Botulinum toxins in clinical practice
Gaps in knowledge

Richard L. Barbano, MD, PhD

Since the first clinical use of botulinum toxins over a quarter of a century ago, they have proven themselves a versatile tool, especially in the fields of movement disorders and rehabilitation medicine. A practice guideline update on botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache has recently been published in Neurology®.¹

For practitioners who have already integrated botulinum toxin injections into their practice, the update offers few surprises. Certainly, important issues regarding payment policies exist. In this issue of Neurology® Clinical Practice, Govindarajan et al.² discuss some of these issues.

From a clinical perspective, the thoroughness of the guideline review provides supporting evidence that botulinum toxin therapy should be considered as a treatment option for cervical dystonia, blepharospasm, adult spasticity, and chronic migraine. Likewise, sufficient data suggest that it should not be offered for episodic migraine. Often times, however, gaps exist in available evidence and in such situations clinical judgment must be exercised. These gaps include the choice of specific botulinum toxin, the use of botulinum toxin in other conditions, and the decision where this therapy fits among various treatment options.

In this updated guideline, the botulinum toxins are addressed as unique products, noting pharmacologic differences between the various preparations such as potency and duration of action, for which evidence exists in animal models.³ Each product has its own unique properties including molecular weight and complexing proteins, which can lead to varying clinical properties and side effect profiles.⁴ While the approach of addressing each preparation for different indications is laudable, it does result in questions regarding the interchangeability of the different formulations as well as the use in other indications not covered by the guideline. Lack of evidence of certain preparations in particular indications reminds one of the old adage that “absence of evidence is not evidence of absence.”

In regards to the interchangeability of the different products, questions remain as to how different are the products in clinical practice. Certainly, any clinician considering using botulinum toxin in his or her practice must become familiar with the differences between the preparations. Notably, however, head-to-head comparisons, where available, show little clinical differences among the formulations of the botulinum toxin products, especially the different preparations of serotype A. As noted in the guideline, onabotulinum toxin and incobotulinum toxin had the same effect and duration in blepharospasm; onabotulinum toxin, abobotulinum toxin, and rimabotulinum toxin had the same magnitude and duration of effect in cervical dystonia, though rimabotulinum toxin showed increased dysphagia. Thus, in practice, once a provider becomes familiar with appropriate dosing, it is likely that any of these formulations can be used to effectively treat patients with these conditions.

Movement Disorders Division, University of Rochester Medical Center, NY.

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Correspondence to: richard_barbano@urmc.rochester.edu

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But what about other conditions discussed in the guideline? Not all of the formulations have been shown to be effective in all of the conditions discussed, nor do all formulations have Food and Drug Administration approval for each specific indication. However, off-label use is common in clinical practice. Little data exist to indicate that any of the different formulations, with attention to appropriate dosing and side effects, would not be effective in treating these other conditions. There are also a number of other neurologic conditions not discussed in the guideline in which botulinum toxin has shown efficacy, such as hemifacial spasm and other focal dystonias.\textsuperscript{5,6} Lack of sufficient high-level evidence to support a Level A or B guideline recommendation does not negate their potential utility and likewise, there is little evidence to recommend one formulation over another.

Perhaps one of the more important issues facing practicing neurologists is when to choose to use botulinum toxin therapy. The upcoming years promise to bring major changes to health care delivery. The concept of value has gained increasing importance. This is particularly germane to more costly interventions, and especially true for relatively common conditions, such as chronic migraine and spasticity. For example, while the guideline clearly shows clinically significant improvements in spasticity, for those practitioners who are part of accountable care organizations, it is unclear where this amount of improvement provided by botulinum toxin fits among existing alternative treatment options. For chronic migraine, data exist that it is cost-effective, depending of course on an agreed-upon cost per quality-adjusted life-year.\textsuperscript{7} As successfully treated patients become headache-free, the practitioner will be faced with the decision of when to switch to a less costly preventive option.

In the setting of accountable care organizations and other future health care delivery models, physicians will increasingly become stewards of cost-effectiveness. Medical economic analyses will be needed to determine the most cost-effective means of improving patients’ quality of life. Some value judgments will come into play, but there will be an increasing need to explore pertinent endpoints while understanding the reality of the variability of individual patient needs. Although spasticity (by various measures) is reduced with botulinum toxin therapy, functional endpoints are much less consistently met. Pretreatment discussion with the patient or caregiver to set reasonable and worthwhile goals should help determine whether or not to continue treatment after an initial trial.

Botulinum toxin therapy has proven to be a powerful tool in the treatment of a number of neurologic disorders. The development of 2 serotypes and several formulations has added to the options available to the practicing neurologist. With appropriate attention to the differences in formulation dosing and side effect profiles where they exist, along with appropriate patient selection, this therapy will continue to bring notable value-added improvement in patients’ lives.

REFERENCES

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