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Review

Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome

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ABSTRACT

Botulinum neurotoxin (BoNT) can be injected to achieve therapeutic benefit across a large range of clinical conditions. To assess the efficacy and safety of BoNT injections for the treatment of spasticity associated with the upper motor neuron syndrome (UMNS), an expert panel reviewed evidence from the published literature. Data sources included English-language studies identified via MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Central Register of Controlled Trials. Evidence tables generated in the 2008 Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) review of the use of BoNT for autonomic disorders were also reviewed and updated. The panel evaluated evidence at several levels, supporting BoNT as a class, the serotypes BoNT-A and BoNT-B, as well as the four individual commercially available formulations: abobotulinumtoxinA (A/Abo), onabotulinumtoxinA (A/Ona), incobotulinumtoxinA (A/Inco), and rimabotulinumtoxinB (B/Rima). The panel ultimately made recommendations on the effectiveness of BoNT for the management of spasticity, based upon the strength of clinical evidence and following the AAN classification scale. While the prior report by the AAN provided recommendations for the use of BoNT as a class of drug, this report provides more detail and includes recommendations for the individual formulations. For the treatment of upper limb spasticity, the evidence supported a Level A recommendation for BoNT-A, A/Abo, and A/Ona, with a Level B recommendation for A/Inco; there was insufficient evidence to support a recommendation for B/Rima. For lower limb spasticity, there was sufficient clinical evidence to support a Level A recommendation for A/Ona individually and BoNT-A in aggregate; the clinical evidence for A/Abo supported

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a Level C recommendation; and there was insufficient information to recommend A/Inco and B/Rima (Level U). There is a need for further comparative effectiveness studies of the available BoNT formulations for the management of spasticity.

1. Introduction

The motor behavior of patients with an upper motor neuron syndrome (UMNS) is characterized by highly variable mixtures of impaired voluntary movement control (negative signs of UMNS) combined with behaviors of involuntary muscle contraction (positive signs of UMNS). Spasticity is characterized by excess muscle tone and exaggerated tendon jerks occurring as part of the UMNS. Spasticity occurs commonly in a variety of diseases and conditions including cerebral palsy (CP), spinal cord or traumatic brain injury, multiple sclerosis, and as a consequence of stroke. Within these populations, spasticity is estimated to affect approximately 17%–38% (Lundstrom et al., 2008; Sommerfeld et al., 2004; Watkins et al., 2002; Welmer et al., 2006) of patients with stroke, 17%–53% of patients with multiple sclerosis (Barnes et al., 2003; Goodin, 1998; Rizzo et al., 2004), 40%–78% of those with spinal cord injury (Anson and Shepherd, 1996; Johnson et al., 1998; Maynard et al., 1990; Noreau et al., 2000; Skold et al., 1999; Walter et al., 2002), and as many as 34% of patients with traumatic brain injury (Wedekind and Lippert-Gruner, 2005).

Patients affected by UMNS are at risk of developing contractures and painful limb deformities. These are caused by combinations of voluntary and involuntary motor behaviors that produce a net balance of forces to promote stereotypic patterns of movements and posture, such as the flexed elbow, the clenched fist, and the equinovarus foot. The literature describes a number of UMNS patterns commonly observed by clinicians (Barnes et al., 2010; Brashear et al., 2004; Hesse et al., 1998; Kaji et al., 2010b; Smith et al., 2000) that often lead to problems of passive and active function or symptoms (Esquenazi and Mayer, 2004).

Clinical treatment strategies have focused on modifying the degree of muscle imbalance that characterizes these UMNS patterns, with a predominant emphasis on weakening the contractile effects of involuntary muscle overactivity within a given pattern. In simple terms, the principal objective of spasticity management is to reduce muscle overactivity and prevent irreversible soft-tissue changes and tendon contractures by maintaining muscle length and normalizing limb positioning.

Treatment options range from conservative to interventional measures, including physical and occupational therapies, oral and intrathecal medications, surgery, and focal chemical denervation with phenol, alcohol, and botulinum neurotoxin (BoNT) (Mayer and Esquenazi, 2003; Sheean, 2003). The choice of therapy is dictated by the duration and severity of disease, including the number of limb segments affected. The management of spasticity aims to meet individual patient needs with the overall goal of achieving enhanced functional capacity with the fewest adverse effects.

The use of BoNT to manage spasticity encompasses a wide range of underlying neuromuscular disorders. This review will evaluate the evidence for the therapeutic application of BoNT to upper and lower limb spasticity in adults caused by stroke, multiple sclerosis, and spinal cord or brain injury. In general, the therapeutic benefit of BoNT in spasticity derives from its inhibitory actions on muscular contraction by blocking the release of the neurotransmitter acetylcholine at the neuromuscular junction (Sheean, 2003). Accordingly, the primary effect of BoNT is relaxation of the affected muscle. Recovery at the neuromuscular junction occurs a few weeks postinjection, and within 3–6 months postinjection, the neuromuscular junction function returns to the preinjection level (Sheean, 2003).

1.1. Objectives

The aim of this review of evidence is to assess the effectiveness of interventions involving injections of BoNT for the treatment of spasticity; the intent is to evaluate not only BoNT as a class but also individual BoNT formulations when the evidence allows. Two BoNT serotypes (A and B) are approved by the Food and Drug Administration (FDA) for clinical use in the United States and some countries in the European Union. Approved BoNT-A formulations are onabotulinumtoxinA (A/Ona; Allergan, Inc.), abobotulinumtoxinA (A/Abo; Ipsen Limited), and incobotulinumtoxinA (A/Inco; Merz Pharmaceuticals); the only approved BoNT-B formulation is rimabotulinumtoxinB (B/Rima; Solstice Neurosciences, LLC). These agents are marketed under the brand names Botox®, Dysport®, Xeomin®, and Myobloc® (Neurobloc® in Europe), respectively. In the United States, only onabotulinumtoxinA is FDA-approved for the treatment of spasticity, and only for the upper extremity. The use of other formulations and treatment of lower limb spasticity is considered “off label” in the United States.

2. Methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

All studies comparing BoNT injection or BoNT injection plus other pharmacologic and nonpharmacologic therapies to placebo, no treatment, or active comparators or studies comparing doses of BoNT were considered.

2.1.2. Types of subjects

Adults with upper extremity or lower extremity spasticity and muscle overactivity within the selected diagnosis were included.

2.1.3. Types of interventions

Comparisons of BoNT injection to placebo, BoNT injection to other interventions, and different formulations/doses of BoNT were included.