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# Does Treatment With OnabotulinumtoxinA Improve the Quality of Life in Patients With Urinary Incontinence Not Adequately Controlled With Anticholinergics?

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**Does Treatment With OnabotulinumtoxinA Improve The Quality  
Of Life In Patients With Urinary Incontinence Not Adequately  
Controlled With Anticholinergics?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not treatment with onabotulinumtoxinA improves the quality of life in patients with urinary incontinence not adequately controlled with anticholinergics.

**STUDY DESIGN:** Review of three English language, randomized controlled trials published in 2013.

**DATA SOURCES:** Randomized, double-blind, controlled clinical trials comparing onabotulinumtoxinA intradetrusor injections with saline placebo. All articles were found using PubMed.

**OUTCOMES MEASURED:** Each of the three trials assessed the patient's quality of life after treatment with onabotulinumtoxinA using the following assessment tools: Incontinence Quality of Life Questionnaire (I-QOL), Modified Overactive Bladder Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ), King's Health Questionnaire (KHQ), Patient Global Assessment (PGA), and Treatment Benefit Scale.

**RESULTS:** Both the Chancellor et al. and the Sussman et al. studies found a statistically significant improvement in the change from baseline in the I-QOL and OAB-PSTQ for the patients who received onabotulinumtoxinA compared to placebo ( $p$  value  $< 0.001$ ). Nitti et al. demonstrated an improvement range of 19.6 to  $23.9 \pm$  SD change from baseline in the I-QOL score for the onabotulinumtoxinA treatment group. 60.8% of the experimental group in Nitti et al. reported a positive treatment response after onabotulinumtoxinA while only 29.2% of placebo patients reported this response ( $p$  value  $< 0.001$ ). Sussman et al established an inverse correlation between I-QOL total scores and UI frequency with a Pearson's correlation coefficient of -0.508 at week 12 establishing that decreased frequency in urinary incontinence events are associated with improved quality of life.

**CONCLUSIONS:** Based on the three trials, onabotulinumtoxinA does improve quality of life in patients with urinary incontinence not adequately controlled with anticholinergics by improving patient satisfaction with treatment, urinary incontinence symptoms, and healthcare related quality of life.

**KEY WORDS:** Urinary incontinence, Overactive bladder, OnabotulinumtoxinA

## INTRODUCTION

Urinary incontinence (UI) is a condition in which there is an involuntary loss of urine and includes the classifications of stress, urge, overflow, and mixed incontinence. Urge incontinence, which is also known as overactive bladder (OAB), is detrusor overactivity that results in uninhibited bladder contractions and subsequent leakage of urine.<sup>1</sup> This paper evaluates three randomized, double blind, controlled trials comparing the efficacy of onabotulinumtoxinA for improving overall health related quality of life (HRQOL) in patients who have uncontrolled urge incontinence.

Overactive bladder is a disorder that is quite common in the medical field. The incidence of urge urinary incontinence in the US is 2.6-14.2% in men and 8.9-36.3% in women with increasing incidence in females, increased age, increased BMI, and limited physical activity.<sup>1,2</sup> Incidence is expected to increase from 11.6% in 2013 to 23.6% in 2018.<sup>2</sup> The estimated total national cost for urge urinary incontinence is \$65.9 billion annually and is expected to increase due to the aging population.<sup>2</sup> Overall, the mean annual cost of care for individual incontinence management is \$751.<sup>3</sup> The exact number of healthcare visits is unknown due to the fact that many patients do not report symptoms of urge urinary incontinence to their medical providers due to reasons such as embarrassment and lack of knowledge.

Symptoms of OAB include an intense urge to urinate, leakage of urine, and nocturia. The etiology of urge incontinence is typically idiopathic but it can be also be contributed to bladder stones, bladder tumors, urinary tract infections, central nervous system lesions, or nerve injury.<sup>1</sup> These symptoms can have a profound impact on a patient's life causing patients to avoid social situations, feel embarrassment, and prevent them from performing various activities.

There are various methods that are utilized in order to treat urge incontinence. Lifestyle modifications such as weight loss and caffeine reduction are helpful in patients whose symptoms are minor. Kegel exercises with or without biofeedback can be done frequently to strengthen pelvic floor muscles, thus providing support and strength for the detrusor muscles.<sup>1</sup> Bladder training or prompted voiding are other methods to alleviate symptoms. The mainstay of drug therapy is antimuscarinic oral therapy, which is available in either short acting or long acting formulations. Examples of such anticholinergic treatment are Tolterodine or Oxybutynin taken 2-3 times per day<sup>1</sup>. Other treatment includes onabotulinumtoxinA injections in the detrusor muscle, which is considered alternative treatment for refractory cases. Adjunctive therapy such as alpha blockers and topical estrogens can also be utilized for effective treatment.<sup>1</sup> If all of the aforementioned treatment fails, surgery and nerve stimulation can be performed.

There are various severities associated with urge urinary incontinence and the treatment options mentioned above have all been proven to be effective treatments. Besides anticholinergic medications, there are limited pharmacological options for urinary incontinence. Intradetrusor injections of onabotulinumtoxinA has been utilized as an effective treatment for patients who have not had success with anticholinergic treatment. Its effects and efficacy have been thoroughly studied and continue to be monitored, leading to the rise of its utilization in treatment for OAB patients.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not treatment with onabotulinumtoxinA improves the quality of life in patients with urinary incontinence not adequately controlled with anticholinergics.

## **METHODS**

An established criteria was utilized for the selection of each study. The chosen population was males and females 18-80 years old diagnosed with overactive bladder whose symptoms were not adequately managed with anticholinergic drug therapy. The common intervention among all studies was intradetrusor injections of onabotulinumtoxinA in dosages of either 100, 200, or 300 units. Patients received either 1 mL of onabotulinumtoxinA for 30 intradetrusor injections or 0.5 mL for 20 intradetrusor injections. Comparisons were made between the treatment group who received onabotulinumtoxinA and the experimental group of patients who received a placebo of normal saline administered via cystoscopy or intradetrusor injection. The outcomes that were measured were the impact of onabotulinumtoxinA on the patient's health related quality of life (HRQOL) and overall patient satisfaction with treatment.

All 3 studies were randomized, double blind, placebo controlled clinical trials (RCT). Each article was published in a peer-reviewed journal and in the English language. Key words that were utilized in searching include "urinary incontinence", "overactive bladder", and "onabotulinumtoxinA". Data sources for the systematic review were selected from PubMed by the author throughout December of 2013. Articles were selected based on their relevance to the author's clinical question and if they included patient oriented outcomes (POEM). Inclusion criteria included RCTs that were published after 2007 and patients greater than 18 years old with overactive bladder. Exclusion criteria included patients less than 18 years old and patients whose overactive bladder symptoms were controlled by anticholinergic therapy. A summary of the statistics reported or used in the 3 RCTs include control event rate (CER), experimental event rate (EER), relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), Pearson's coefficient, confidence interval (CI), and p-values.

**Table 1:** Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Chancellor <sup>4</sup> (2013)	RCT	416	18-80	-Age 18-80 years old with multiple sclerosis or spinal cord injury who had $\geq 14$ urinary incontinence episodes/wk due to neurogenic detrusor overactivity -Symptoms not adequately controlled by anticholinergics	-Patients with pelvic or urologic abnormalities -Previous botulinum toxin therapy for urologic conditions -Symptoms adequately controlled by anticholinergics	17	30 intradetrusor injections (1 mL each) of onabotulinumtoxinA 200 or 300 U
Nitti <sup>5</sup> (2013)	RCT	557	$\geq 18$	- $\geq 18$ years old with idiopathic overactive bladder - $\geq 3$ urgency urinary incontinence episodes in a 3 day period - Average $\geq 8$ micturitions/day - Symptoms not adequately controlled by anticholinergics	-Patients with a predominance of stress incontinence -Post void residual urine volume $\leq 100$ mL -Patients unwilling to perform clean intermittent catheterization if required	65	20 intradetrusor injections (0.5 mL each) of onabotulinum toxinA 100 U
Sussman <sup>6</sup> (2013)	RCT	275	18-80	-Age 18-80 years old with multiple sclerosis or spinal cord injury who had $\geq 14$ urinary incontinence episodes/wk due to neurogenic detrusor overactivity -Symptoms not adequately controlled by anticholinergics	-History of or current bladder conditions -Any surgeries that could affect bladder function -Previous botulinum toxin therapy for urologic conditions -24-hour total voided volume $> 3,000$ mL -Post-void residual $> 200$ mL	0	30 intradetrusor injections (1 mL each) of onabotulinum toxinA 200 or 300 U

## OUTCOMES MEASURED

All outcomes that were measured were those of patient-oriented evidence (POEM) and were collected via patient-reported questionnaires. For all 3 randomized clinical trials, questionnaires were filled out by patients repeatedly throughout the study at various post-treatment visits. Statistical analysis was performed on the intent-to-treat population.

In both the Chancellor et al study and the Sussman et al study, the Incontinence Quality of Life Questionnaire (I-QOL), the Modified Overactive Bladder Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ), and the Patient Global Assessment (PGA) were utilized.<sup>4,6</sup> I-QOL is a 22 item questionnaire that assesses the impact of UI on a patient's life. Scores range from 0-100 with higher scores reflecting better quality of life.<sup>4,6</sup> Included in this questionnaire are the three other domain scores of avoidance and limiting behavior, psychosocial impact, and social embarrassment.<sup>4,6</sup> OAB-PSTQ consists of 12 questions scored on a 6-point scale with lower scores reflecting greater satisfaction with treatment which assesses a medication's impact on OAB symptoms, ability to interact in social situations, and cost.<sup>4,6</sup> PGA is a scale that assesses patient's symptoms, quality of life, activity limitations, and overall emotions related to urinary incontinence.<sup>6</sup> Each item is scored on a scale from -7 (a very great deal worse) to +7 (a very great deal better).<sup>6</sup>

In the Nitti et al study, the King's Health Questionnaire (KHQ), the Treatment Benefit Scale (TBS), and the I-QOL were utilized to assess patient's overall satisfaction with treatment and quality of life. KHQ assesses a patient's perception of quality of life with UI, yielding two scores that were calculated using a series of formulas, with lower scores indicating better HRQOL.<sup>5</sup> Part 1 assesses the patient's general health and incontinence impact while part 2 assesses quality of life, including physical and social limitations, relationships, emotions, sleep,

and severity.<sup>5</sup> TBS assesses a patient's perception of treatment benefit by rating the progress of their condition as either greatly improved, improved, not changed, or worsened.<sup>5</sup>

## RESULTS

In the 2013 study by Chancellor et al<sup>4</sup>, 407 patients with urinary incontinence received treatment with either 200 U onabotulinumtoxinA (n=135), 300 U onabotulinumtoxinA (n=132), or a placebo of 0.9% saline (n=149), with 399 patients remaining at the end of the 12 week study (98%). No differences in efficacy were established between the two doses of onabotulinumtoxinA.<sup>4</sup> Specifically, these patients had either multiple sclerosis or spinal cord injury, which contributed to their urinary incontinence, and had no other pelvic or urologic abnormalities nor prior treatment with botulinum toxin therapy. Based on the I-QOL Questionnaire, there was a significant improvement in scoring, with a large percentage of patients having a  $\geq 11$  point increase from baseline after treatment with onabotulinumtoxinA as compared to placebo (p value < 0.001). The domain scores of avoidance/limiting behavior, psychosocial impact, and social embarrassment also showed marked improvement after treatment with onabotulinumtoxinA as compared to placebo (p value < 0.001, 95% CI). In relation to the OAB-PSTQ, improvement was shown by an increase in total scoring after treatment with onabotulinumtoxinA. At the start of the trial, 45% of all the patients classified themselves as being somewhat or very satisfied with their current therapy, with this number increasing to 75% in the experimental group after treatment with onabotulinumtoxinA (see Table 2). Only 45% of patients at week 6 and 30% of patients at week 12 reported this level of satisfaction in the placebo group. The PGA revealed that patients who received the placebo

**Table 2: Improvement of patient satisfaction and quality of life after treatment with onabotulinumtoxinA**

<i>CER</i>	<i>EER</i>	<i>RBI</i>	<i>ABI</i>	<i>NNT</i>	<i>P-value</i>
45%	75%	66.7%	30%	4	<0.001

showed no change in overall symptoms, QOL, activity limitations, or overall emotions while the experimental group with onabotulinumtoxinA reported improvements over time (p value  $\leq$  0.001).<sup>4</sup>

Of the 557 randomized patients in the Nitti et al study<sup>5</sup>, 89% of patients who received 100 U of onabotulinumtoxinA and 88% of patients who received 10 mL saline placebo completed the trial. Overall, the patients had a mean duration of 6.7 years of OAB, an average use of 2.4 years worth of 2.5 anticholinergics prior to the study, and an average of 5.3 episodes of UI. Nitti et al established that there was a statistically significant difference between onabotulinumtoxinA and placebo.<sup>5</sup> Per the Treatment Benefit Scale, 60.8% of the experimental group reported a positive treatment response after onabotulinumtoxinA while only 29.2% of placebo patients reported this response (p value  $<$  0.001) (See Table 3). The Incontinence Quality of Life Questionnaire and the King's Health Questionnaire showed large, clinically significant improvements in all domains after onabotulinumtoxinA compared to placebo treatment (p value  $<$  0.001, 95% CI). There was an improvement range of 19.6 to 23.9  $\pm$  SD change from baseline in the I-QOL score for the onabotulinumtoxinA treatment group and only a 6.1-7.3  $\pm$  SD change from baseline for the placebo group. Similar improvements were noted in

<b>Table 3: Improvement of patient satisfaction and quality of life after treatment with onabotulinumtoxinA</b>					
<i>CER</i>	<i>EER</i>	<i>RBI</i>	<i>ABI</i>	<i>NNT</i>	<i>P-value</i>
29.2%	60.8%	108.2%	31.6%	4	$<$ 0.001

the KQH. Adverse effects were limited and most often occurred within the first 12 weeks of the study. 15.5% of onabotulinumtoxinA patients and 5.9% of placebo contracted an uncomplicated urinary tract infection not involving the upper urinary tract. Other complications from the

onabotulinumtoxinA group included dysuria (12.2%), bacteriuria (5.0%), and urinary retention (5.4%). Discontinuation rate due to adverse effects was 1.8% for the onabotulinumtoxinA group and 1.4% for the placebo group. One death from the placebo group was reported but was unrelated to the treatment in this study.<sup>5</sup>

In the study by Sussman et al.<sup>6</sup>, 275 patients with either multiple sclerosis or spinal cord injury were randomized, with 92 receiving an intradetrusor placebo, 92 receiving 200 U of onabotulinumtoxinA, and 91 receiving 300 U of onabotulinumtoxinA. Both doses of onabotulinumtoxinA effectively reduced episodes of urinary incontinence, deeming no differences in efficacy between the two doses of 200 U and 300 U. For both doses of the experimental group of onabotulinumtoxinA, there was a significantly greater mean improvement in I-QOL total score (p value < 0.001) as well as in the domain scores for avoidance/limiting behavior, psychosocial impact, and social embarrassment (p value < 0.01) compared to the placebo group. An inverse correlation between I-QOL total scores and UI frequency (Pearson's correlation coefficient at week 6 being -0.483 and -0.508 at week 12) established that decreased frequency in urinary incontinence events were associated with improved quality of life. The OAB-PSTQ also showed an overall improvement in total score compared to baseline for the onabotulinumtoxinA group versus placebo (p value < 0.001). This questionnaire also reported that a greater percentage of patients post onabotulinumtoxinA treatment reported being "somewhat" or "very" satisfied with treatment and having "significantly met" or "exceeded" expectations for their treatment compared to placebo (p value < 0.001) (see Table 4).

<b>Table 4: Improvement of patient satisfaction and quality of life after treatment with onabotulinumtoxinA</b>					
<i>CER</i>	<i>EER</i>	<i>RBI</i>	<i>ABI</i>	<i>NNT</i>	<i>P-value</i>
39.5%	77.5%	96.2%	38%	3	<0.001

81.9% of patients receiving placebo by week 12 reported no side effects while only 62.0%-63.5% of the onabotulinumtoxinA patients reported no side effects. Similar findings from the Patient Global Assessment showed that the patients receiving onabotulinumtoxinA reported improvement in quality of life than those who received placebo.<sup>6</sup>

## DISCUSSION

The goal of this systemic review was to determine whether or not onabotulinumtoxinA improves the quality of life in patients who have urinary incontinence, specifically overactive bladder whose symptoms were not adequately controlled with anticholinergic treatment. Urinary incontinence is an emotionally debilitating condition that has profound effects on a person's quality of life due to embarrassment, fear of UI episodes occurring in public, as well as due to added medical complications and costs. Therefore, adequate treatment is significantly correlated with regards to quality of life. Due to the fact that there are few pharmacological treatments besides anticholinergics for overactive bladder, it is important to establish that onabotulinumtoxinA causes a statistically significant improvement in quality of life. All three randomized controlled trials were able to establish this correlation between onabotulinumtoxinA and quality of life.

OnabotulinumtoxinA, brand name Botox in the United States, is an FDA approved neurotoxin that is produced by the anaerobic bacillus *Clostridium botulinum*.<sup>7</sup> Its mechanism of action is that it prevents the release of acetylcholine, producing a state of denervation.<sup>7</sup> Specifically, onabotulinumtoxinA targets the efferent pathways of detrusor activity as well as various targets in the bladder wall that may contribute to overactive bladder.<sup>5</sup> Its uses are indicated for bladder dysfunction, including detrusor overactivity and overactive bladder, blepharospasm, cervical dystonia, chronic migraines, focal spasticity, strabismus, primary

axillary hyperhidrosis, and for cosmetic uses to reduce facial lines.<sup>7</sup> There is a black box warning due to the potential of the toxin to spread beyond the area of injection within hours to weeks after injection, leading to toxin effects, including potentially fatal swallowing and breathing difficulties.<sup>7</sup> A three day discontinuation of antiplatelet therapy and three days worth of prophylactic antibiotic therapy should be given prior to and after the administration of intradetrusor onabotulinumtoxinA to decrease the risk of urinary tract infection.<sup>7</sup>

OnabotulinumtoxinA should not be administered via intradetrusor injection to any patient with a urinary tract infection, urinary retention, or in a patient with a post-void residual volume > 200 mL who is not utilizing self-catheterization.<sup>7</sup> OnabotulinumtoxinA is widely available in the US and is covered by most major insurance plans, including Medicare and Medicaid, with various programs available to help off-set any remaining out of pocket costs. Its use has been increasing in various specialties of medicine and as alternative treatment for many disorders.

There were various limitations to the RCTs utilized in this systematic review. Both Chancellor et al. and Sussman et al. used the PGA which is not a validated measure for patients with neurogenic detrusor overactivity due to spinal cord injury.<sup>4,6</sup> Another limitation was that the data utilized in Chancellor et al. cannot be generalized to patients with idiopathic overactive bladder.<sup>4</sup> Not all patients completed the OAB-PSTQ at each treatment visit by Sussman et al. which could subsequently alter their results.<sup>6</sup> For all studies, it was indicated that some patients needed to initiate clean-catch intermittent catheterization (CIC) because treatment with onabotulinumtoxinA has the potential to compromise bladder emptying. According to Chancellor et al., this did not have a negative impact on treatment benefit with onabotulinumtoxinA due to similar improvements in HRQOL assessments between patients who did and did not require CIC.<sup>6</sup>

## **CONCLUSION**

The results of the three randomized clinical trials demonstrated that treatment with onabotulinumtoxinA does improve the quality of life in patients with urinary incontinence not adequately treated with anticholinergics. Along with the clinical aspects of reduced weekly urinary incontinence episodes and improved urodynamics, patients reported increased treatment satisfaction and as well as treatment goal attainment, ultimately improving their quality of life and allowing them to live more fulfilled lives both emotionally and physically. An increasing number of recent studies have found similar findings and more studies are continuing to further explore the efficacy of onabotulinumtoxinA. Future exploration with onabotulinumtoxinA should involve other types of urinary incontinence such as stress or overflow. Further research is warranted to see if there is a synergistic effect between treatment with both onabotulinumtoxinA and anticholinergics.

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