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Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions

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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 certain urologic conditions, including detrusor sphincter dyssynergia (DSD), lower urinary tract symptoms due to benign prostatic hyperplasia (BPH), and detrusor overactivity (both neurogenic [NDO] and idiopathic [IDO]), 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, for the serotypes BoNT-A and BoNT-B, as well as for 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 use of BoNT for the management of these urologic conditions based upon the strength of clinical evidence and following the AAN classification scale. For the treatment of DSD, the evidence supported a Level B recommendation for the use of A/Ona; A/Abo, A/Inco, and B/Rima received a Level U recommendation. For the treatment of NDO, there was sufficient clinical evidence to support a Level A recommendation for BoNT-A as well as for both A/Ona and A/Abo; no published data were identified for either A/Inco or B/Rima (Level U). For the treatment of IDO, the evidence supported a Level A recommendation for A/Ona; A/Inco, A/Abo, and B/Rima received a Level U recommendation. For the management of BPH, the evidence supported a Level B recommendation for BoNT and A/Ona; no published studies were identified for A/Abo, A/Inco, or B/Rima, warranting a Level U recommendation for these three formulations. Further studies are needed to evaluate the efficacy and safety of BoNT for the management of urologic conditions.

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1. Introduction

The therapeutic applications of botulinum neurotoxin (BoNT) in urology include detrusor sphincter dyssynergia (DSD), lower urinary tract symptoms due to benign prostatic hyperplasia (BPH), and detrusor overactivity (both neurogenic and idiopathic). DSD is common among patients with spinal cord lesions, which includes patients with multiple sclerosis (MS), spinal cord tumors, spinal cord disease, or traumatic spinal cord injuries (SCIs).

BPH is a histologic diagnosis that takes on clinical significance when it is associated with lower urinary tract symptoms, prostatic enlargement, or bladder outlet obstruction. About 50% of men over the age of 40 years will develop BPH in an age-dependent manner (Roehrborn, 2011). Standard medical therapy includes use of alpha-adrenergic blockers and 5-alpha-reductase inhibitors.

Detrusor overactivity is defined on the basis of urodynamic assessments and is characterized by involuntary detrusor contractions during the filling phase. Detrusor overactivity is subdivided into neurogenic (NDO) and idiopathic (IDO) detrusor overactivity. The prevalence of detrusor overactivity in the adult population is estimated to be 16.6% (Milsom et al., 2001). In the majority of affected patients, the cause of the detrusor overactivity is unknown (idiopathic). NDO occurs mainly in patients with spinal cord disease.

In patients with detrusor overactivity, a good clinical history will point the clinician to effective management plans through recognition of the factors that make symptoms better or worse, the time of day when symptoms are most severe, and the level of lesion. Standard-of-care therapies for urinary incontinence (UI) associated with detrusor overactivity include behavioral techniques (bladder training), physical therapies (pelvic floor muscle strengthening, electrical stimulation), and pharmacotherapy (antimuscarinic and anticholinergic drugs). When these approaches are ineffective or poorly tolerated, new approaches including neuromodulation and BoNT have shown promise as alternatives to more complex surgical interventions such as bladder augmentation and urinary diversion.

Current medical and surgical treatments for these urologic disorders have adverse effects and limited efficacy. Accordingly, over recent years, BoNT has been explored as a therapeutic option to reduce the symptoms of these disorders.

The mechanism(s) of action for the therapeutic actions of BoNT in urologic disorders is not fully understood. As the underlying pathophysiology of these disorders differs substantially, it is likely that the mechanism of action of BoNT also varies across these urologic disorders. In the bladder, BoNT is thought to act primarily by inhibiting acetylcholine release from parasympathetic nerve endings to induce detrusor muscle relaxation. However, recent human tissue studies suggest that BoNT may also act by impairing bladder sensory mechanisms (Apostolidis et al., 2006). It is likely that this putative sensory component of BoNT mechanism of action involves inhibition of neurotransmitters other than acetylcholine.

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 urologic disorders. Two BoNT serotypes (A and B) are approved by the Food and Drug Administration (FDA) for clinical use in the United States. 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, Inc.). These agents are marketed under the brand names Botox®, Dysport®, Xeomin®, and Myobloc® or Neurobloc®, respectively.

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 comparator and studies comparing various doses of BoNT were considered.

2.1.2. Types of subjects

Adults and children were included, depending on the relevance of each age group to each of the specific therapeutic indications of interest.

2.1.3. Types of interventions

Evidence tables were created for assessments of 1) effectiveness (placebo-controlled studies), 2) comparative effectiveness (active-controlled studies), and 3) methodology, defined as studies comparing different modes of administration including location, type of imaging, and other forms of guidance for injection, and nonpharmacologic treatments.

2.1.4. Types of outcome measures

From the reviewed literature, a variety of outcome measures were identified by the review authors as potential measures of effectiveness, taking into account the relevance of the outcomes to the disease/disorder of interest. Outcome measures could include variables related to body functions and body structures, and patient- and/or investigator-reported outcomes such as health-related quality of life (QoL) and perceived improvements.

2.2. Search methods for identification of studies

The following terms were used to search several databases including MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Controlled Trials Register. In addition, clinicaltrials.gov was searched for additional studies that may not have been indexed in the former databases as of the cutoff data for inclusion (September 30, 2011). Only English-language articles were considered. Articles that were included were fully published (i.e., online and in print) or available as full text online. The

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