



TITLE: Botulinum Toxin A for the Management of Pelvic Pain and Urinary Incontinence in Women: A Review of the Clinical-Effectiveness and Safety

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CONTEXT AND POLICY ISSUES:

Botulinum toxin type A (BTX-A) is a neurotoxin produced by the gram-positive anaerobic spore-forming organism *Clostridium botulinum*.¹ BTX-A is commercially available in North America under the brand name Botox® (Allergan, USA) and in Europe under the brand name Dysport® (Ipsen-Biotech, France).² These two formulations differ in potency and are not interchangeable.² Health Canada has approved BTX-A for use in cervical dystonia, blepharospasm associated with dystonia, strabismus, dynamic equinus foot deformity in pediatric patients with cerebral palsy, hyperhidrosis of the axilla, and focal spasticity.¹ However, BTX-A is often used off-label in a number of different conditions, many of which are urological. These include urinary incontinence caused by detrusor overactivity, and pelvic pain caused by interstitial cystitis or vulvodynia.^{3,4}

Detrusor overactivity occurs when the detrusor muscles in the bladder wall involuntarily contract causing urgency, frequency, urinary incontinence, and nocturia.⁵ Neurogenic detrusor overactivity is secondary to neurological disorders such as traumatic spinal cord injury or multiple sclerosis.³ Individuals with neurogenic detrusor overactivity often have difficulty emptying their bladder and require clean intermittent self-catheterization (CISC).² Idiopathic detrusor overactivity is not associated with neurological disorders.³ Patients with idiopathic detrusor overactivity do not usually have difficulty voiding, and do not usually require CISC.⁶ Conventional therapies for detrusor overactivity include lifestyle modification, bladder retraining, and the use of antimuscarinic medications.⁷ However, antimuscarinic medications are commonly associated with adverse effects including blurred vision, dry mouth, constipation, and urinary retention.⁸ Furthermore, some cases of detrusor overactivity are refractory to treatment with conventional therapies.⁸ In these cases, BTX-A has been used to induce detrusor paralysis and reduce the symptoms of bladder overactivity.⁶ BTX-A injections can be performed using a

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rigid cystoscope in a day-case or inpatient setting or using a flexible cystoscope in an outpatient setting.²

Generalized vulvodnia is a type of vulvar pain characterized by unprovoked, constant, burning pain involving most of the vulva (labia majora, labia minora, clitoris, and often the vestibule).⁹ It occurs in the absence of relevant visible infectious, inflammatory, or neoplastic findings or neurologic disorder.¹⁰ Vestibulodynia refers to a specific type of vulvar pain characterized by severe pain upon vestibular touch or attempted vaginal entry, tenderness to pressure localized within the vulvar vestibule, or physical findings limited to vestibular erythema.¹¹ Although the etiology of vulvodnia remains unclear, hypotheses involving neuropathic pain, neural hyperplasia, neurogenic inflammation, abnormal perception of pain, and pelvic floor dysfunction have all been proposed.¹² Treatment options include pelvic floor exercises and biofeedback, medical treatment with tricyclic antidepressants, topical anesthetics, local steroidal injections, or excision surgery of the vulva.^{9,10,13} There is no consensus as to which modality should be offered as first-line therapy because few long-term prospective studies exist.¹²

Interstitial cystitis (also known as painful bladder syndrome) is a chronic inflammatory condition of the bladder that causes pelvic pain and irritable bladder dysfunction (including urinary frequency and urgency) in the absence of any other identifiable pathology such as urinary tract infection, bladder carcinoma, or radiation cystitis.¹⁴ Oral treatment options include bladder surface mucin analogues, antihistamines, narcotics, tricyclic antidepressants and anticonvulsants.¹⁴ Intravesical therapy with agents such as heparin sulphate or dimethylsulfoxide is usually used second-line.¹⁴ However, improvements in bladder capacity, frequency, urgency, and pain are sometimes limited with conventional treatment options.¹⁴

Using medications for unapproved indications often raises questions about the clinical benefits and harms relative to other treatment options. This report will review the evidence for clinical effectiveness of BTX-A for the management of urinary incontinence and pelvic pain related to motor vehicle accidents, vulvodnia, or interstitial cystitis in women.

RESEARCH QUESTIONS:

1. What is the clinical-effectiveness and safety of botulinum toxin A for the management of urinary incontinence in women?
2. What is the clinical-effectiveness and safety of botulinum toxin A for the management of pelvic pain associated with motor vehicle accidents, vulvodnia, or interstitial cystitis in women?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and April 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), controlled clinical trials, observational studies, and safety data. This search was supplemented by hand searching the bibliographies of selected papers.

Several systematic reviews and RCTs assessing the use of BTX-A in the management of urinary incontinence were retrieved in the literature search. As a result, only results from relevant systematic reviews and RCTs were included for this research question.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs, controlled clinical trials, and observational studies.

SUMMARY OF FINDINGS:

Three systematic reviews^{2,15,16} and six RCTs¹⁷⁻²² were identified assessing BTX-A for the management of urinary incontinence as a result of detrusor overactivity. Three observational studies²³⁻²⁵ were identified assessing the use of BTX-A for the management of vulvodynia. Four observational studies²⁶⁻²⁹ were identified evaluating BTX-A for the management of interstitial cystitis. No health technology assessments or controlled clinical trials were identified for the indications of interest. No literature was identified assessing the use of BTX-A for the management of pelvic pain associated with motor vehicle accidents.

Health technology assessments

No literature identified.

Systematic reviews

Urinary incontinence due to detrusor overactivity:

A systematic review (2008) examined the efficacy and safety of intradetrusor injections with BTX-A in adults with neurogenic detrusor overactivity and urinary incontinence or overactive bladder symptoms of neurogenic origin.² A literature search for clinical studies fully published between 1993 and March 2007 was used to select reports for inclusion. A total of 18 clinical studies (two RCTs, 16 open-label observational studies) in a total of 678 patients (percentage of women not specified) were selected. Only studies evaluating Botox[®] were included. Overall, a 300 unit (U) dose of BTX-A was most commonly used (11 studies). The remaining studies used doses of 200 U (two studies), between 200 U and 300 U (three studies), between 100 U and 300 U (one study), and 400 U (one study). Follow-up ranged from 12 weeks to 36 weeks, except for two studies evaluating the impact of repeated injections which followed patients for two to four years.

One RCT (n=59; 36 males, 23 females) noted statistically significant improvements versus placebo in the number of incontinence episodes, quality of life, and urodynamic parameters within two weeks after a BTX-A injection at a dose of 200 U or 300 U.²¹ The 200 U dose appeared to be as effective as the 300 U dose for all outcome parameters. However, no definitive conclusions could be made regarding the optimal dose as the trial was not powered to compare the different doses. Maximum improvements were reached between two and six weeks and were maintained throughout the 24 week study period. Several open-label case series supported this finding. Up to 26 weeks after BTX-A injection, the percentage reduction in the mean number of daily incontinence episodes (between CISC) from baseline was approximately 60% to 80%. Furthermore, between 42% and 87% of patients became completely continent between CISC following treatment with BTX-A. The mean number of daily frequency episodes was also reduced from baseline by approximately 40% to 60%. The decrease in frequency and urinary incontinence was associated with an improvement in the

patient's quality of life by 35% to 65% versus baseline. Two long-term, open-label observational studies suggested that the beneficial effects of intradetrusor injections of BTX-A may last up to 36 weeks. The second included RCT (n=75; percentage of women not specified) found intradetrusor BTX-A at a dose of 300 U to be statistically significantly superior to resiniferatoxin (a capsaicin analogue) for reducing the maximum pressure of uninhibited detrusor contractions in patients with spinal cord injury and refractory detrusor overactivity.³⁰ With both treatments there was a significant reduction in the number of episodes of incontinence at six, 12 and 24 months when compared to baseline. No local adverse effects were detected with either treatment.

Four open-label observational studies evaluating the impact of BTX-A on the use of other drugs showed that antimuscarinic agents could be discontinued in 28% to 58% of patients. In most other patients, the dose of antimuscarinics could be reduced. BTX-A appeared to be well tolerated in all 18 studies, although the occurrence of local or systemic adverse effects was poorly reported. The most frequent adverse effects were injection site pain, procedure-related urinary tract infections (in 2% to 32% of patients) and mild hematuria (in 2% to 21% of patients). In some cases, an increase in post-void residual volume resulted in urinary retention (0% to 33% of patients) and the need for CISC (6% to 88% of patients). However, the majority of patients were already having difficulty emptying their bladder and were already using CISC. Systemic adverse effects like muscle weakness were not reported.

The authors concluded that BTX-A injections into the detrusor were well tolerated and provided clinically significant improvements in adults with neurogenic detrusor overactivity refractory to antimuscarinics.

The Cochrane Incontinence Group published a systematic review (2007) comparing intravesical BTX injection with other treatments for neurogenic or idiopathic overactive bladder in adults.¹⁵ A literature search for RCTs or quasi-RCTs in the English language was used to select reports for inclusion. Seven RCTs (n=223) evaluating the management of idiopathic (two trials; n=45), neurogenic (four trials; n=164), or either neurogenic or idiopathic (one trial; n=14) overactive bladder syndrome in adults (percentage of women not specified) with BTX-A (brand not specified) were included in the report. One crossover RCT evaluating the clinical effectiveness of BTX-B in twenty adults with idiopathic or neurogenic overactive bladder was also included. Generally, the studies reported superiority of BTX-A when compared with placebo for improvements in the number of incontinence episodes, bladder capacity, maximum detrusor pressure, and quality of life. The authors stated that overall, low doses of BTX-A (100 U to 150 U) appeared to have beneficial effects, but some studies indicated that higher doses (300 U) may be more clinically effective. One RCT (n=59; 36 males, 23 females) showed that a single intravesical injection of BTX-A given at a dose of 200 U or 300 U (Botox[®]) statistically significantly reduced incontinence episodes in patients with neurogenic detrusor overactivity when compared with placebo for up to 24 weeks with a corresponding improvement in quality of life.²¹ Another RCT (n=25; 18 males, 7 females) reported a statistically significant decrease in daily urinary incontinence episodes when 300 U BTX-A (brand not specified) was compared with intravesical resiniferatoxin in patients with refractory neurogenic detrusor overactivity at 12 and 18 months following treatment.²² No local adverse effects were reported for BTX-A or resiniferatoxin. However, there was a significant rise in post-void residual volume when BTX-A was compared to placebo²¹ or resiniferatoxin²² which increases the risk for urinary tract infection or requirement for CISC. The population in the included studies showed a wide range of variation in their requirements for CISC prior to treatment. This makes it difficult to quantify the risks associated with BTX-A.

The authors concluded that although intravesical BTX-A shows promise as an alternative therapy for overactive bladder symptoms, there are too few controlled trials on comparative safety and efficacy relative to other interventions or placebo to support routine use. Furthermore, the authors noted that available trial data could not be used to determine the optimal dose of BTX-A for efficacy and safety. Three^{21,22,31} of the eight included RCTs were full publications. Details of study methodology (including details for allocation concealment and blinding) in the remaining five abstracts as well as some of the full publications were unclear. All included studies were of small size ranging from 14 to 50 patients. The length of follow-up varied from six weeks to 24 months making long-term durability, effectiveness, and safety of BTX-A unclear.

MacDonald et al. conducted a systematic review (2007) specifically evaluating the effectiveness and adverse effects of BTX (brand not specified) for the treatment of urinary incontinence related to detrusor overactivity.¹⁶ A literature search for RCTs published between 1966 and October 2006 in the English language was used to select reports for inclusion. Three RCTs (n=104; 45% women) studying the clinical effectiveness of BTX-A^{21,22} or BTX-B³¹ for the management of patients with urinary incontinence caused by detrusor overactivity refractory to antimuscarinic treatment were included. These were the same three studies that were identified as the only full publications in the Cochrane systematic review¹⁵. Based on findings from these three trials, the authors concluded that BTX may be an effective and relatively safe treatment option for temporarily reducing urinary incontinence in patients with refractory detrusor overactivity. The authors noted, however, that evidence to support optimal dosing and the long-term efficacy and safety is lacking and requires the conduct of larger RCTs using standardized and validated clinical outcome measures.

Randomized controlled trials

We considered the three systematic reviews a reliable estimate of the body of literature concerning the clinical effectiveness and safety of BTX-A for the management of urinary incontinence due to detrusor overactivity. Four RCTs published subsequent to these reports are summarized.

Urinary incontinence due to idiopathic detrusor overactivity:

In a multicenter, double-blind, placebo-controlled RCT, Brubaker et al. compared 200 U dose of intradetrusor BTX-A (Botox[®]) with placebo in 43 women with refractory idiopathic urge incontinence.¹⁷ All participants were followed for a maximum of 13 months. There were no significant differences in baseline demographic characteristics between the two groups. Results showed that 60% of women who received BTX-A had a clinical response based on the Patient Global Impression of Improvement (PGI-I) score. The mean PGI-I score two months after the initial injection was significantly better in the BTX-A group (2.7 versus 4.0 with placebo, p=0.003). The median duration of response in the BTX-A group was 373 days which was statistically significantly longer than the placebo group median duration of response which was 62 days (p< 0.0001). The rates of increased post-void residual volume (43%) and urinary tract infection resulting in the requirement for CISC in those with increased post-void residual volume (75%) in the BTX- group exceeded expected ranges. Urinary tract infections developed in twice as many subjects in the BTX-A group when compared to the placebo group (44% versus 22%). As a result, further injections were halted after 43 patients were randomized (28 in the BTX-A group and 15 in the placebo group). The authors concluded that local injection of 200 U BTX-A

was an effective and durable treatment for refractory urge incontinence in women with idiopathic detrusor overactivity. However, due to a high rate of high post-void residual volume and initiation of CISC observed in the study, the authors noted that BTX-A should be used with caution in this patient population.

Sahai et al. studied the clinical effectiveness and safety of BTX-A for the management of refractory idiopathic detrusor overactivity in a randomized, placebo-controlled, double-blind study.¹⁸ Participants (15 males and 19 females) were randomized to 200 U BTX-A (Botox[®]) or placebo. Follow-up occurred at 4 and 12 weeks after injection, at which point the study was unblinded. Further follow-up in the BTX-A group occurred at 24 weeks. Baseline characteristics between groups were comparable except for more severe urgency, less concomitant anticholinergic use, and a lower post-void residual volume in the BTX-A group. BTX-A was statistically significantly superior when compared to placebo for improving urge incontinence episodes at four and 12 weeks ($p=0.03$ and $p=0.008$, respectively). Statistically significant improvements were also noted for frequency, urgency, cystometric capacity, and quality of life in patients treated with BTX-A compared to placebo. Of the six patients in the BTX-A group taking antimuscarinics, five were able to discontinue them, compared with none in the placebo group. No statistics were reported on this difference. The extension study showed that statistically significant improvements in urge incontinence, frequency, urgency, quality of life, and cystometric capacity were maintained for at least 24 weeks in patients who received BTX-A compared to placebo. In patients receiving BTX-A, post-void residual volume increases were statistically significant at four weeks ($p=0.024$ versus placebo) but became non-significant by 12 weeks ($p=0.46$ versus placebo). A total of six patients in the BTX-A group required CISC. Symptomatic urinary tract infections developed in seven patients (six of which were performing CISC). No patients experienced acute urinary retention (defined as the complete inability to pass urine), or generalized muscle weakness. The authors concluded that BTX-A at a dose of 200 U is safe and effective for idiopathic detrusor overactivity but careful patient counseling is necessary especially concerning the possible need for CISC.

Urinary incontinence due to neurogenic detrusor overactivity:

In a placebo-controlled double-blind study, Ehren *et al.* studied the effect of BTX-A on the use of antimuscarinic therapy, bladder compliance, continence, and quality of life in 31 patients (17 males, 14 females) with incontinence due to neurogenic detrusor overactivity.¹⁹ Patients were randomized to receive intravesical injections of either 500 U BTX-A (Dysport[®]) or placebo and were followed for 26 weeks. There were no statistically significant differences in baseline characteristics between the two groups. Patients in the BTX-A group had a significantly lower intake of antimuscarinics throughout the study compared to those in the placebo group ($p=0.003$). Patients in the BTX-A group had statistically significant improvements in frequency of urinary incontinence, cystometric capacity, and quality of life when compared to placebo up to 26 weeks after treatment. No adverse effects related to treatment with BTX-A were observed. The authors concluded that intravesical injection of 500 U of BTX-A in patients with neurogenic detrusor overactivity is effective for reducing use of oral antimuscarinics, reducing the frequency of urinary incontinence, and improving quality of life.

Schurch et al. evaluated the impact of BTX-A on health-related quality of life in 56 patients (33 males, 23 females) with refractory neurogenic urinary incontinence in a randomized, placebo-controlled double-blind study.²⁰ Patients were randomized to BTX-A at a dose 200 U or 300 U (Botox[®]) or placebo. Incontinence Quality of Life questionnaire (I-QOL) scores at screening and after treatment at weeks two, six, 12, 18 and 24 were recorded. At screening, median total I-

QOL scores were similar for all three treatment groups. All patients were performing regular CISC but were incontinent between catheterizations. Median I-QOL scores increased significantly from screening with either dose of BTX-A for up to 24 weeks compared with placebo. No treatment-related adverse events were reported. The authors concluded that BTX-A significantly improves urinary incontinence-associated health-related quality of life in patients with neurogenic urinary incontinence.

Controlled clinical trials

No literature identified.

Observational studies

Vulvodynia:

Yoon et al. injected 20 U of BTX-A (Botox[®]) into the vestibule, levator ani muscle or the perineal body in seven women with pain that was refractory to conventional pain management.²³ The time interval to the first assessment was two weeks, with a repeat injection of 40 U if the first treatment was not successful. All procedures were performed at an outpatient clinic. Of the seven women, five required a second injection. The mean visual analog pain scale (VAS) score improved from 8.3 to 1.4 and none of the women experienced a recurrence during a mean follow-up period of 11.6 months. No significant bleeding, infection, muscle paralysis, voiding difficulty, bowel problems or other BTX-related complications were observed. The authors concluded that BTX-A appears useful and safe for managing vulvodynia of muscular or neuroinflammatory origin. However, the women treated in this study were a heterogeneous group with a variety of diagnoses in addition to vulvodynia.

Dykstra et al. examined the effect of BTX-A in 12 women with provoked vestibulodynia in an open-label dose-escalation pilot study.²⁴ The primary outcome measure was scores obtained using the VAS. Secondary measures were improvements in quality of life and change in medication use. Seven women received a dose of 35 U BTX-A (Botox[®]) and were followed-up at 30 days, 12 weeks, or when the pain score returned to baseline. A second group of 12 women (seven from the first group and five new patients) were injected with 50 U of BTX-A (Botox[®]). The seven patients from the first group were injected with BTX-A when pain scores returned to baseline. Mean pain scores statistically significantly decreased in both BTX-A groups at 30 days (VAS reduced from 8.1 to 2.9 for 35 U, $p < 0.001$ and 7.4 to 1.8 for 50 U, $p < 0.001$). The improvement in pain lasted eight weeks after the injection of 35 U of BTX-A and 14 weeks after the injection of 50 U of BTX-A. No adverse effects from BTX-A injections were reported. All patients decreased the use of oral pain medications. However, only 25% of patients reported a significant improvement in quality of life upon follow-up. The authors reported that overall these findings indicated that pain of vulvar origin may be relieved using BTX-A injections.

In a case series by Brown et al., BTX-A injections into the pelvic floor muscles were assessed for the treatment of coital pain, pelvic floor tension, and vestibular hyperalgesia (increased sensitivity to pain) in two women with provoked vestibulodynia.²⁵ Both women received 20 U of BTX-A (brand not specified) at baseline and 40 U 12 weeks later. After 12 weeks, BTX-A reduced coital pain in one woman (15% reduction in VAS from baseline), but was ineffective in the other woman (3% reduction in VAS from baseline). Pelvic floor hypertonicity and variability were reduced in both women, but there was a negligible change in vestibular hyperalgesia. The

authors concluded that BTX-A injections may be effective in reducing coital pain in women with vestibulodynia but had little effect on vestibular hyperalgesia.

Interstitial cystitis:

Giannantoni et al. conducted a pilot study evaluating the efficacy and tolerability of BTX-A intravesical injections in patients with interstitial cystitis refractory to conventional treatment modalities.²⁶ Twelve women and two men were injected with 200 U of BTX-A (Botox®). Assessments of voiding charts, VAS pain scores, and urodynamics were performed at baseline, one month, and three months after treatment. Overall, 12 patients (85.7%) reported subjective improvement in painful bladder symptoms. Three months after injection, the mean VAS score was statistically significantly lower when compared to baseline ($p < 0.01$). Furthermore, statistically significant improvements in the maximum cystometric bladder capacity and the mean daytime and nighttime urinary frequencies were also noted relative to baseline. Twenty-four hours after BTX-A treatment, two patients (one man and one woman) reported incomplete bladder emptying and needed CISC. However, no systemic adverse effects were noted during or after treatment. One month after treatment, BTX-A impaired detrusor contractility in six of 14 patients, even though it was administered submucosally. At five months after treatment, bladder pain had recurred in 10 of 14 patients and one of the two patients who reported incomplete bladder emptying 24 hours after treatment still required CISC. The authors concluded that intravesical BTX-A injections were effective in the short-term management of interstitial cystitis.

The same authors evaluated the one-year efficacy and tolerability of BTX-A in patients with painful bladder symptoms refractory to conventional treatments.²⁷ Three men and 12 women were injected with 200 U of BTX-A (Botox®). Patients were assessed one, three, five, and 12 months after treatment. Overall, 13 patients (86.6%) reported subjective improvement at the one and three month follow-up visits. At the one and three month follow up visits, the mean VAS score, the daytime urinary frequency, and the nighttime urinary frequency were significantly decreased ($p < 0.01$, $p < 0.01$ and < 0.05 for both visits, respectively). At the five month follow-up, bladder pain recurred in 11 patients (73.3%). Furthermore, the mean daytime and nighttime urinary frequency and VAS scores progressively increased relative to the three month follow-up. It was unclear whether this difference was statistically significant. At 12 months after treatment, bladder pain had recurred in all patients and urodynamic parameters reverted to baseline. One month after treatment, BTX-A impaired detrusor contractility in nine of 15 patients, even though it was administered submucosally. Three months after treatment, CISC was required in two patients. One of these patients still required CISC at the five month follow-up. No systemic adverse effects were noted. The authors concluded that temporary relief of interstitial cystitis can be achieved through BTX-A injections but at risk of the requirement for CISC after treatment.

Ramsay et al. assessed the safety, tolerability, efficacy, and durability of intravesical BTX-A in 11 women with interstitial cystitis refractory to other treatments.²⁸ Primary outcome measures were the Bristol Female Lower Urinary Tract Symptom Score (BFLUTS), Kings Health Questionnaire (KHQ) and the 24-hour frequency-volume chart. Urodynamics were assessed before treatment and six weeks after treatment. Patients were injected with a total of 300 U ($n=2$) or 200 U ($n=9$) of BTX-A (brand not specified). All 11 patients tolerated the procedure well and no major adverse effects were reported. Results showed significant symptom relief for at least 10 to 14 weeks. Median frequency also showed statistically significant improvement at 10 and 14 weeks following BTX-A injection relative to baseline. Although no specific pain questionnaire was used, the BFLUTS score included a two-part pain question that indicated

statistically significant improvement in pain at six weeks ($p=0.009$) and 10 weeks ($p=0.009$) relative to baseline. Two patients developed voiding difficulty at four and six weeks after BTX-A injection necessitating CISC. One of these patients required permanent CISC. The authors concluded that BTX-A is a potential treatment option when conventional therapies have failed to produce symptomatic improvement in patients with interstitial cystitis.

In a multicenter case series, Smith et al. reported symptomatic improvement in nine of 13 (69%) women with refractory interstitial cystitis after intravesical BTX-A (100 U to 200 U of Botox[®] or Dysport[®]).²⁹ Symptom improvement began approximately five to seven days after treatment and lasted a mean of 3.72 months (range one to eight months). The Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index mean scores improved by 71% and 69%, respectively (both $p<0.05$). Significant decreases were noted in daytime frequency (44%), nocturia (45%), and VAS pain scores (79%) (all $p<0.01$). The first desire to void and maximal cystometric capacity increased by 58% and 57%, respectively ($p<0.01$). No systemic complications were observed. Straining to void was observed in two patients, although none of these patients developed urinary retention or the need for CISC. The authors concluded that BTX-A produces both symptomatic and urodynamic improvements in patients with refractory interstitial cystitis.

Limitations

Three systematic reviews were included that assessed BTX-A for the management of urinary incontinence due to detrusor overactivity. Only one of the three systematic reviews specified the percentage of each gender in the total study population. Therefore, it is unclear to what extent the conclusions may be generalized to women. The majority of the identified evidence was from small, relatively short-term, uncontrolled observational studies that were subject to selection bias. Furthermore, evidence for clinical effectiveness and safety in patients with idiopathic detrusor overactivity was sparse. The few RCTs that have been published were small in size, and while many were double-blinded, details as to blinding and allocation concealment were lacking in the methods. Many RCTs included both genders in the study population, so conclusions were not specific to women. There was an absence of data on optimal dosing for Botox[®] or Dysport[®], timing for repeat injections, and long-term efficacy and adverse effects.

Poor quality evidence from uncontrolled observational studies were included for BTX-A in the management of pelvic pain due to vulvodynia or interstitial cystitis. These observational studies are subject to many methodological weaknesses including small sample size, lack of a control group, and selection bias. There was no evidence to support the use of BTX-A for the management of pelvic pain following motor vehicle accidents.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

There is some good quality evidence that BTX-A injections using either Botox[®] or Dysport[®] into the detrusor muscle is a promising alternative to surgery for treating urinary incontinence in adults with neurogenic or idiopathic detrusor overactivity when antimuscarinic medications fail or are intolerable. Further studies are required to confirm if this finding can be generalized to women. In both conditions, the duration of effect seems to be at least six months, and overall success rates seem to be similar in both patient populations. Treatment with BTX-A seems to be well tolerated with minimal injection site reactions and no systemic adverse effects. However, optimal dosing for BTX-A is unclear and long-term follow-up studies are needed to evaluate

complications and long-term clinical effectiveness. This is of particular importance in women with idiopathic detrusor overactivity due to the risk of urinary retention and the need for CISC.

There is a paucity of good quality evidence to support the clinical effectiveness and safety of BTX-A for the management of pelvic pain associated with vulvodynia or interstitial cystitis in women. There is limited evidence from observational studies that BTX-A (Botox[®]) may be clinically effective for relieving vulvar pain with no significant adverse effects. There is limited evidence from observational studies that BTX-A (either Botox[®] or Dysport[®]) is clinically effective for the short-term management of pain and symptoms associated with interstitial cystitis, but clinicians should take into account the risk for urinary retention and the requirement for CISC. There is no evidence to support the use of BTX-A for the management of pelvic pain following motor vehicle accidents.

Overall, authors of the included studies state that before BTX-A can be routinely prescribed as treatment for the management urinary incontinence and pelvic pain related to vulvodynia and interstitial cystitis, more high-quality studies that also report long-term adverse events are required. In addition, the evidence suggests that clinicians should monitor patients for systemic adverse effects and take into account the risk for the requirement of CISC, especially in patients with idiopathic detrusor overactivity and interstitial cystitis who do not have pre-existing voiding problems.

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REFERENCES:

1. Botox botulinum toxin type A: neuromuscular paralytic agent allergen. In: *e-therapeutics+*. [database online]. Ottawa (ON): Canadian Pharmacists Association; 2008. Available: <https://www.e-therapeutics.ca> (accessed 2009 Apr 29).
2. Karsenty G, Denys P, Amarenco G, De Seze M, Game X, Haab F, et al. Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *Eur Urol* 2008;53(2):275-87.
3. Apostolidis A, Fowler CJ. The use of botulinum neurotoxin type A (BoNTA) in urology. *J Neural Transm* 2008;115(4):593-605.
4. Sinha D, Thomson AJ. Botulinum toxin for pelvic pain in women. *Women's Health (Lond Engl)* 2008;4(2):173-81.
5. Cartwright R, Srikrishna S, Cardozo L. New pharmacological interventions for overactive bladder. *Expert Review of Obstetrics and Gynecology* 2008;3(1):129-36.
6. Schurch B. Botulinum toxin for the management of bladder dysfunction. *Drugs* 2006;66(10):1301-18.
7. Gamble T, Sand PK. Evaluation and treatment of female urinary incontinence. *Minerva Urol Nefrol* 2007;59(4):431-50.
8. Robinson D, Cardozo L. Pharmacotherapy of overactive bladder syndrome. *Exp Rev Clin Pharmacol* 2008;1(1):163-75.
9. Petersen CD, Lundvall L, Kristensen E, Giraldi A. Vulvodynia. Definition, diagnosis and treatment. *Acta Obstet Gynecol Scand* 2008;87(9):893-901.
10. Goldstein AT, Burrows L. Vulvodynia. *J Sexual Med* 2008;5(1):5-15.
11. Pukall CF, Smith KB, Chamberlain SM. Provoked vestibulodynia. *Womens Health* 2007;3(5):583-92.
12. Gunter J, Brewer A, Tawfik O. Botulinum toxin a for vulvodynia: A case report. *J Pain* 2004;5(4):238-40.
13. Landry T, Bergeron S, Dupuis MJ, Desrochers G. The treatment of provoked vestibulodynia: A critical review. *Clin J Pain* 2008;24(2):155-71.
14. Amrute KV, Moldwin RM. Pharmacotherapy of interstitial cystitis in women. *Womens Health* 2007;3(1):63-72.
15. Duthie J, Wilson DI, Herbison GP, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Database Syst Rev* 2007;(3):CD005493. Available: [http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005493/pdf fs.html](http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005493/pdf_fs.html) (accessed 2009 May 6).

16. MacDonald R, Fink HA, Huckabay C, Monga M, Wilt TJ. Botulinum toxin for treatment of urinary incontinence due to detrusor overactivity: a systematic review of effectiveness and adverse effects. *Spinal Cord* 2007;45(8):535-41.
17. Brubaker L, Richter HE, Visco A, Mahajan S, Nygaard I, Braun TM, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. *J Urol* 2008;180(1):217-22.
18. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol* 2007;177(6):2231-6.
19. Ehren I, Volz D, Farrelly E, Berglund L, Brundin L, Hultling C, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. *Scand J Urol Nephrol* 2007;41(4):335-40.
20. Schurch B, Denys P, Kozma CM, Reese PR, Slaton T, Barron RL. Botulinum toxin A improves the quality of life of patients with neurogenic urinary incontinence. *Eur Urol* 2007;52(3):850-8.
21. Schurch B, De Seze M, Denys P, Chartier-Kastler E, Haab F, Everaert K, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. *J Urol* 2005;174(1):196-200.
22. Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E, Porena M. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. *J Urol* 2004;172(1):240-3.
23. Yoon H, Chung WS, Shim BS. Botulinum toxin A for the management of vulvodynia. *Int J Impot Res* 2007;19(1):84-7.
24. Dykstra DD, Presthus J. Botulinum toxin type A for the treatment of provoked vestibulodynia: an open-label, pilot study. *J Reprod Med* 2006;51(6):467-70.
25. Brown CS, Glazer HI, Vogt V, Menkes D, Bachmann G. Subjective and objective outcomes of botulinum toxin type A treatment in vestibulodynia: pilot data. *J Reprod Med* 2006;51(8):635-41.
26. Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, Porena M. Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: a pilot study. *Eur Urol* 2006;49(4):704-9.
27. Giannantoni A, Porena M, Costantini E, Zucchi A, Mearini L, Mearini E. Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year followup. *J Urol* 2008;179(3):1031-4.
28. Ramsay AK, Small DR, Conn IG. Intravesical botulinum toxin type A in chronic interstitial cystitis: results of a pilot study. *Surg* 2007;5(6):331-3.

29. Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. *Urology* 2004;64(5):871-5.
30. Giannantoni A, Mearini E, Di Stasi SM, Costantini E, Zucchi A, Mearini L. New therapeutic options for refractory neurogenic detrusor overactivity. *Minerva Urol Nefrol* 2004;56(1):79-87.
31. Ghei M, Maraj BH, Miller R, Nathan S, O'Sullivan C, Fowler CJ, et al. Effects of botulinum toxin B on refractory detrusor overactivity: a randomized, double-blind, placebo controlled, crossover trial. *J Urol* 2005;174(5):1873-7.