

CLINICAL GUIDELINES

No more mistaken identities for botulinum neurotoxins

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The American Academy of Neurology (AAN) has updated its guidelines on the use of botulinum neurotoxins in neurological disorders. The new guidelines provide individual recommendations for the four products that are commercially available in the USA; however, the clinical differences between the products are still not clear.

Refers to Simpson, D. M. et al. 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. Neurology <http://dx.doi.org/10.1212/WNL.0000000000002560>

In April 2016, the American Academy of Neurology (AAN) published updated guidelines for the clinical use of BoNT products¹. In these guidelines, the four BoNT products that are marketed in the USA are, for the first time, reviewed as individual drugs. Unlike the previous AAN guidelines published in 2008, the new guidelines discuss only four licensed neurological indications — blepharospasm, cervical dystonia, limb spasticity and headache — and exclude the on-label indication of hemifacial spasm and several off-label neurological indications that were included in the previous AAN guidelines^{2–4} (TABLE 1).

BoNT products that are licensed for medical use are prepared by fermentation, using bacteria from proprietary batches. In North America and Europe, four licensed BoNT brands exist, and several others are available for clinical use in other countries, particularly in Asia. These BoNT products differ by toxin and protein content, and their potency is measured using proprietary units that are not interchangeable between different brands⁵.

Notwithstanding differences in manufacturing and dosing, the commercially available BoNT products have overlapping clinical indications. They are all licensed for the treatment of focal dystonias — including cervical dystonia, the most prevalent focal dystonia — for limb spasticity, and for cosmetic indications. Licensing has regional variations. Since the

1980s, the number of suggested new indications for BoNTs has increased, and experts from many medical specialties have generated a long list of potential therapeutic uses, including nondystonic disorders of involuntary muscle activity, drooling as a secondary symptom of a neurological disorder, and smooth muscle hyperactive disorders.

The majority of studies on new indications for BoNTs, including several randomized controlled trials, have been spontaneous, investigator-initiated trials with the aim to identify new ways of using the existing BoNT products. The majority of these spontaneous trials used BoNT brands that were already available at the investigating sites, and BoNTs were implicitly assumed to be interchangeable. When other toxin brands were subsequently tested for the same indication, the results were generally comparable.

Many of the new indications developed by investigator-initiated trials remained off-label because BoNT manufacturers did not request specific licenses from regulatory agencies. For example, BoNTs have been proven to be efficacious for upper limb and adductor laryngeal dystonia³, two indications that are still off-label. The AAN guidelines published in 2008 recognized the available evidence for efficacy of BoNTs in these indications (TABLE 1), and health insurance companies have widely reimbursed them. The European Federation of Neurological Societies also

reviewed and rated all the published indications for BoNT use in dystonia, including both on-label and off-label use⁶ (TABLE 1). Outside the field of neurology, the American Society of Colon and Rectal Surgeons rated the efficacy of BoNT treatment for anal fissure as 1C (strong recommendation with low-quality evidence), although the use remains unlicensed⁷.

In 2010, the FDA announced changes in the generic (that is, nonproprietary) names of all the versions of injectable BoNTs⁵. Until then, the BoNT products on the market had been considered as a single pharmacological class. Subsequently, practising clinicians have become acquainted with the (almost unpronounceable) names that differentiate the BoNT brands that are sold in the USA. These new generic names have not been adopted by other regulatory agencies, such as the European Medicines Agency, which currently differentiates BoNT products on the basis of their trade names.

The AAN committee worked for ~5 years to prepare the new guidelines, which discuss the BoNTs individually, according to the differentiation policy dictated by the FDA¹. The guidelines seem to be a valuable effort, although they have some inevitable limitations. First, the document has a limited scope, as it discusses only a few neurological indications for which BoNTs are currently approved, and does not provide an update on the important area of off-label BoNT use in neurology, which is not only common practice but is also reimbursed by most insurance companies in the USA and elsewhere⁸. Furthermore, hemifacial spasm, which was included in the original search strategy, was not included in the final document. The 2008 guidelines, therefore, remain as the most recent AAN document discussing the several indications that are not covered by the new guidelines.

As a consequence of addressing BoNTs as unique products, the new guidelines have lowered the level of evidence for some BoNT brands: onabotulinumtoxinA, the most widely used BoNT product, is now ranked only level B ('probably effective') for cervical dystonia, because the evidence supporting the use of this drug comprises older studies with inadequate design. The phenomenon of a drug being in wide use without formal definitive proof of its efficacy is reminiscent of levodopa: the drug

Table 1 | Comparison of AAN and EFNS guidelines for BoNT use

Indication	AAN 2008	EFNS 2011	AAN 2016			
			OnaA	AboA	IncoA	RimaB
Blepharospasm	B	A	B	C	B	U
Cervical dystonia	A	A	B	A	B	A
Upper limb dystonia	B	A, C	NA	NA	NA	NA
Lower limb dystonia	C	NA	NA	NA	NA	NA
Adductor laryngeal dystonia	B	B	NA	NA	NA	NA
Abductor laryngeal dystonia	U	U	NA	NA	NA	NA
Motor tics	C	NA	NA	NA	NA	NA
Hemifacial spasm	C	NA	NA	NA	NA	NA
Upper limb spasticity	A	NA	A	A	A	B
Lower limb spasticity	A	NA	A	A	NA	NA
Chronic migraine	U	NA	A	NA	NA	NA
Episodic migraine	B (I)	NA	A (I)	NA	NA	NA
Chronic tension-type headache	B (I)	NA	B (I)	NA	NA	NA

Levels of evidence: A, established as effective (should be offered); A (I), established as ineffective (should not be offered); B, probably effective (should be considered); B (I), probably ineffective; C, possibly effective (may be considered); NA, data not available (not discussed); U, unknown (insufficient evidence). AAN, American Academy of Neurology; BoNT, botulinum neurotoxin; EFNS, European Federation of Neurological Societies. OnaA, onabotulinumtoxinA; AboA, abobotulinumtoxinA; IncoA, incobotulinumtoxinA; RimaB, rimabotulinumtoxinB.

was introduced into neurological practice as a treatment for Parkinson disease in 1967, and only 30 years later was recognized to have Class I efficacy in a clinical trial.

Another limitation of the new guidelines is that they provide little evidence to recommend one formulation over another; as a consequence, the differentiation of the various BoNT products has little clinical value. Furthermore, the document does not express any position on the relative potency or conversion factors for proprietary BoNT units. The majority of the studies reviewed in the guidelines were not designed to highlight differences or specificities of individual BoNT products. For example, in most of the included studies, injections were performed at fixed-dose intervals and with a relatively narrow dose range, which did not enable differences in potency and duration of action to be established. Given the effort to provide detail on the individual characteristics and indications of the BoNT products on the market, it would have been valuable to state in the main document that no recommended conversion rates for BoNT units between products exist, and that there are no clear clinical differences in potency and duration of action.

Further research is required to define the extent of similarity between the available BoNT products with overlapping indications. Two recent European consensus papers reviewed the practical management

of cervical dystonia, highlighting commonalities and differences among BoNTs^{9,10}. The positions expressed in these reviews were finalized by a consensus panel to enrich the mere ranking of evidence by responding to questions of daily clinical practice, which the AAN guidelines do not directly address. Regarding practical issues, such as dilution, number of injections per site, and muscle targeting, the BoNT products can still be considered as a single pharmacological class with shared characteristics.

The recently published AAN guidelines should be considered as a novel first step towards differentiation of the clinical use of the various BoNT brands; consequently, forthcoming new BoNT products will be requested to have a well-defined identity. The implementation of these guidelines will require clinical trials with a clear strategy to directly compare the different BoNT products, so as to provide a basis for future recommendations.

Guidelines are important documents that facilitate clinical decision-making, have a considerable influence on patients' lives, and guide payment policies. The new AAN guidelines could immediately influence reimbursement policies in the USA and elsewhere. A companion article discussing the implications of the AAN guidelines on payment policies, published simultaneously with the guidelines, tried to address the reimbursement issues that could potentially arise in the USA⁸, but different issues may emerge outside the USA.

In Europe in particular, national guidelines on BoNT use are necessary to ensure that insurance companies continue to recognize off-label indications without limitations. Hospital tenders, especially at European hospitals, might, on the basis of the existing guidelines, choose just one BoNT product for each indication, and the statements contained in the new guidelines could have a substantial influence on such choices. The process of differentiation between BoNT products that has been started may limit the choice of BoNT products available to neurologists. For example, hospital formularies may include only products established as effective (rated A): only two BoNTs have such a rating for cervical dystonia. A possible consequence of the AAN guidelines is that doctors might have fewer BoNT products available for each indication, resulting in a restricted choice of agents to treat their patients.

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Competing interests statement

The author has received speaker's honoraria from Allergan, Ipsen and Merz.