Title: Botulinum Toxin for Detrusor External Sphincter Dyssynergia: Clinical and Cost Effectiveness and Guidelines for Use

Date: 26 June 2008

Context and policy issues:

Botulinum toxins (serotypes of the toxin A, B, C1, D, E and F) are neurotoxins that cause food-related poisoning (botulism) and are produced by Clostridium botulinum, an anaerobic bacterium. The toxins prevent the release of acetylcholine, a neurotransmitter, into the synaptic cleft, the result of which is the blockade of neuromuscular transmission and muscular paralysis. Site specific delivery (e.g. intramuscularly or subcutaneously) of small amounts of botulinum toxins A and B can be of benefit in a number of conditions characterized by excessive muscular contraction. Injecting the toxin locally at therapeutic dosages leads to partial chemical denervation of the muscle, which decreases muscular activity in such conditions. Reinnervation of the muscle eventually occurs and the effects of the botulinum toxin wears off.

Botulinum toxin type A (BTX-A) is available on the Canadian market and is approved 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, including upper limb spasticity associated with stroke. A cosmetic version of BTX-A is also available and is approved for use in the treatment of upper facial wrinkles. In addition to these approved indications, botulinum toxins are also used off-label in a number of different conditions, many of which are urological. Detrusor-sphincter dyssynergia (DSD) is one such condition and generally occurs in people with spinal cord injuries when they lose what is described as the reciprocal relationship between bladder and urethral function. With normal function, the detrusor muscle contracts and the external urethral sphincter relaxes in order to empty the bladder. In DSD, instead of relaxing when the detrusor muscle contracts, the external urethral sphincter also contracts, which impedes bladder emptying. This leads to increased pressure in the bladder, poor emptying, recurrent urinary tract infections, and hydronephrosis. Without treatment, progressive kidney damage and significant morbidity occur.

Disclaimer: The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information on available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
There are several treatment options available in DSD. Pharmacotherapy with spasmolytic agents, alpha-blockers or antimuscarinic agents can be used, but are often ineffective and poorly tolerated.\textsuperscript{4-6} Self-catheterization is a treatment option, but may not be feasible in individuals with upper limb impairment.\textsuperscript{1} Surgical options are also available to manage DSD, including urethral stents and external sphincterotomy,\textsuperscript{4,5} a transurethral incision of external urethral sphincter. Botulinum toxin is another alternative that has been explored in patients with DSD. The toxin is injected into the external urethral sphincter in order to weaken its ability to contract and, by doing so, allow the bladder to empty.\textsuperscript{7} Using medications in unapproved indications often raises concerns about the safety, efficacy and cost-effectiveness, particularly in the context of the publicly funded health care system. This report will review the evidence for use of botulinum toxin in DSD, which could potentially help in decision-making at the level of the health care system.

Research questions:

1. What is the clinical effectiveness of botulinum toxin for the treatment of detrusor external sphincter dyssynergia refractory to anticholinergics, tricyclic antidepressants, and calcium channel blockers compared with other treatment modalities including neuromodulation or surgical interventions?

2. What is the cost-effectiveness of botulinum toxin for the treatment of detrusor external sphincter dyssynergia refractory to anticholinergics, tricyclic antidepressants, and calcium channel blockers compared with other treatment modalities including neuromodulation or surgical interventions?

3. Is there evidence that a difference exists in effectiveness, safety and cost of treatment when botulinum toxin is used for neurogenic versus non-neurogenic detrusor external sphincter dyssynergia?

4. What are the guidelines for use of botulinum toxin for the treatment of detrusor external sphincter dyssynergia including the best route of administration and dosing?

Methods:

A limited literature search was conducted on key health technology assessment resources, including OVID MEDLINE, OVID EMBASE, PubMed, the Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and May 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

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 economic evaluations, randomized controlled trials (RCTs), observational studies and evidence-based guidelines.

Summary of findings:

No health technology assessments, meta-analyses, or economic analyses were identified that addressed the safety, clinical effectiveness or cost-effectiveness of botulinum toxin in individuals with DSD. A number of systematic reviews, RCTs and observational studies were identified.
Systematic reviews

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (ANN) systematically reviewed botulinum toxin in the treatment of autonomic disorders and pain and made recommendations based on the results. DSD was one of the many indications included in the review. Studies were selected for inclusion if they were relevant to the clinical questions of efficacy, safety, tolerability, or mode of use of botulinum toxin and involved human subjects. Studies that were selected for inclusion were classified as Class I through IV (in terms of level of evidence) using the AAN guideline process. Three studies of botulinum toxin in DSD were identified, one of which was a RCT of botulinum toxin A in patients with multiple sclerosis (MS) who had DSD (Class I study), and two of which were small observational studies (Class II studies), that included a total of 18 spinal cord injury patients with DSD treated with BTX-A. The reported dosage of BTX-A was 100 U in two studies. The dosage in the other study was not reported in the review. In patients with spinal cord injury, BTX-A was injected into the external sphincter transperineally in one study and via cytoscope in the other. In patients with MS, BTX-A was injected transperineally. In the two studies involving patients with spinal cord injury, there were significant decreases in post-void residual urine volume with BTX-A, but not in the study involving patients with MS. Based on these three studies, the review panel concluded that botulinum toxin should be considered for DSD in patients with spinal cord injury. This was given a Level B recommendation, meaning that botulinum toxin is probably effective for the given condition in the specified population. However, on the basis of the one Class I study, it was concluded that botulinum toxin did not provide significant benefit for the treatment of DSD in patients with MS. This systematic review had some limitations in that the methodology was not clearly reported and the search strategy was limited in scope. As well, the recommendation in spinal cord injury was based on two small observational studies that included only 18 patients treated with BTX-A, 17 of which were male. This may limit the generalizability of the conclusions.

Another systematic review described the common indications and evidence for use of botulinum toxin in urology. Again, DSD was one of the conditions included in the review which included peer-reviewed articles identified from a search of MEDLINE from 1966 to 2004. A total of 21 studies were identified, nine of which were in patients with DSD. The level of evidence of each study was graded from I to IV according to guidelines from the Agency for Health Care Policy and Research. Of the studies of botulinum toxin in patients with DSD, one study was graded level II (well-designed, but without randomization), six studies were graded level III (well-designed non-experimental descriptive studies) and two studies were graded level IV (expert committee reports or opinion). Two studies were double-blind, one of which was placebo controlled and the other involved lidocaine as the comparator. The remaining trials were open-label, without control groups. The number of patients included ranged from 1 to 29. Outcomes reported in the review included post-void residual volumes and bladder pressures. Injection techniques and dosages were not reported in the report, but all studies used BTX-A. Effects of botulinum toxin were not consistent in all studies as six of nine studies reported decreases in post-void residual volumes and five of nine studies reported decreases in bladder pressure. The authors concluded that it was difficult to make a recommendation about the use of BTX-A in DSD given the variability of findings across studies, but gave it a clinical efficacy rating of (+), meaning that beneficial results have been seen in individual studies. The authors also identified a number of limitations in the studies included in the review and factors that made it difficult to make comparisons across studies, such as differences in toxin formulations, dosages, and methods of injection. As well, the authors felt that both subjective (e.g. health-related quality of life) and objective endpoints should have been measured and that detrusor leak point pressure would have been the most appropriate objective measure. Patient characteristics (including...
whether DSD was related to neurogenic or non-neurogenic causes) were not reported, which makes it difficult to assess the generalizability of the results.

Randomized controlled trials

One RCT was identified (included in the two systematic reviews above) that evaluated the efficacy and safety of BTX-A in the treatment of DSD.\textsuperscript{9} It was a multicentre, double-blind, placebo-controlled trial that included 86 patients with MS who had chronic urinary retention due to DSD. Previous treatments for DSD were not reported. Patients received a single transperineal injection of 100 U of BTX-A (n=45) or placebo (n=41) into the striated sphincter. All patients were also treated with 5 mg slow release alfuzosin (an alpha blocker) twice daily over 4 months. The primary outcome was post-voiding residual urine volume measured one month after injection. Secondary outcomes included a large number of voiding and urodynamic variables assessed monthly for four months. The average age of study participants was 50 ± 10 years of age and 67% were female. Of the original 86 patients, 83 completed the study, but a number of patients were missing data on outcomes. Analysis of the primary outcome was performed after every 20 patients were enrolled and the study was stopped early when BTX-A was not found to be significantly different than placebo. One month after injection, the post-voiding residual urine volumes in the placebo and BTX-A groups were 206 ± 145 mL and 186 ±158 mL (p = 0.45), respectively.

For the secondary voiding and urodynamic variables measured at 30 days post-injection, the BTX-A and placebo groups did not differ for 12 of 15 variables. However, the BTX-A group had an average voiding volume of 197 ± 143 mL, compared to 128 ± 95 mL (p=0.02) in the placebo group. As well, the pre-micturition and maximal detrusor pressures were 29% and 21% lower, respectively, in the BTX-A group compared to the placebo group (p = 0.02 for both comparisons relative to the placebo group). When looking at secondary outcomes until day 120, voiding volume also increased between days 30 and 60, but again, the residual urine volume did not change. Up to day 120, BTX-A did not have a significant effect on most voiding and urodynamic variables. The overall conclusion of the authors was that in patients with MS who have DSD, a single injection of BTX-A did not improve post-voiding residual urine volume. One limitation of this study was the number of patients with missing data on a number of voiding and urodynamic variables (up to 51% for some measures). As well, it is not clear if the results would be generalizable beyond the population with multiple sclerosis.

Dose comparison studies

Kuo (2007)\textsuperscript{12} compared the effects of urethral injections of 50 U and 100 U of BTX-A in patients with voiding dysfunction who had failed treatment with conventional medication. Patients were randomly assigned to treatment with 50 U (n = 33) or 100 U (n = 33) of BTX-A. Six of these patients had DSD and were equally randomized to each dose. BTX-A was injected into the urethral sphincter in four locations using cystoscopic guidance in men, and transcutaneously and periurethrally in women. An excellent outcome was defined as a greater than or equal to two points improvement on a quality of life scale, combined with a 50% reduction in post-void residual volume, and 25% reduction in maximal urethral closure pressure. Changes in the urodynamic parameters were also compared between patients who received the two different dosages of BTX-A, but were not reported according to underlying cause of voiding dysfunction. Characteristics of the study participants were not included in the report. All patients with DSD who were treated with 100 U of BTX-A (n=3) and two of the three patients treated with 50 U of BTX-A had excellent outcomes (p=0.27 for the comparison between dosages) assessed one month after treatment. The author concluded that urethral injection of 50 U of BTX-A was
equally efficacious as 100 U in the treatment of voiding dysfunction of any etiology, but it should be pointed out that the small sample size in patients with DSD would limit the ability to detect significant differences between the two dosages. As well, the study did not have a control group (placebo or another active treatment), which increases the risk of confounding in the study. Assessment of the generalizability of the results of this study is limited by the small sample size and the lack of description of patient characteristics.

Observational studies

Franco et al. (2007)\textsuperscript{13} evaluated the effects of BTX-A injection into the external sphincter on post-void residual urine volume in a series of neurologically normal children (n=16) with external sphincter dyssynergia through retrospective chart review. All children had previously failed to respond to alpha-blockers and biofeedback. Approximately 33% had failed to respond to oxybutynin and 20% did not respond to tricyclic antidepressants. One patient was on intermittent catheterization. All patients were also treated with bowel regimens and timed voiding. The number of injections of BTX-A administered to the 16 children ranged from 1 to 3, with 14 patients receiving a single injection. Three-hundred units of BTX-A were used in most cases, but 200 U were injected in two cases. In males, the BTX-A was injected at four sites into the external sphincter via an endoscope and via a cystoscope placed in the urethra in females. The average duration of follow-up was 21 months (range 1.5 to 39). The average patient age was 9.0 years (range 6 to 16) and the proportion of males was not reported. Prior to BTX-A injection, the average post-void residual urine was 107 mL (range 49 to 218), compared to 43 mL (range 0 to 141) after BTX-A injection. At their two week post-injection follow-up visits, 75% of patients were dry. Uroflowmetry data were not consistently available and were not evaluated. The authors concluded that endoscopic injection of BTX-A into the external sphincter was a safe and efficacious treatment option in refractory non-neurogenic voiding dysfunction in children with external sphincter dyssynergia. Limitations of this study included the small sample size, the retrospective design, lack of control group for comparison, lack of data on some outcome measures, lack of reporting of adverse events, and varying dosages. Because of these limitations, it is difficult to draw conclusions about the generalizability of the study results.

In a retrospective study, Liao and Kuo (2007)\textsuperscript{14} assessed factors associated with failure of urethral injection of BTX-A in patients with a variety of causes of voiding dysfunction refractory to conventional medication. The study included a total of 200 patients who received urethral BTX-A injections for voiding dysfunction refractory to conventional medication during a 5-year period. Forty-eight of these patients had DSD due to spinal cord injury or multiple sclerosis. Patients received 50 or 100 U of BTX-A injected into the urethral sphincter, but it was not clear how patients were allocated to the two dosages. The injection technique was not described. Patient outcomes were categorized as successful or unsuccessful. Successful treatment was defined as subjective patient satisfaction, in addition to one of the following: spontaneous resumption of voiding in patients with chronic urinary retention; a reduction in post-void residual volume of more than 50% in patients with large post-void residual volumes; or voiding with a lower detrusor pressure or lower abdominal pressure to urinate adequately. Successful treatment was further categorized as excellent outcome or improved outcome based upon the patients’ subjective assessment. Patient characteristics of the DSD subgroup were not reported. One month after treatment, 6.3% of patients with DSD experienced therapeutic failure of BTX-A, but the factors associated with failure in the DSD group were not reported separately. Excellent outcomes were reported in 39.6% and improved outcomes in 54.2% of patients with DSD. The authors concluded that urethral injection of BTX-A is an alternative to clean intermittent catheterization in patients with voiding dysfunction that does not respond to other treatments. Limitations to this study included its retrospective design, lack of a control group, and lack of
reporting of adverse events, injection technique used, patient characteristics and some outcomes specific to DSD. As with the previous study, these factors increase the risk of bias in the study and limit the ability to draw conclusions about its generalizability.

Kuo (2003)\textsuperscript{15} evaluated the effectiveness of BTX-A in the treatment of lower urinary tract dysfunction of different etiologies in 103 patients with chronic urinary retention or severely difficult urination refractory to conventional treatment. Twenty-nine of these patients had DSD. It was not clear how the study population was selected. Patients received urethral injection of either 50 U or 100 U of BTX-A, but it was not clear what the distribution of dosages was in patients with DSD or how patients were assigned to the two dosages. Patients who failed on treatment with 50 U were treated again with 100 U. The authors did not report the time that elapsed between dosages. The injection technique was not described, but was referenced to a previous report. Clinical effects and urodynamic parameters were compared at baseline and after treatment. Treatment outcome was defined as excellent if spontaneous voiding or voiding through abdominal straining occurred in patients with chronic urinary retention, or if maximum flow rate, voiding pressure or post-void residual volume improved by 25% over baseline. An improved outcome was defined as an improvement of less than 25%. Patients were asked to report adverse events, but this information is not included as an outcome. Patient characteristics of the DSD group were not reported separately. Overall, 27.6% (n=8) of patients with DSD had an excellent outcome, 51.7% (n=15) improved and 20.7% (n=6) failed on treatment. It was not clear how long after injection that this outcome was assessed. Failure was attributed to low detrusor contractility (n=3), urethral overactivity (n=2) and bladder neck obstruction (n=1). In the DSD group, voiding pressure and maximum flow rate improved significantly over baseline, but cystometric capacity and post-void residual volume did not. These outcomes were only available for 20 of the 29 patients with DSD. The authors concluded that BTX-A urethral injections at doses of 50 or 100 units were effective in decreasing urethral sphincter resistance in patients with various types of lower urinary tract dysfunction. Limitations of this study included the small sample size, and lack of description of the patient characteristics, timing of the outcome assessment and allocation to the two different dosages. Issues with study reporting make it difficult to assess the risk of bias in this study.

Guidelines

The Consortium for Spinal Cord Medicine produced clinical practice guidelines in 2006 that addressed bladder management for adults with spinal cord injuries.\textsuperscript{16} The consortium consisted of more than 20 American organizations that provide care and support to individuals with spinal cord injuries. The process of guideline development consisted of twelve steps that led to panel consensus and organizational endorsement. The guidelines were based upon systematic review of the scientific literature and expert opinion. The level of evidence was ranked from I (RCTs or meta-analysis of RCTs) to V (expert opinion) and the strength of evidence to support each recommendation was categorized as A (supported by one or more level I studies), B (supported by one or more level II studies) or C (supported only by one or more level III, IV, or V studies).

The following recommendations were made regarding the use of botulinum toxin in patients with spinal cord injuries:

1. Consider the use of botulinum toxin injections into the sphincter to help improve voiding in individuals with SCI with detrusor sphincter dyssynergia.
   (Scientific evidence–III; Grade of recommendation–C; Strength of panel opinion–Strong)
2. Monitor individuals after botulinum toxin injections and inform them that onset may be delayed up to 1 week and that the drug may lose its effectiveness in 3 to 6 months. (Scientific evidence—III; Grade of recommendation—C; Strength of panel opinion—Strong)

3. Consider avoiding the injection of botulinum toxin into the sphincter of SCI individuals who:
   - Have a neuromuscular disease.
   - Have a known allergy to or previous adverse effect from botulinum toxin.
   - Are currently on an aminoglycoside.
   - Have insufficient hand skills or caregiver assistance.
   - Are unable to maintain a condom catheter.
   - Are female. (Scientific evidence—None; Grade of recommendation—None; Strength of panel opinion—Strong)

4. Advise individuals with SCI of the potential for complications of botulinum toxin injections into the sphincter, such as:
   - Autonomic dysreflexia during the injection (T6 and above).
   - Hematuria during the injection. (Scientific evidence—None; Grade of recommendation—None; Strength of panel opinion—Strong)

5. Consider injecting botulinum toxin into the detrusor muscle of individuals on intermittent catheterization with detrusor overactivity. (Scientific evidence—I/III; Grade of recommendation—A/C; Strength of panel opinion—Strong)(p3)

The European Association of Urology produced practice guidelines in 2003 that addressed the management of lower urinary tract dysfunction and included recommendations about the use of botulinum toxin in individuals with DSD. No information was provided about the guideline development process, but it was stated that the guidelines reflected the current opinion of the experts involved. Levels of evidence were not provided and recommendations were not graded. The following recommendation was made:

(Laser) sphincterotomy is the standard treatment for DSD or other increased bladder outlet resistance at the sphincteric area. Botulinum sphincter injections will be the first choice in patients ineligible for interventional surgery. Bladder neck incision is effective in a fibrotic bladder neck. Urethral stents still have too many complications.(p21)

**Limitations**

Overall, the quantity and quality of evidence of clinical and cost-effectiveness of BTX-A in patients with DSD was limited. While two systematic reviews were identified, these reviews were comprised of relatively low quality, small, observational studies that did not have control groups. Only one RCT was identified, but it was specific to patients with multiple sclerosis, so it is not clear if the results would be generalizable to other patients with DSD of neurogenic and non-neurogenic etiologies. While one study included children with DSD unrelated to a neurogenic cause, it involved only 16 patients and was weak in design, so again, its generalizability is questionable. Further, outcomes were generally assessed after one month. Given the relatively short length of follow-up, these studies do not provide insight into the duration of action of BTX-A in patients with DSD, which may be an important consideration. Also, given the outcomes that were assessed, it is not clear what impact BTX-A would have on complications of DSD such as renal damage and urinary tract infections.
Conclusions and implications for decision or policy making:

The relative clinical effectiveness and cost-effectiveness of BTX-A compared to other treatment modalities is unclear as studies to date have not compared BTX-A to other active treatments. Most of the studies identified included patients who had DSD refractory to other treatments and success rates of treatment with BTX-A did appear to be reasonable in these patients, but the quality of the studies’ methodology make it difficult to draw strong conclusions in this regard. The comparative efficacy, safety and cost of BTX-A in patients with DSD of neurogenic and non-neurogenic origins is also unclear, but dosages administered in neurologically normal children with DSD were higher,\textsuperscript{13} and therefore, likely more costly than those used in studies of patients with DSD related to multiple sclerosis or spinal cord injury.\textsuperscript{9,14} No economic studies were identified. Despite the limited evidence, clinical practice guidelines recommended botulinum toxin for use in patients with DSD, but do not provide specific advice with regards to the best route of administration and dosing. Based on the limited evidence and recommendations from clinical practice guidelines, BTX-A appears to be a reasonable alternative for patients with DSD who fail to respond to other therapies.

Prepared by:
Ron Pohar, BScPharm, Clinical Pharmacist
Kelly Farrah, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
References:


