AAN Summary of Practice Guideline Update for **Clinicians**

Practice Guideline Update Summary: Botulinum Neurotoxin for the Treatment of Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache

This is a summary of the American Academy of Neurology (AAN) practice guideline update, "Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache," which was published in *Neurology*® online on April 18, 2016, and appears in the May 10, 2016, *Neurology* print issue.

Please refer to the full guideline at AAN.com/guidelines for more information, including the definitions of the classifications of evidence and recommendations.

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

BoNT pharmacology is reviewed in the 2008 AAN guidelines.[1-3] BoNT is commercially available in two serotypes, A and B. There are four 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.

Table 1. BoNT Preparations and FDA-approved Indications

BoNT Preparation	Brand Name (Manufacturer)	FDA-approved Indications[a]
OnabotulinumtoxinA	Botox (Allergan, Inc., Irvine, CA)	Blepharospasm, CD, upper limb spasticity, lower limb spasticity, CM
AbobotulinumtoxinA	Dysport (Ispen Ltd, Paris, France)	CD, upper limb spasticity
IncobotulinumtoxinA	Xeomin (Merz Pharmaceuticals, Frankfurt, Germany)	Blepharospasm, CD, upper limb spasticity
RimabotulinumtoxinB	Myobloc, Neurobloc (US WorldMeds/Solstice Neurosciences, Louisville, KY)	CD

Abbreviations: BoNT = botulinum neurotoxin; CD = cervical dystonia; CM = chronic migraine.

[a]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.

What Are the Safety and Efficacy of BoNT in the Treatment of Blepharospasm?

Moderate Evidence	OnaBoNT-A and incoBoNT-A injections should be considered as treatment options for blepharospasm (**Level B**).
Weak Evidence	AboBoNT-A may be considered as a treatment option for blepharospasm (**Level C**).

Clinical Context

BoNT is considered the first-line treatment of blepharospasm by most movement disorder specialists.[4] All three type A toxins appear to have similar efficacy and can continue to be efficacious over long periods.

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What Are the Safety and Efficacy of BoNT in the Treatment of CD?

Strong Evidence	AboBoNT-A and rimaBoNT-B should be offered **(Level A**) as options for the treatment of CD.
Moderate Evidence	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.

What Are the Safety and Efficacy of BoNT in the Treatment of Spasticity in Adults?

Upper Extremity Spasticity	
Strong Evidence	For focal manifestations of adult spasticity involving the upper limb, aboBoNT-A, incoBoNT-A, and onaBoNT-A should be offered (**Level A**) as treatment options.*
Moderate Evidence	For focal manifestations of adult spasticity involving the upper limb, rimaBoNT-B should be considered (**Level B**) as a treatment option.*
Lower Extremity Spasticity	
Strong Evidence	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.*
Insufficient Evidence	There is insufficient evidence to support or refute a benefit of incoBoNT-A or rimaBoNT-B for treatment of adult lower limb spasticity (**Level U**).
Comparative Studies	
Moderate Evidence	OnaBoNT-A should be considered as a treatment option before tizanidine (TZD) for treating adult upper extremity spasticity (**Level B**).
Techniques to Optimize Response to BoNT	
Moderate Evidence	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**).

**For effect on tone and passive function, not active function*

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.

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What Are the Safety and Efficacy of BoNT in the Treatment of Headache?

In the initial literature search for the 2016 update, the available evidence for headache affected only the 2008 conclusions and recommendations that pertain to chronic migraine (CM).

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

Clinical Context

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

Episodic Migraine	
Strong Evidence	OnaBoNT-A should **not** be offered as a treatment for episodic migraine (**Level A**).
Tension-type Headaches	
Moderate Evidence	No new studies were identified that would have changed the conclusion of the 2008 guideline.[3] BoNT injection is **probably ineffective** for treating chronic tension-type headaches (two Class I studies) (**Level B**, **as determined in 2008 guideline**).

This guideline was endorsed by the American Association of Neuromuscular & Electrodiagnostic Medicine and by the American Society of Plastic Surgeons.

References

1. 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;70:1691–1698.
2. 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;70:1699–1706.
3. Assessment: botulinum toxin 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. Neurology 2008;70:1707–1714.
4. Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013;67:94–114.

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