN** = American Academy of Neurology; **aboBoNT-A** = abobotulinumtoxinA; **AE** = adverse event; **BDI** = Blepharospasm Disability Index; **BoNT** = botulinum neurotoxin; **CD** = cervical dystonia; **CI** = confidence interval; **CM** = chronic migraine; **DAS** = Disability Assessment Scale; **EM** = episodic migraine; **incoBoNT-A** = incobotulinumtoxinA; **onaBoNT-A** = onabotulinumtoxinA; **QOL** = quality of life; **RD** = risk difference; **rimaBoNT-B** = rimabotulinumtoxinB; **RMT** = randomized, masked trials; **TWSTRS** = Toronto Western Spasmodic Torticollis Rating Scale; **TZD** = tizanidine.

This article summarizes information provided in the complete guideline, available on the *Neurology*® Web site at [Neurology.org](http://Neurology.org). Tables e-1 through e-6 and appendices e-1 through e-5, cited in the full guideline (data supplement), as well as references e1 through e16, cited in this summary, are available at [Neurology.org](http://Neurology.org).

In 2008, the American Academy of Neurology (AAN) published guidelines on the uses of botulinum neurotoxin (BoNT).<sup>1-3</sup> New research on 4 indications—blepharospasm, cervical dystonia (CD), spasticity, and headache—prompted this update.

BoNT pharmacology is reviewed in the 2008 AAN guidelines.<sup>1-3</sup> BoNT is commercially available in 2 serotypes, A and B. There are 4 US Food and Drug Administration–approved preparations of BoNT: onabotulinumtoxinA (onaBoNT-A), abobotulinumtoxinA (aboBoNT-A), incobotulinumtoxinA (incoBoNT-A), and rimabotulinumtoxinB (rimaBoNT-B) (table 1). The regulatory-approved indications do not necessarily correspond to those in the evidence-based recommendations presented here.

Supplemental data  
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**Table 1** BoNT preparations and FDA-approved indications

BoNT preparation	Brand name (manufacturer)	FDA-approved indications <sup>a</sup>
OnabotulinumtoxinA	Botox (Allergan, Inc., Irvine, CA)	Blepharospasm, CD, upper extremity spasticity, lower extremity spasticity, CM
AbobotulinumtoxinA	Dysport (Ipsen Ltd., Paris, France)	CD, upper extremity spasticity
IncoBotulinumtoxinA	Xeomin (Merz Pharmaceuticals, Frankfurt, Germany)	Blepharospasm, CD, upper extremity spasticity
RimabotulinumtoxinB	Myobloc Neurobloc (US WorldMeds/Solstice Neurosciences, Louisville, KY)	CD

Abbreviations: BoNT = botulinum neurotoxin; CD = cervical dystonia; CM = chronic migraine; FDA = Food and Drug Administration.

<sup>a</sup>FDA approvals relevant to this review.

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. 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 (appendices e-1 and e-2) assembled an author panel, balanced in regard to those with and those without potential conflicts, to develop the guideline following the processes described in the 2004 AAN guideline process manual.<sup>4</sup> A nonconflicted panel member confirmed the rating of each study.

We performed a systematic review to identify relevant studies published since the prior guidelines. In general, only randomized, masked trials (RMTs) were considered. To assess long-term outcomes, including safety, we used evidence from nonrandomized trials.

Twenty-three articles on blepharospasm, 23 on CD, 86 on spasticity, and 28 on headache met inclusion criteria. Table 2 summarizes the conclusions from this review.

**ANALYSIS OF EVIDENCE** **Blepharospasm.** Blepharospasm is a dystonia that can cause disabling eyelid closure. The 2008 guideline<sup>2</sup> concluded that BoNT as a class is probably safe and effective 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, 1 Class I RMT found that incoBoNT-A (doses of up to 50 U/eye)<sup>5</sup> was

superior to placebo (difference in change in Jankovic Rating Score<sup>6</sup> at week 6, 1.0, 95% confidence interval [CI] 0.5–1.4). Benefit lasted a median of 10.6 weeks.

A Class II placebo-controlled RMT<sup>7</sup> observed that aboBoNT-A (40 U, 80 U, or 120 U) improved disability in a dose-related manner on active treatment as measured by the Blepharospasm Disability Index<sup>8</sup> (BDI) (median change in BDI after 80 U –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 comparing onaBoNT-A with incoBoNT-A (1:1 dosing)<sup>9</sup> found comparable magnitude (change in BDI –2.0,  $p = 0.148$ ) and duration of benefit (13 weeks) between BoNT preparations.

A second Class II RMT compared onaBoNT-A and incoBoNT-A at the same dose with injections to one eye with one drug and the other eye with the other drug (injected side randomly assigned). No differences were found with multiple measures over 5 treatment sessions.<sup>10</sup>

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

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,<sup>11</sup> onaBoNT-A for 10 years in 83 patients,<sup>12</sup> and incoBoNT-A for 69 weeks in 82 patients.<sup>13</sup> 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).<sup>14</sup>

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, and aboBoNT-A (1 Class II study) is possibly effective, for treating blepharospasm. 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 [Class I and 1 Class II]) are 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

**Table 2** Evidence-based conclusions and recommendations for the efficacy of various botulinum neurotoxin formulations by indication

Indication	Level A <sup>a</sup> effective	Level B <sup>b</sup> probably effective	Level C <sup>c</sup> possibly effective	Level U <sup>d</sup> insufficient evidence	Level A <sup>e</sup> ineffective	Level B <sup>f</sup> ineffective
Blepharospasm		OnabotulinumtoxinA, incobotulinumtoxinA	AbobotulinumtoxinA	RimabotulinumtoxinB		
Cervical dystonia	AbobotulinumtoxinA, rimabotulinumtoxinB	OnabotulinumtoxinA, incobotulinumtoxinA				
Upper limb spasticity <sup>g</sup>	AbobotulinumtoxinA, onabotulinumtoxinA, <sup>h</sup> incobotulinumtoxinA	RimabotulinumtoxinB				
Lower limb spasticity	OnabotulinumtoxinA, abobotulinumtoxinA			IncobotulinumtoxinA, rimabotulinumtoxinB		
Chronic migraine	OnabotulinumtoxinA <sup>i</sup>					
Episodic migraine					OnabotulinumtoxinA	
Tension-type headache						OnabotulinumtoxinA

Abbreviations: aboBoNT-A = abobotulinumtoxinA; incoBoNT-A = incobotulinumtoxinA; onaBoNT-A = onabotulinumtoxinA; rimaBoNT-B = rimabotulinumtoxinB.

<sup>a</sup> Level A recommendation for effectiveness signifies intervention should be offered.

<sup>b</sup> Level B recommendation for effectiveness signifies intervention should be considered.

<sup>c</sup> Level C recommendation for effectiveness signifies intervention may be considered.

<sup>d</sup> Level U recommendation signifies insufficient evidence to support or refute effectiveness of intervention.

<sup>e</sup> Level A recommendation for ineffectiveness signifies intervention should not be offered.

<sup>f</sup> Level B recommendation for ineffectiveness signifies intervention should not be considered.

<sup>g</sup> Evidence demonstrates efficacy in reducing spasticity but is inadequate to determine improvement in active function associated with limb spasticity.

<sup>h</sup> Probably superior to tizanidine and exercise alone for reducing spasticity.

<sup>i</sup> Established as effective for decreasing the number and severity of headaches; probably effective in improvement of health-related quality of life.

disorder specialists.<sup>15</sup> All 3 type A toxins appear to have similar efficacy and can continue to be efficacious over long periods.

**Cervical dystonia.** 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.<sup>16</sup>

The 2008 guideline<sup>2</sup> 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, 1 placebo-controlled Class I study<sup>17</sup> found that incoBoNT-A (120 U, 240 U) improved Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)<sup>18</sup> total scores from baseline to week 4 (placebo = -2.2, 120 U = -9.9, and 240 U = -10.9,  $p < 0.001$ ). A second study (Class II) comparing 2 doses of incoBoNT-A (120 U or 240 U)<sup>19</sup> demonstrated that both 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. 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 in the incoBoNT-A groups in this study was dysphagia (23.4% in the 240 U dose group and 10.7% in the 120 U dose group).

Another placebo-controlled study (Class II) of onaBoNT-A (the original Botox formulation containing 25 mg of neurotoxin complex protein per 100 U)<sup>20</sup> found that 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)<sup>21,22</sup> randomized patients with CD to onaBoNT-A (150–250 U) or rimaBoNT-B (10,000 U) and noted similar durations of effect and no significant difference in improved 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<sup>23</sup> compared the effect of onaBoNT-A 70–240 U with aboBoNT-A 240–720 U and observed no difference in the improvement of posttreatment Tsui scores at 4 weeks (mean difference 0.2, 95% CI -0.7 to 1.1, lower scores with aboBoNT-A). 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.<sup>24</sup> 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. 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.<sup>25</sup>

Three long-term, prospective, open-label studies (Class IV)<sup>26-28</sup> evaluated the clinical response of repeated injections of onaBoNT-A and found persistent benefit for up to 2 years.

**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, 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 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 the evidence levels may differ across BoNT serotypes and brands, 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.** A 2010 AAN guideline provides recommendations for BoNT treatment of spasticity in pediatric patient populations,<sup>29</sup> and therefore this review discusses only adult spasticity.

The 2008 guideline<sup>1</sup> 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).

**Upper extremity spasticity. AboBoNT-A.** Four new Class I trials<sup>30-33</sup> investigating aboBoNT-A demonstrated significant reductions in upper limb tone as measured by the modified Ashworth scale. These studies also measured functional outcomes. The first study<sup>30</sup> demonstrated no significant difference in quality of life (QOL) but observed significantly greater global benefit in patients given BoNT. The second study<sup>31</sup> 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<sup>32</sup> demonstrated no significant change in functional assessment scores. The fourth, a more recent study,<sup>33</sup> showed improved response rate (>1 point) on the principal target 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<sup>34</sup> 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 ( $p = 0.001$ ).

**OnaBoNT-A.** Four studies (3 Class I,<sup>35-37</sup> 1 Class II<sup>38</sup>) demonstrated consistent efficacy in tone reduction in the upper limb from onaBoNT-A. Scores on the DAS improved only in patients choosing improved limb position<sup>35,38</sup> and dressing<sup>36</sup> as principal treatment goals. One of the Class I studies<sup>37</sup> enrolled 21 patients and failed to demonstrate significant effects of BoNT on many functional outcomes. However, this study was underpowered to exclude potentially important differences. In these studies 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) randomized participants to 1 of 2 groups: onaBoNT-A plus standard of care or placebo plus standard of care. 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 standard of care vs placebo plus standard of care at week 24, but not at week 12 or week 52.<sup>39</sup>

**IncoBoNT-A.** Two new Class I trials<sup>40,e1</sup> 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 1.9–8.3). 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 showed persistence of benefit without detection of neutralizing antibodies.<sup>e2</sup>

**RimaBoNT-B.** In a newer Class I study,<sup>e3</sup> patients were randomized to 1 of 2 doses of rimaBoNT-B or placebo. Patients randomized to either BoNT dose had improved active elbow extension vs placebo ( $+8.3^\circ$ , 95% CI  $1.1^\circ$ – $15.5^\circ$ ). 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.** One placebo-controlled Class I study<sup>e4</sup> published since the 2008 guideline examined aboBoNT-A use in multiple sclerosis and 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%–46%). Three Class I studies of onaBoNT-A in the treatment of adult lower limb spasticity<sup>e5–e7</sup> demonstrated significant reduction in tone but found inconsistent results in regard to functional measures.

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 improvement of active function in 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 incoBoNT-A or rimaBoNT-B for treatment of adult lower limb spasticity.

**Comparative studies.** In a Class I study of patients with adult upper limb spasticity, onaBoNT-A was superior to tizanidine (TZD) for improving wrist and finger flexor tone, whereas TZD showed no benefit over placebo. Notably, the high incidence of AEs with TZD limited dose titration (90.5% of patients receiving TZD experienced one or more AEs).<sup>35</sup>

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

**Recommendations.** 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.** Two Class I studies<sup>e8,e9</sup> demonstrated that high-volume injections of onaBoNT-A and endplate targeting into proximal upper extremity muscles are probably effective strategies for enhancing tone reduction in adult spasticity. One Class II study<sup>e10</sup> compared 3 different techniques for guiding BoNT injection placement (manual needle placement, electrical stimulation, and ultrasonography) and did not find consistent outcomes favoring one technique.

**Conclusions.** Both high-volume, low-potency injections of onabotulinum toxin A and endplate targeting into proximal upper extremity muscles are probably effective strategies for enhancing tone reduction in adult spasticity (1 Class I study for each technique).

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

**Recommendations.** Both high-volume, low-potency injections of onabotulinum toxin A and endplate targeting of onabotulinum toxin 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 in spasticity, the impact of BoNT injections on functional outcomes is mixed, suggesting that potential functional gains are highly patient-specific. 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.

**Headache. Chronic migraine.** 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.<sup>e11</sup> Episodic migraine (EM) refers to migraine with a lesser frequency of attack. The 2008 guideline found inconsistent results from 4 Class II studies comparing onabotulinum toxin A with placebo, resulting in insufficient evidence to support or refute a benefit of BoNT for treatment of CM.<sup>3</sup>

**Comparison of BoNT with placebo.** Two Class I placebo-controlled studies<sup>e12,e13</sup> published since the 2008 guideline met inclusion criteria. In one study,<sup>e12</sup> onabotulinum toxin A was ineffective for changes from baseline for total headache episodes but 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,<sup>e13</sup> onabotulinum toxin A was effective for reducing total headache days/28 days from baseline to weeks 21–24 posttreatment. 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.

Several follow-up reports describing pooled analyses of both Class I studies have been published. One Class I follow-up report<sup>e14</sup> 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 scores 67.6% of patients given BoNT vs 78.2% of patients given placebo,  $p < 0.001$ ).

**Comparison of BoNT with other headache preventive treatments.** One Class III study<sup>e15</sup> demonstrated similar efficacy for onabotulinum toxin 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 onabotulinum toxin A included neck pain and muscle weakness.

**Conclusions.** Onabotulinum toxin A is established as safe and effective for reducing the number of headache days in CM (2 Class I studies) and probably effective for improving 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.** Onabotulinum toxin 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 onabotulinum toxin 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 guideline conclusion,<sup>3</sup> based on 2 Class I and 2 Class II studies, indicates onabotulinum toxin A injection is probably ineffective for treatment of EM. One Class I study<sup>e16</sup> published since the 2008 guideline compared onabotulinum toxin A at doses of 75 U, 150 U, and 225 U with placebo, using 3 treatment cycles 3 months apart. Onabotulinum toxin A was ineffective for reducing migraine frequency from baseline to day 180.

**Conclusion.** Onabotulinum toxin A is ineffective for the treatment of EM (3 Class I studies, 2 from the 2008 report).

**Recommendation.** Onabotulinum toxin A should not be offered as a treatment for EM (Level A).

**Tension-type headache.** No new studies were identified that would have changed the conclusion of the 2008 guideline.<sup>3</sup> BoNT injection is probably ineffective for treating chronic tension-type headaches (2 Class I studies).

## AUTHOR CONTRIBUTIONS

David M. Simpson: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Mark Hallett: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Eric J. Ashman: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Cynthia L. Comella: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Mark W. Green: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Gary S. Gronseth: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Melissa J. Armstrong: acquisition of data, analysis or

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