

## Efficacy and safety of onabotulinum toxin A for overactive bladder

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### Abstract

Overactive bladder (OAB) syndrome is a condition which affects 16.9% of women and 16.2% of men with a significant negative impact on quality of life. It is a condition characterized by urgency, with or without

urge incontinence, frequency and nocturia. Behavioral modifications and oral anti-muscarinic medications are first and second-line therapies for OAB but are frequently ineffective or poorly tolerated. For refractory cases of OAB, onabotulinum toxin can be offered and this therapy was approved by the Food and Drug Administration in January of 2013. In this editorial, we will review the indications, usage, efficacy and safety data for intradetrusor injection of onabotulinum toxin A.

**Key words:** Onabotulinum toxin A; Botox; Overactive bladder; Overactive bladder; Neurogenic bladder; Urinary bladder; Detrusor overactivity

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**Core tip:** Overactive bladder (OAB) remains a highly prevalent and frequently, a recalcitrant constellation of symptoms. For patients who are refractory to oral medical therapy, there is sufficient level I evidence to support the use of onabotulinum toxin A injection therapy. It is a safe and very effective 2<sup>nd</sup> line treatment for OAB, even in the elderly population. The suggested Food and Drug Administration approved dose is 100 U to maximize the benefits and minimize the adverse effects of this therapy. Risks of the intradetrusor injection of onabotulinum toxin A include urinary tract infection, increased post void residual, urinary retention which may lead to necessity of self catheterization for a period of time.

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### BACKGROUND

Overactive bladder (OAB) is defined by the International

Continence Society as "urinary urgency, usually accompanied by frequency and nocturia with or without urgency urinary incontinence in the absence of pathological or metabolic conditions that might explain these symptoms"<sup>[1]</sup>. Based on the National Overactive Bladder Evaluation Program, a validated United States national telephone survey, the overall prevalence of OAB in women is 16.9% and men is 16.2%<sup>[2]</sup>. OAB negatively impacts work productivity, mental well-being as well as sleep. These patients have significantly lower quality of life (QOL) scores compared to patients without OAB and which can lead to higher levels of depression and anxiety<sup>[3,4]</sup>. Furthermore, patients with OAB are burdened with time consuming and costly treatments for management of their bothersome symptoms<sup>[5]</sup>. The American Urological Association and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a comprehensive evidence-based guideline on the diagnosis and management of OAB in 2012<sup>[6]</sup>. In this guideline, treatments are recommended in a step-wise, hierarchical fashion. First line therapies consist of behavioral therapy which may consist of bladder training, bladder control strategies, pelvic floor muscle training and fluid management. Complete symptom relief is rarely achieved with behavioral strategies alone but QOL improvement may be seen. Medications are second line therapy and by far, the most common treatment for OAB. Options include oxybutynin, solifenacin, fesoterodine, darifenacin, trospium, tolterodine as well as the newer beta 3 agonists. The side effect profile of these antimuscarinics may vary slightly but overall are very similar and they can be quite bothersome for some patients. Common side effects include dry mouth, constipation, dry eyes, blurred vision, dyspepsia and impaired cognitive function<sup>[7]</sup>. The cognitive side effects can be further debilitating for the elderly, who represent a significant proportion of patients with OAB. In a study published by Brostrom and Hallas<sup>[8]</sup>, the continuation rates of the majority of antimuscarinics at 6 mo was less than 50%. Third line therapies of OAB after failure or discontinuation of second line treatments consist of sacral neuromodulation, peripheral tibial nerve stimulation and intradetrusor injection of onabotulinum toxin A. Intradetrusor injection of onabotulinum toxin A was approved by the Food and Drug Administration (FDA) for the management of OAB in January of 2013. This editorial will focus on the mechanism of action, delivery, efficacy and side effect profile of this therapy.

## BOTULINUM TOXIN

Botulinum toxin is a potent neurotoxin produced from a gram positive anaerobic bacterium, *Clostridium botulinum*, was first isolated by van Ermengem in 1897<sup>[9]</sup>. Of the specific subtypes, botulinum toxin A has the longest duration of action and is used in clinical medicine<sup>[10]</sup>. For proper neuromuscular function and release of acetylcholine at the synapse, three proteins

are required which make up the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex. The light chains of the botulinum toxin disrupt the SNARE complex by cleaving the integral proteins responsible for the exocytosis of ACh, specifically synaptobrevin, SNAP-25, and syntaxin, making attachment of the ACh vesicles to the SNARE complex and release of the ACh into the synaptic cleft impossible<sup>[11]</sup>. Further research is ongoing to further elucidate the mechanism in more detail with several other hypotheses being studied<sup>[12,13]</sup>.

## INDICATIONS AND CLINICAL USE FOR ONABOTULINUM TOXIN A

Onabotulinum toxin A was first introduced into urology as a treatment for detrusor external sphincter dyssynergia<sup>[14]</sup>. Subsequently, the FDA has approved onabotulinum toxin A injections for neurogenic detrusor overactivity as well as OAB. Onabotulinum toxin A is injected into several sites in the bladder wall *via* flexible or rigid cystoscopy in the clinic or ambulatory setting with either general or local anesthesia. Before injecting, the bladder should be filled to ensure adequate visualization. An injection needle is inserted *via* the cystoscope and the onabotulinum toxin A is then injected into the detrusor at multiple sites, usually avoiding the trigone. For an OAB patient, 100 U of onabotulinum toxin A is the approved FDA dose. The 100 U of onabotulinum toxin A is reconstituted in 10 cc of sterile saline and injected into the detrusor muscle just underneath the level of the bladder mucosa. The depth of injection is approximately 2 mm into the detrusor. If the injection site is too superficial, the patient will not have a therapeutic effect, and if placed too deep, the toxin may leak into adjacent structures. Injections can be started in the midline just above the inter-ureteric ridge and then, moving to either direction, at 0.5 cm intervals to the level of the bladder sidewall. Once the initial set of injections is completed, the surgeon can move upward 0.5 to 1 cm and start another series of injections<sup>[15]</sup>. Maximal effect of the onabotulinum toxin A injection is seen after one week.

## EFFICACY OF ONABOTULINUM TOXIN A

The use of onabotulinum toxin A for OAB has been tremendously successful and has revolutionized treatment for this syndrome. Multiple, placebo-controlled, randomized controlled trials have shown that injection of onabotulinum toxin A is superior to placebo in both objective and subjective measurements. One of the earliest of these studies was published by Brubaker *et al*<sup>[16]</sup>. In their sample size of 43 females, they showed that local injection of 200 U onabotulinum toxin A was an effective and durable treatment for refractory overactive bladder. In 2011, Rovner *et al*<sup>[17]</sup> randomized 313 patients with OAB to double-blind intradetrusor injection with placebo or 50 to 300 U of onabotulinum

toxin A. They found that changes from baseline in maximum cystometric capacity and volume at first involuntary detrusor contraction in the onabotulinum group were superior to placebo at week 12. Also, they reported continence rates of 16% in the placebo group compared to 30%-57% in the botulinum group. More recently, in 2013, two large scale randomized controlled trials were published which demonstrated onabotulinum toxin A was well tolerated and demonstrated significant and clinically relevant improvement in all aspects of OAB. Chappel *et al*<sup>[18]</sup> performed a multi-center, double-blind, randomized, placebo-controlled trial with > 270 patients in each arm. The onabotulinum toxin group had significantly decreased urinary incontinence episodes at week 12 as well as reductions from baseline in all other OAB symptoms. They reported clinically meaningful improvements from baseline in all Incontinence Quality of Life (I-QOL) and King's Health Questionnaire (KHQ) multi-item domains indicating a positive impact on health-related quality of life. Nitti *et al*<sup>[19]</sup> reported the results of another large scale (557 patients), phase 3, placebo-controlled trial of onabotulinum toxin A in patients with OAB and urinary incontinence inadequately managed with anticholinergics. In this cohort, there was a 47.9% reduction in urinary incontinence episodes from baseline in the onabotulinum toxin A group compared to 12.5% in the placebo group. Complete continence was achieved by 22.9% of patients treated with onabotulinum toxin A compared to 6.5% of those receiving placebo. On the treatment benefit scale, 60.8% of patients in the onabotulinum group reported a positive response compared to 29.2% of patients in the placebo group. Statistically significant differences between onabotulinum toxin A and placebo were noted for all of secondary endpoints (decreases from baseline at week 12 in mean micturition, urgency, and nocturia, as well as impact on patient health-related quality of life using I-QOL and KHQ). In summation, all of these high quality studies suggest that intradetrusor injection of onabotulinum toxin A for OAB treatment is associated with significant subjective and objective improvements in OAB refractory to oral medications.

## SIDE EFFECTS OF BOTULINUM

The most common adverse effects in trials for onabotulinum toxin A were urinary tract infection (UTI) and urinary retention necessitating clean intermittent catheterization. Systemic effects are rarely observed with lower urinary tract injection of onabotulinum toxin A. However, due to its paralytic mechanism, theoretical concerns for systemic adverse effects do remain. Rare cases of generalized weakness have been reported with 300 U of onabotulinum toxin A and the reported duration of such symptoms varies from two weeks to 2 mo<sup>[20]</sup>. Rates of UTI from published trials range from 3.6% to 54.5% with rates generally increasing in a dose dependent fashion<sup>[21]</sup>. In a more contemporary, phase III, double-blinded study, Nitti *et al*<sup>[19]</sup> reported an

overall UTI rate of 15.5% in the onabotulinum toxin A group in the first 12 wk of the injection. All UTIs were uncomplicated. In our practice, a prophylactic antibiotic is provided to the patient prior to the procedure. Urinary retention is quantified by measuring a post void residual (PVR) and the definition of an elevated PVR varies across studies, with most studies using a threshold of 150 mL. Although elevations in PVR do occur following this procedure, this does not necessitate self catheterization in all patients<sup>[17,22]</sup>. Similar to the rates of UTIs, rates of urinary retention increase in a dose dependent pattern, ranging from 5% to 21.2%. In their study of 278 randomized patients who received onabotulinum toxin A, Nitti *et al*<sup>[19]</sup> reported a PVR > 200 in 8.7% of patients with an overall rate of self catheterization of 6.1%. The duration of urinary retention is variable and the condition can persist for the duration of the effect of the drug as demonstrated by Visco *et al*<sup>[23]</sup>. In their study of women receiving 100 U of onabotulinum toxin, 5% of women were in retention at 2 mo, 3% at 4 mo and 1% at 6 mo. Furthermore, in patients requiring self catheterization, their QOL scores were comparable to those who did not need self catheterization<sup>[24]</sup>. In 2011, Kuo *et al*<sup>[25]</sup> investigated the risk factors of increasing adverse effects after onabotulinum toxin A injection in 217 patients with refractory idiopathic detrusor overactivity<sup>[25]</sup>. They performed a multivariate analysis and demonstrated that male gender and baseline PVR of > 100 mL were independent predictors of acute urinary retention. Further studies are needed to better define the risk factors predisposing patients to urinary retention and subsequent self catheterization. In patients receiving multiple onabotulinum toxin A injections, their risk for urinary retention remains stable over subsequent injections. Of patients who had a successful first injection, 87% had another retention-free result after their second injection<sup>[26]</sup>. As our population is aging and due to the considerable cognitive side effects of antimuscuranics, onabotulinum toxin A injection serves as a reasonable alternative in these patients; however, the question arises whether this therapy is safe in the elderly? White *et al*<sup>[27]</sup> investigated this question and showed that this onabotulinum toxin A therapy is safe and effective in the elderly<sup>[27]</sup>. In 21 patients with a mean age of 81.2 years, they found that after a single 200 U intradetrusor injection, 76% of patients showed a positive clinical response with no treatment related complications. Liao *et al*<sup>[28]</sup> performed a larger study in 2013, and subdivided 166 patients into three groups: Frail elderly (61), elderly without frailty (63) and younger than 65 years (42)<sup>[28]</sup>. Frail elderly was defined as age greater than 65 years and 3 or more of these criteria: Unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and/or low physical activity. Even though they reported a lower long term success and higher PVR in the frail elderly group, they concluded that the safety and efficacy of the therapy was similar between elderly patients without frailty and younger patients. Based on these

above studies, age in itself should not be a deterrent for receiving onabotulinum toxin A injection therapy. Lastly, there have been reports of onabotulinum toxin A resistance in a small percentage of patients undergoing repetitive treatment for non-urolological conditions<sup>[29]</sup>. Concerns of treatment resistance and the role of antibody formation are currently being investigated.

## SUMMARY

OAB remains a highly prevalent and frequently, a recalcitrant constellation of symptoms. For patients who are refractory to oral medical therapy, there is sufficient level I evidence to support the use of onabotulinum toxin A injection therapy. It is a safe and very effective 2<sup>nd</sup> line treatment for OAB, even in the elderly population. The suggested FDA-approved dose is 100 U to maximize the benefits and minimize the adverse effects of this therapy. Risks of the intradetrusor injection of onabotulinum toxin A include UTI, increased PVR, urinary retention which may lead to necessity of self catheterization for a period of time.

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