Evidence-Based Practice Group Answers to Clinical Questions

BOTOX® Long-term Use and Adverse Events

By

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Clinical Services – Worker and Employer Services

About this report

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objective

To examine safety of long-term BOTOX® use in adult populations, in FDA approved conditions, which might be relevant in work-related injury/disease; such as headaches, spastic torticollis, and focal spasticity.

Background

Botulinum toxin is the neurotoxin produced by an anaerobic, spore-forming bacteria, Clostridium botulinum. The bacteria has different strains which create serologically distinct neurotoxins (i.e., A, B, C –C1, C2–, D, E, F, G, and H). When people are infected by Clostridium botulinum or acquire preformed toxin from an external source, the neurotoxin causes botulism, a neuroparalytic and potentially deadly disease. [1, 2] However, ironically, in contemporary medicine the paralytic effect of this neurotoxin is also being used in treating conditions with persistent muscle contraction (e.g., upper extremity muscle spasticity, cervical dystonia, blepharospasm, overactive bladder).

BOTOX® is the brand name for the formulary that uses onabotulinumtoxinA, serotype A Botulinum neurotoxin, as a therapeutic agent. There are also formularies marketed as Dysport®, Xeomin® and Myobloc®, which use abobotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB, respectively. Except for rimabotulinumtoxinB (Myobloc®), which contains serotype-B Botulinum, all therapeutic formularies in the market contain serotype-A neurotoxin.

For this rapid review, we focused on the side effects/adverse reactions in long-term use of BOTOX® only; not the other formularies. BOTOX® has been used for cosmetic and medical indications, as per the ability of onabotulinumtoxinA to combat excessive muscle contractions and glandular activity by blocking release and synaptic transmission of acetylcholine. The temporary paralytic effect in the target organ may last for months.

The US Food and Drug Administration (FDA) originally approved BOTOX® in 1989 for strabismus and blepharospasm associated with dystonia. [3] Since then, other indications have been added. The Allergan company BOTOX® website lists seven clinical indications for BOTOX® prescriptions; **blepharospasm, cervical dystonia, chronic migraine, overactive bladder, focal spasticity, severe underarm sweating, strabismus**. The company also has a specific product, BOTOX® Cosmetic, for temporarily improvement of the moderate to severe forehead lines, crow's feet lines, and frown lines between the eyebrows in adults. [4] Where BOTOX® is available in

50/100/200 unit vials; BOTOX® Cosmetic comes in vials of 50 and 100 units. [5, 6] The application is mostly via intramuscular injections, except for axillary hyperhidrosis where it is injected into the skin. Besides these standard/licensed indications for BOTOX®, countries have their own regulations and may approve other indications. For example, one additional indication that was not listed by Allergan [4] or by the US Food and Drug Administration (FDA), [5] dynamic equinus foot deformity (for pediatric cerebral palsy patients, two years of age or older) was included in the Health Canada product information indication list. [7]

The main issue with BOTOX® treatment (either for medical or cosmetic purposes) is the limited duration of its effect and hence, the need for continuous, repeated injections. The question arises as 'until when?'. The product information documents for BOTOX® and BOTOX® Cosmetic (referred to in both the Allergan and the US FDA websites) include the warning "Do not exceed a total dose of 400 Units administered in a 3 month interval". One other specific note states; "It is not known if BOTOX® Cosmetic is safe and effective for use more than 1 time every 3 months". [5, 6] However, how much these warnings are taken into consideration in clinical and cosmetic practices remains to be determined. Long-term usage becomes a concern not only for the muscle atrophy and functional loss issues with continuing injections, but also for the increased chances of adverse reactions and drug interactions.

For example, the Allergan BOTOX® website includes a warning statement; "BOTOX® and BOTOX® Cosmetic may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking BOTOX® and BOTOX® Cosmetic. If this happens, do not drive a car, operate machinery, or do other dangerous activities." [4]

Another warning section from the FDA product information document refers to the distant spread of toxin effect: "The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms." [5, 6]

Beyond the risk of serious adverse effects with the actual BOTOX® applications, iatrogenic botulism may also develop with attempts to administer non-FDA approved Botulinum toxin products with much higher toxin concentrations as a substitute for BOTOX®. [8]

One other issue to keep in mind when using BOTOX® is the possibility of development of neutralizing antibodies, in about 4-10% of the recipients, which leads to treatment failure by making botulinum toxin type A ineffective. This risk increases when the injections are frequent, with high injected toxin doses and used long-term; as well as with higher foreign protein content of the preparation. [1, 9]

BOTOX® at WorkSafeBC

At WorkSafeBC, BOTOX® coverage is limited; including certain indications, not necessarily listed by Allergan, FDA or Health Canada. Generally, decisions are based on a case-by-case approach. A preliminary scan of the coverage data captured claims with BOTOX® prescriptions. Some of these claims included single administration of BOTOX®, others were supplied multiple times. A number of these claims were highly costly and lengthily. The exact indication for BOTOX® prescription cannot be determined solely by the International Classification of Diseases (ICD) codes attached to these claims and requires a deeper study of each claim individually, which is out of the scope of this rapid review. For example, when the ICD-9 code points to "fracture cervical, closed with spinal cord lesion", the related BOTOX® indication can potentially be cervical dystonia or focal muscular spasticity. In general, the ICD-9 codes were related with musculoskeletal problems; such as, fractures, strains, displacements, tendonitis & bursitis, osteoarthrosis, and carpal tunnel and rotator cuff syndromes. The longer duration usage of BOTOX® seemed to follow injuries of head, neck, spine, and extremities; resulting in fractures, concussions, contusions, strains.

The Evidence-Based Practice Group (EBPG) undertook a number of rapid reviews on Botox applications in the past. The one which is available through the WorkSafeBC public website was on the effectiveness of Botulinum toxin in treating painful neuroma [9] and concluded that despite some low level evidence of benefit from a few low quality small case series, one higher quality study did not find evidence for neuroma patients benefiting from Botox injections in reducing pain.

BOTOX® Coverage - Other organizations

In British Columbia, PharmaCare covers BOTOX® only for a restricted number of conditions, which are listed as; spasmodic torticollis, blepharospasm, strabismus, equinus foot deformity due to spasticity, focal spasticity, and urinary incontinence due to neurogenic detrusor overactivity.

The coverage is limited to one year, except for urinary incontinence, for which the coverage might be renewed at the end of the first year. [10] The BC Government raised the potential for dosing errors due to varying BOTOX® vials (200, 100 and 50 Unit) in one of its PhamaNet Bulletins. [11] The Medical Policy document from Anthem Blue Cross (updated in 2017) lists coverage on Botulinum toxin type A and B products (including BOTOX®), when they are deemed "medically necessary" (e.g., strabismus, blepharospasm, cerebral palsy, facial nerve (VII) dystonia, hemifacial spasm, hereditary spastic paraparesis, idiopathic torsion dystonia, multiple sclerosis, neuromyelitis optica, organic writer's cramp, orofacial dyskinesia (that is, jaw closure dystonia), Schilder's disease, spasmodic dysphonia or laryngeal dystonia (a disorder of speech due to abnormal control of the laryngeal muscles present only during the specific task of speaking), spastic hemiplegia, spasticity related to stroke, spinal cord injury, or traumatic brain injury, symptomatic torsion dystonia, other forms of upper motor neuron spasticity, achalasia, anal fissures. There are also conditions covered if certain requirements are met. For example, initial or subsequent injections for treatment of cervical dystonia (spasmodic torticollis), significant drooling, neurogenic overactive bladder, idiopathic overactive bladder, operated Hirschsprung disease, primary and secondary hyperhidrosis. When certain criteria are met, initial and continuing prevention of chronic migraine headaches were considered medically necessary and covered; but considered "investigational and not medically necessary" and not covered for other headaches, such as tension, episodic migraine (14 migraine days per month or less), or chronic daily headaches. Other listed conditions not to be covered are: pelvic floor dyssynergia, Behcet's syndrome, benign prostatic hyperplasia, brachial plexus palsy, carpal tunnel syndrome, chronic motor tic disorder, disorders of the esophagus (except as listed above in the medically necessary section), epicondylitis, fibromyalgia/fibromyositis, gastroparesis, low back pain, myofascial pain syndrome, neck pain (without aforementioned conditions), nystagmus, Parkinson's disease, post-mastectomy reconstruction syndrome, Reynaud's syndrome, sphincter of Oddi dysfunction, stuttering, tics (with Tourette's Syndrome), tinnitus, Tourette's Syndrome, tremors, urinary and anal sphincter dysfunction (except for aforementioned conditions), vaginismus, whiplash-related disorders, zygomatic fractures. The Anthem Blue Cross states that for coverage besides the clinically "medically necessary" criterion, the cost effectiveness of Botulinum toxin treatment compared to other treatment options might be required. The webpage has a good summary table for FDA-approved indications (except for cosmetic indications) and indications for off-label drug use criteria. [12]

One very well organized and presented coverage policy document on Botulinum toxin A (including BOTOX®) can be found at the Blue Cross Blue

Shield of Michigan website. This document includes a list of references and was recently updated in September 2017. [13]

In the workers' compensation context one example from Canada would be the Ontario Workplace Safety & Insurance Board's (WSIB) Formulary Drug Listing Decisions on Botulinum toxin A: BOTOX®, BOTOX COSMETIC®, and XEOMIN®. The document lists the generally accepted indications for Botulinum toxin A (i.e., blepharospasm, strabismus, cervical dystonia, dynamic equinus foot deformity due to spasticity, post-stroke spasticity, and hyperhidrosis of the axilla); and based on their Drug Advisory Committee recommendations suggesting "limited evidence for its efficacy in conditions relevant to the WSIB worker population", concluded that "review of the clinical efficacy, safety, and cost-effectiveness" of Botulinum toxin A in the treatment of chronic non-cancer pain "did not demonstrate any significant therapeutic or non-therapeutic advantage over appropriate comparators available in Canada" and Botulinum toxin A products NOT to be listed on any WSIB formularies. [14] However, in addition, BOTOX® and XEOMIN® are listed in the WSIB list of the frequently requested non-formulary drugs and it is stated that the criteria for funding consideration would be on an exception basis for the treatment of cervical dystonia only if all of the set conditions are met. [15]

Washington State Department of Labor & Industries states that a maximum of two courses of treatment with Botulinum toxin products are covered only for the FDA approved indications, and with prior authorization. No off-label indications are covered. To obtain prior authorization for the first course of Botulinum toxin injection the health condition has to be causally related to industrial/occupational injury/disease, to be FDA-approved, has not responded to conservative treatments, and the worker should not have contraindications or had severe, distant or delayed adverse events with Botulinum toxin before. A second course of Botulinum toxin treatment may be authorized only if the first course worked and at least 90 days has passed after the initial course. In the case of catastrophic injuries there are exemptions. [16]

State of Colorado Department of Labor and Employment Division of Workers' Compensation Medical Treatment Guidelines on Chronic Pain Disorders has a section on Botulinum toxin injections. This document lists conditions which produce dystonia or piriformis syndrome as indications for Botulinum toxin usage, also making a distinction between true dystonia and spasm. Cervical dystonia or torticollis is stated to be the most common dystonia in workers. Nevertheless, it is required that there should be evidence of limited range-of motion prior to the injection. The evidence statement indicates that "A single injection of botulinum toxin type B is more effective than placebo in

alleviating the severity and pain of idiopathic cervical dystonia. The duration of effect of botulinum toxin type B is not certain but appears to be approximately 12 to 18 weeks"; hence, the frequency of the re-admission of the Botulinum toxin is expected to be "no less than 3 months". [17]

Commonly reported side effects/adverse reactions with BOTOX®

The Allergan website Medication Guide for BOTOX® and BOTOX® Cosmetic warns the users about potential serious side effects that can be life threatening (e.g., swallowing, speaking, or breathing) and can happen in hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. [18] Some of these effects may result from the spread of the toxin; but some may only be related with the original injection. In the case of spread, the Allergan Medication Guide lists "**loss of strength and muscle weakness all over the body, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice** (dysphonia)**, trouble saying words clearly** (dysarthria)**, loss of bladder control, trouble breathing, trouble swallowing**". [18] There are also other side effects listed by Allergan; such as **dry mouth, discomfort or pain at the injection site, tiredness, headache, neck pain, eye problems** (double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes)**, urinary tract infection, painful urination, inability to empty your bladder on your own** (in people who are already being treated for various urinary problems)**, allergic reactions** (e.g., itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint). [18]

The Health Canada Drug Product Database refers to the detailed product information cited by Allergan (Product monograph/Veterinary Labelling). [7] In this document general side effects are described in a special section and in addition, potential side effects for each individual indication are presented. The general side effects listed are: injection site symptoms/signs (pain, tenderness and/or bruising), general unwell feeling, weakness, changes in heart beats, chest pain, skin rash, allergic reactions (shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin), anaphylaxis, cardiovascular events, seizures, dysphagia, and respiratory compromise. It is mentioned that skin rash, itching, allergic reaction, and facial paralysis may happen rarely (<0.1%), as well as serious adverse events (e.g., arrhythmia, myocardial infarction and related fatality). Local or remote muscle weakness may develop due to diffusion and/or injection technique; for example, ptosis and diplopia, swallowing and speech disorders, respiratory failure, dysphagia, aspiration pneumonia.

Methods

Systematic literature search was conducted on April 30, 2018.

Selected commercial medical databases including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and MEDLINE Daily Update, Electronic Publications Ahead of Print were searched under the OvidSP platform.

Relevant keywords identified through scoping searches were used and combined with appropriate Boolean Operators (i.e., 'OR', 'AND')

Search strategy was as follows:

[(botox) OR (botulinum toxin A) OR (onabotulinumtoxinA)**] AND [**(long term) OR (frequent) OR (prolonged) OR (repeated) OR (multiple)**] AND [**safety**]**

There were 1540 citations identified with this search strategy.

We limited the search to include citations from studies on humans, adult populations (ages 19 and up), written in English, published in the last 10 years. The number of citations were down to 1053.

After removal of the duplicates, the number of citations was 851.

We limited publications to meta-analysis, systematic reviews, randomized clinical trials, and controlled clinical trials (discarded citations for observational studies, conference abstracts, notes, editorials, protocols, short surveys).

Abstracts for the remaining 153 citations were scanned employing the inclusion/exclusion criteria outlined below.

In total 21 articles were collected in full text, and 9 of them were included in this review.

Include articles

- on FDA accepted indications for onabotulinumtoxinA type Botulinum toxinA [5]
    - blepharospasm
    - cervical dystonia
    - chronic migraine
    - overactive bladder
    - focal spasticity
    - severe underarm sweating
    - strabismus
- on long term (i.e., at least 12 weeks), repeated, frequent applications
- focusing on safety (e.g., side effects, adverse events) in adult populations
- studies including a 'placebo' or 'no treatment' arm
- published in English
- published in the last 10 years
- which are the most recent publications from an ongoing/terminated study

Exclude articles

- on abobotulinumtoxinA and incobotulinumtoxinA types of Botulinum toxinA
- on conditions not indicated for onabotulinumtoxinA type Botulinum toxinA use by FDA
- on singular, one time only uses of onabotulinumtoxinA type Botulinum toxinA
- on multiple onabotulinumtoxinA types
- not addressing safety issues (e.g., side effects, adverse events) for onabotulinumtoxinA type Botulinum toxinA
- in the publication formats of single case reports, conference abstracts, narrative reviews, study protocols, letters to editors
- published prior to the last 10 years
- published in languages other than English

Results

Five out of the nine selected articles were on onabotulinumtoxinA use for overactive bladder, [19-23] three were on chronic migraine [24-26] and one on post-stroke upper limb spasticity. [27]

The only Cochrane systematic review/meta-analysis collected was on overactive bladder syndrome [22] and there were two other systematic reviews with meta-analysis on the same subject. [19, 20] The three studies on migraine prevention were one single-centre randomized controlled trial [24] and two multicenter studies [25, 26] Other multicenter trials were (i.e., on overactive bladder, [21, 23] and post-stroke limb spasticity. [27]

Selected articles (OvidSP search)

Management of Overactive Bladder With OnabotulinumtoxinA: Systematic Review and Meta-analysis (Lopez Ramos, 2016) [19]

The authors studied the efficacy and safety of onabotulinumtoxinA in the management of overactive bladder (OAB) syndrome. After 12 weeks they evaluated primary outcomes for efficacy (urge incontinence, urinary frequency, and urinary urgency); and primary (urinary tract infection, urinary retention) and secondary outcomes (quality of life) for safety. The 10 selected studies were randomized clinical trials, which met the criteria for CONSORT (Consolidated Standards of Reporting Trials). The number of onabotulinumtoxinA injections were 10 to 20 times, across the studies. The authors assessed biases (e.g., selection bias, performance bias, detection bias, wear bias, incomplete data results, and reporting bias) for each included study. They were interested in comparing onabotulinumtoxinA versus placebo, different doses of onabotulinumtoxinA, and the use of onabotulinumtoxinA versus antimuscarinics. Employing meta-analysis they were able to compare primary outcomes for efficacy in six and primary outcomes for safety in 10 studies. They did not find any statistically difference between different dose applications. The meta-analysis revealed a risk ratio (RR) of 11.49 (95% confidence interval (CI): 4.60-28.70) for frequency of urinary retention among patients who received 100U of onabotulinumtoxinA compared to those who received placebo. Also, there was a statistically significant difference in urinary tract infection (UTI) episodes (RR: 02.73; 95% CI: 1.98-3.78) for a dose of 100U onabotulinumtoxinA versus placebo. However, this association disappeared with higher doses of onabotulinumtoxinA. Since included studies measured quality of life using different scales, meta-analysis was not attempted for this

outcome. The authors concluded that the efficacy of 100U onabotulinumtoxinA was statistically significantly better than placebo at 12 weeks of injection; however, adverse events (i.e., urinary tract infection and urinary retention) were more frequent. They also referred to the heterogeneity in reporting of the primary and secondary outcomes as a limitation of this systematic review.

OnabotulinumtoxinA for neurogenic detrusor overactivity and dose differences: a systematic review (Zhang, 2015) [20]

After a comprehensive literature search the authors included eight studies to systematically review, and conducted meta-analysis for certain outcomes (i.e., urodynamic parameters MCC (three studies), MDP (three studies), and the rate of UTI (four studies)) to assess the efficacy and safety of onabotulinumtoxinA. All of the studies reported a follow up duration of 12 weeks or beyond. Risk of bias assessment revealed unclear allocation concealment, incomplete outcome data, and selective outcome reporting for most of the primary studies. The four studies which reported on QOL (quality of life) were not suitable for meta-analysis due to subjective measurement. Majority of the studies compared the frequency of urinary incontinence episodes with onabotulinumtoxinA and placebo, or different doses of onabotulinumtoxinA (i.e., 200U or 300U). Adverse events were also studied, allowing meta-analysis only for UTI, but not for dysreflexia or muscular weakness. Six of the primary studies mentioned how long the clinical effect of onabotulinumtoxinA lasted. The authors mentioned the heterogeneity in reporting of the results and did not attempt to specifically assess the "duration of the clinical effect, reinjection effect, interval between reinjections, or other symptoms as urgency". The authors applied the GRADE scale to measure the overall quality of evidence. They found moderate quality evidence (i.e., "*Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate*") for all comparisons, except for 300U BOTOX in comparison to controls in treating MDP, which revealed low quality evidence. They stated that the "long term outcomes, safety, and optimal dose of botulinum toxin for OAB still remain unanswered" and concluded that "OnabotulinumtoxinA appears to be a cost-effective intervention for populations with NDO[neurogenic detrusor overactivity]; however, the findings are not strongly definitive based on limited trials". They also stated that they failed to find any dose differences.

OnabotulinumtoxinA is effective in patients with urinary incontinence due to neurogenic detrusor overactivity [corrected] regardless of concomitant anticholinergic use or neurologic etiology (Ginsberg, 2013) [21]

The authors analyzed pooled data from two double blind, placebo-controlled trials for 381 multiple sclerosis (MS) and 310 spinal cord injury (SCI) patients who were suffering from urinary incontinence (UI) episodes ≥14 per week and were treated with placebo, 200U or 300U onabotulinumtoxinA. Some of the patients were on anticholinergic medication at baseline (SCI 60.0%, MS 50.7%) and were asked to continue with their treatment regime to keep that variable constant over time. Also, some of the patients were using clean intermittent catheterization (CIC) (SCI 84.8%, MS 29.4%) at baseline. Even if the patients had follow up periods over 12 weeks, most of the efficacy results were presented as a comparison between the baseline and week-6 findings (e.g., change in number of UI episodes/week, urodynamics, quality of life (QOL)). The authors found significant reductions in weekly UI episodes both with onabotulinumtoxinA 200U and 300U within the anticholinergic user group, but this was not the case in the 300U onabotulinumtoxinA application in non-users. Adverse events (AEs) were also assessed, some results were presented for week-6, and some for week-12. The mean weekly frequency of CIC was higher (but not significantly) in onabotulinumtoxinA groups compared to placebo, both on week-6 and on week-12. Clean intermittent catheterization (CIC) initiation (for any reason) in the MS group during the treatment cycle was 17%, 40%, and 51% in placebo, onabotulinumtoxinA 200U, and 300U groups, respectively. The incidence of UTI for placebo, onabotulinumtoxinA 200U, and 300U groups, were 43.1%, 58.7%, and 57.4% respectively for anticholinergic users and were 26.5%, 43.8%, and 54.5% for non-users. And the incidence of urinary retention were 2.9%, 14.9%, and 21.7% in users and 4.1%, 25.7%, and 24.8% in non-users in the respective groups. This study was complicated with the heterogeneity in terms of anticholinergic use at baseline and CIC initiations during the study period. One other aspect to be kept in mind is the author-industry interaction as reflected by the long list of conflicts of interest in the article.

Botulinum toxin injections for adults with overactive bladder syndrome (Duthie, 2011) [22]

This was a Cochrane systematic review. The authors tested a wide range of hypotheses to compare intravesical botulinum toxin injection with other treatments for neurogenic and idiopathic overactive bladder (OAB) in adults. The hypotheses they studied were: "whether intravesical injection of botulinum toxin was better than placebo or no treatment; pharmacological

and other non-pharmacological interventions; whether higher doses of botulinum toxin were better than lower doses; whether botulinum toxin in combination with other treatments was better than other treatments alone; whether one formulation of botulinum toxin is better than another; and whether one injection technique was better than another". The authors reviewed 19 primary studies, most of which followed participants after a single botulinum toxin injection (including botulinum toxin type A and B). In general, the studies had small sample sizes (average 37 participants) and limited follow up. For some, methodology (e.g., allocation concealment, blinding) was unclear. The first hypothesis of this Cochrane review, "intravesical injection of botulinum toxin is better than placebo or no treatment" was evaluated quantitatively for different symptoms employing a meta-analysis: change in urinary frequency with intravesical botulinum toxin-A versus placebo (mean difference at 4-6 weeks: -6.50 and at 12 weeks: -3.37, both statistically significant); change in incontinence episodes with intravesical botulinum toxin-A versus placebo (mean difference at 4-6 weeks: -1.58 and at 12 weeks: -2.74, both significant); change in post-void residual volume (PVR) botulinum toxin-A versus placebo (mean difference at 4-6 weeks: 70.22, significant). A few studies also reported on improvements in maximum detrusor pressure (MDP) and maximum cystometric capacity (MCC) with botulinum toxin-A use. Health status and quality of life were measured using different measurement tools across the studies, and even if some studies used the same measurement tools, treatment methods employed were not comparable; hence not allowing for meta-analysis. In terms of adverse events with botulinum toxin-A treatment, the authors mentioned that UTIs were referred to being an acceptable risk in most studies. They also mentioned an increase in PVRs that may require clean intermittent catheterization (CIC) application with botulinum toxin use, and suggested that counselling of patients on this adverse effect should be mandatory. Interestingly, they did not find a drop in overall improvement of the patients as captured by the urinary symptom score even if when CIC was initiated. The authors pointed to the fact that botulinum toxin use was "largely based on descriptive rather than randomized data". They also highlighted that the studied patients were usually with serious OAB, non-responsive to conventional treatment options; hence the findings from these studies cannot be generalized to the broader OAB populations with milder symptoms. The authors concluded that "Intravesical botulinum toxin appears to be an effective therapy for refractory OAB symptoms", but few studies have compared benefits and safety with controlled data and "further robust data are required on long term outcomes, safety, and optimal dose of botulinum toxin for OAB". The authors also noted that "Larger studies with longer follow up would offer more power to identify unusual adverse events" and "Future research would benefit from the creation of a universal criterion for commencing CIC due to elevated PVR".

Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial (Cruz, 2011) [23]

This was a multicentre, international, randomised, double-blind, placebo controlled study, enrolling multiple sclerosis (MS) and spinal cord injury (SCI) patients with urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO) ≥14 UI episodes per week; n=154 and n=121, respectively. The objective was to evaluate the efficacy and safety of onabotulinumtoxinA 200U and 300U for the treatment of UI. After the treatment, patients were followed for at least 12 weeks and remained on their initial treatment during this period. For the analysis, the patients were stratified by aetiology (SCI/MS) and use/nonuse of anticholinergic therapy. The primary outcome for efficacy was measured as the change in the mean weekly UI episodes at baseline and at week-6. There was a significant difference between the change in placebo and onabotulinumtoxinA 200U and 300U groups; -13.2, -21.8, -19.4, respectively. And as secondary outcomes the maximum cystometric capacity (MCC) and detrusor contraction (DC), as well as the Incontinence Quality of Life (I-QOL) total score yielded greater increases in the treatment groups compared to placebo. Even if the "first 12 week of the placebo-controlled treatment cycle 1 was the focus of the efficacy and safety analyses" the authors have chosen to report on these outcomes at week-6. The changes from week-6 to week-12 were small; hence the change in placebo and onabotulinumtoxinA 200U and 300U groups at week-12 from baseline yielded -12.2, -20.5, and -19.4, respectively. They used the 'time to patient request for retreatment' to determine the 'duration of treatment effect' and found that median duration of effect in both onabotulinumtoxinA treatment groups was significantly longer than placebo. Urinary tract infection (UTI) was the most common adverse event during the treatment cycle. The authors also assessed post-void residual volume (PVR) for the patients who were not using clean intermittent catheterization (CIC). They noted that posttreatment CIC initiation as well as the call of urinary retention (an AE) were based on the investigators' clinical judgement. Since how the blinding was maintained was not explained in detail, this might be introducing bias in reporting of adverse events. For the patients not using CIC at baseline PVR significantly increased following onabotulinumtoxinA treatment, with higher residual volume observed in the 300U group, suggesting a dose-response effect. For the MS patients, who did not have high CIC use initially, the number of UTI and urinary retention events were significantly higher in the onabotulinumtoxinA treatment groups. The authors concluded that "both doses of onabotulinumtoxinA were well tolerated, although the 200U group had more favourable safety profile". The authors have included the information that the company Allergan "helped

design and conduct the study, collect data, manage data, conduct analysis, interpret the data, and prepared, reviewed, and approved the manuscript".

Botulinum toxin type A in post-stroke upper limb spasticity (Kaji, 2010) [27]

The authors conducted a double-blind placebo-controlled trial to evaluate efficacy and safety of botulinum toxin type A (BoNTA) injections in Japanes post-stroke patients with upper limb spasticity who received a single dose of BoNTA. Their focus was to compare the effect of high (200–240U) and low doses (120–150U) of BoNTA with placebo. This was an industry funded study and 109 patients were randomized, 77 in higher, and 32 in lower dose groups of BoNTA and placebo. With the goal to improve wrist and finger flexion BoNTA was injected into each of the flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus and flexor digitorum superficialis, and if thumb spasticity existed patients received additional doses. The primary outcome of interest was the change from baseline in the Modified Ashworth Scale (MAS) wrist score in the higher-dose groups compared to placebo. They also studied four areas of Disability Assessment Scale (DAS) (i.e., hygiene, pain, dressing and limb position), and the Clinical Global Impression (CGI) of functional disability. A significantly greater decrease from baseline in the MAS wrist score, finger score, and thumb score were noted at every time point in the higher dose BoNTA group compared to the higher-dose placebo group, as well as in the DAS scores for limb position and dressing (but not for hygiene and pain). Results varied in the lower dose BoNTA group, and some were not significant. Adverse events were recorded throughout the study. In the 12-week follow up period, serious adverse events (e.g., pyothorax, pleurisy, humerus fracture, intracranial haemorrhage) were observed in 8%, 5%, 3% of the high-dose, low-dose treatment groups and combined (both high and low) placebo groups, respectively. And treatment-related adverse events were recorded in 4%, 10%, and 8% of the patients in the high-dose, low-dose and combined placebo groups, respectively. However, it has been noted by the authors that these adverse events were investigator-determined. The authors concluded that "no clinically relevant differences were noted in the frequency of treatment-related adverse events between BoNTA-treated and placebo-treated patients. BoNTA is safe and effective for the localized treatment of post-stroke upper limb spasticity". It should be noted that BoNTA is a product containing not only botulinum toxin type A; but also 0.5mg human albumin and 0.9 mg of sodium chloride; whereas placebo carries only sodium chloride and no human albumin.

OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial (Aurora, 2010) [25]

This was an Allergan company sponsored trial on chronic migraine (CM), conducted in 56 North American sites, and in which the authors presented results from the double-blind, randomized, placebo controlled phase of the trial (first 24 weeks). The trial (PREEMPT 1) also had an open label phase to follow. The PREEMPT 1 trial evaluated the efficacy and safety of onabotulinumtoxinA for prophylaxis of headaches in adults with CM. The study subjects were randomized to onabotulinumtoxinA (n=341) and placebo (n=338) groups. First injection was on the enrollment day and the two injections were to follow were at 12- and 24-weeks. The four weeks prior to the study enrollment was considered as the baseline period. At baseline, even if there were no significant differences in major demographic characteristics between the treatment and placebo groups, there were significant between-group differences in terms of CM related characteristics (i.e., treatment-group had significantly fewer headache and migraine episodes, however had more cumulative hours of headache occurring on headache days during the baseline period). The primary endpoint of the study was 'headache episodes'. The authors reported that despite the within-group decreases observed overtime in both onabotulinumtoxinA and placebo groups there was no significant between-group difference observed in the number of 'headache episodes' at week-24 (p= 0.344; 95% confidence interval [CI] [-1.12, 0.39]). More adverse events (AE) were experienced in the onabotulinumtoxinA-treated patients compared to placebo group (59.7% and 46.7%, respectively). Also, discontinuation rates were higher in the onabotulinumtoxinA-treated group (4.1% vs. 0.9%). The authors concluded that "no between-group difference for the primary endpoint, headache episodes" was observed; but "significant reductions from baseline were observed for onabotulinumtoxinA for headache and migraine days, cumulative hours of headache on headache days and frequency of moderate/severe headache days".

OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial (Diener, 2010) [26]

This was another study sponsored by Allergan, conducted in 66 sites across North America and Europe. This article was on the 24-week, double-blind, placebo-controlled phase of the PREEMPT 2 trial. The objective was similar to the objective of PREEMPT 1 [25], to assess the efficacy and safety of onabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with chronic migraine (CM). Patients were randomized to onabotulinumtoxinA

(n=347) and placebo (n=358) groups and similar to the PEEMPT 1 trial randomization was stratified based on the 'acute headache pain medication use' during the baseline; i.e., "medication overuse–yes" or "medication overuse–no". The trials PREEMPT 1 and PREEMPT 2 had partially overlapping study periods (PREEMPT 1 from January 23, 2006 to July 16, 2008; and PREEMPT 2 from February 7 2006 to August 11 2008). The major difference between these two trials was the choice of primary end-points; i.e., frequency of 'headache episodes' for PREEMT 1 and frequency of 'headache days for a 28-day period' for PREEMT 2 (headache day= a calendar day when the patient reported four or more continuous hours of a headache). The authors underlined that the "protocol and statistical analysis plan for PREEMPT 2 was amended" and the primary and secondary endpoints were changed "subsequent to study initiation, but prior to study completion and treatment unmasking". The 'PREEMPT 1 data' was listed among other factors that led to this change in endpoints. Nonetheless, the PREEMPT 2 trial ensured a balanced demographic and clinical characteristics for the treatment and placebo groups at baseline. The efficacy endpoints (primary and other; except for the 'frequency of acute headache pain medication intakes') were statistically significantly better for the onabotulinumtoxinA treatment group compared to the placebo group, at week-24. Adverse events (AEs) were more frequent in the onabotulinumtoxinA group (65.1%) compared to the placebo group (56.4%). Discontinuations due to AEs were also higher in the onabotulinumtoxinA group (3.5%) compared to the placebo group (1.4%). The authors concluded that "PREEMPT 2 confirms onabotulinumtoxinA (155–195 U) as a safe and effective treatment for adults with CM".

Botulinum toxin type A as migraine preventive treatment in patients previously failing oral prophylactic treatment due to compliance issues (Cady, 2008) [24]

The authors studied the efficacy and tolerability of botulinum toxin type A (BoNTA) as a preventive treatment in migraine patients who were noncompliant, nonadherent, or experienced adverse event with standard oral preventative treatment. An industry sponsored randomized, double-blind, single-center, placebo-controlled study (months 1 to 3) was conducted, which allowed the placebo-treated patients to cross-over to open-label BoNTA treatment (months 4 to 6). Sixty one patients (40 BoNTA; 21 placebo) were randomized. Subjects' headache diaries were analyzed for the primary endpoint (the number of headache episodes or days at months 1 to 3). Between-group comparisons did not demonstrate statistically significant differences between the BoNTA and placebo groups. Also, BoNTA treatment did not affect maximum headache severity compared to baseline or to placebo group during the first 3 months of the study. Headache Impact

Test [HIT]-6 scores decreased significantly within the BoNTA-treated group each month compared to the beginning. The within-group decrease was also significant in placebo-treated subjects in 1 to 3 month period. At 3 months, Migraine Disability Assessment (MIDAS) score reduction was significantly better in the BoNTA treated group compared to the placebo-treated group. At month 3 (blinded period), there were no reports on treatment-related adverse events (AEs) in any of the groups. However, there were 18 possible/probable AEs and these were in the BoNTA group. The majority of treatment-related AEs that happened in the open-label period were transient, and were not severe. None of the study subjects dropped off the study because of AEs. The authors concluded that headache frequency was improved in the BoNTA-treated group compared to the headache frequency at baseline, and the BoNTA-treated group was better off compared to placebo-treated group in terms of headache impact and treatment satisfaction, at multiple time points throughout the study. However, in terms of headache frequency and severity there were no differences between the two groups. The fact that BoNTA contains 0.5mg human albumin and 0.9 mg of sodium chloride alongside botulinum toxin type A, and that placebo carries only sodium chloride and no human albumin should be mentioned here as well.

Summary

- Most of the published BOTOX® studies are either industry sponsored or by authors who have disclosed financial links with the industry
- Due to the scarce number of good quality and independent randomized controlled studies quick adaptation of this treatment method in routine practice might be premature
- Currently, questions on long term safety, optimal dose, and best injection technique for BOTOX® remain unanswered
- Methodological concerns:
    - Most of the primary studies have small sample sizes and insufficient power to test for rare adverse events and to undertake subgroup analyses
    - Many of the randomized trials suffer from methodological issues with regards to blinding and allocation concealment
    - Frequently, primary studies do not report data for all outcomes, and it is difficult to pool results for a meta-analysis
    - Some studies fail to provide information necessary to verify influence of age, sex, or physiological differences
    - Most of the studies switch to open-label study design around 12 weeks; hence, the randomized controlled phase of studies is short making it difficult to determine long term adverse events
    - Some studies have not addressed the quality of life (QOL) measures at all
    - Some BOTOX® patients also use other medications. Lack of data on concomitant medications hinders addressing confounding
- Generalizability concerns:
    - Most of the BOTOX® studies include patients with clinical symptoms that are resistant to conventional therapies; hence do not represent patient populations with milder symptoms
    - Also however, extremely complex cases and potentially poorer responders are often excluded from trials; prompting selection bias [28]
    - Some studies are comprised of patients from one gender only
    - Most of the BOTOX® trials are conducted only in North America and Europe
- In some studies treatment time/duration is not clearly stated (e.g., terms such as 'repeated', 'multiple' are used without a clear definition)
- Also, it appears that there is no consensus on definition of 'adverse event'
- Some studies suggest that "lower doses may offer comparable efficacy with fewer adverse events, albeit for a shorter duration than higher doses" [22]

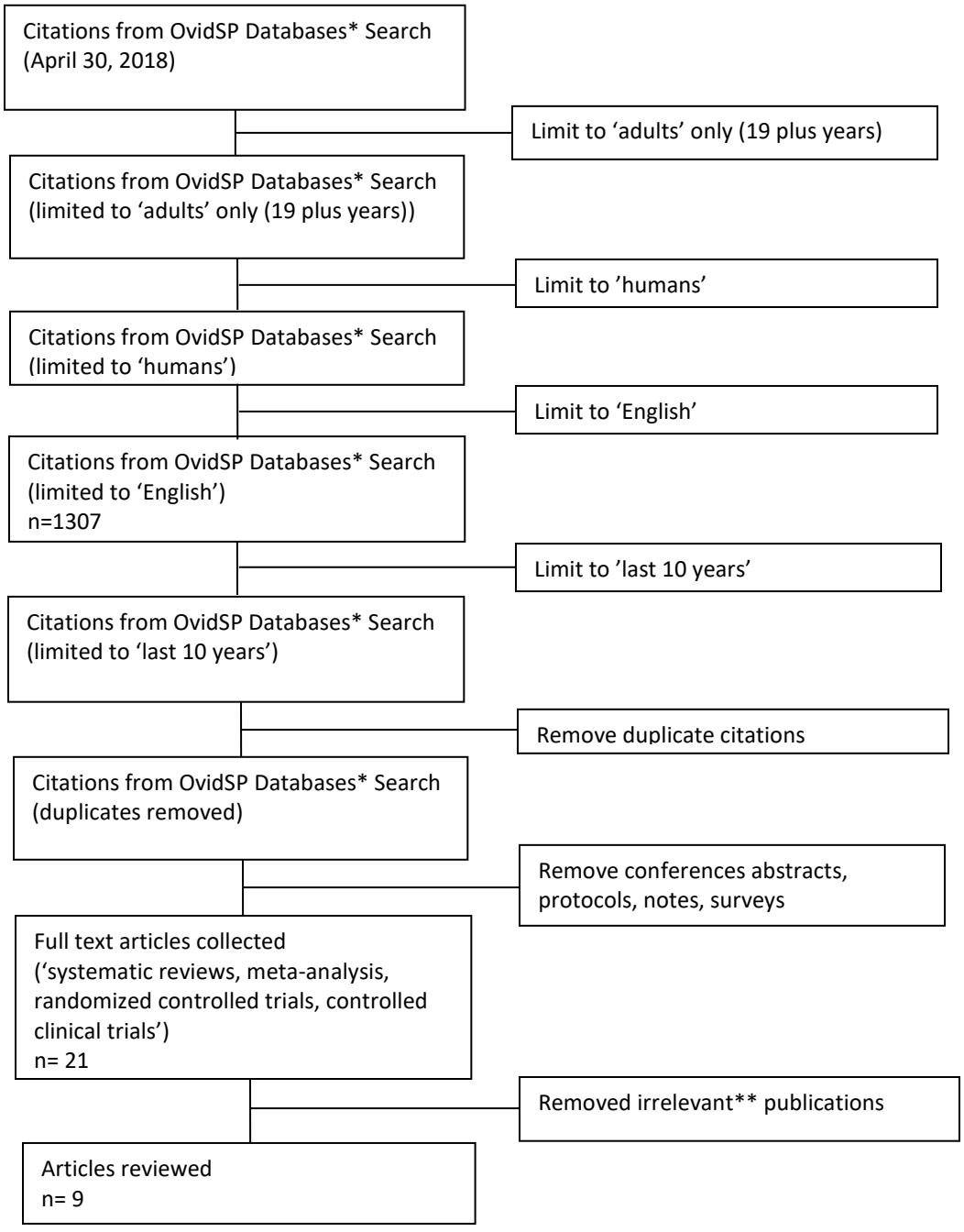
- The time point of injection may affect the magnitude of benefit (e.g., "the longer the patients' lower limb spasticity had evolved, the less they responded to treatment" [29])
- The definition of 'single session' BOTOX® therapy is not consistent across studies
- The schedule and dosage of BOTOX® application/injection varies; the optimal intervals and doses are not clearly established for all indications
- Various vials of BOTOX® (i.e., 50/100/200 units) may be leading to potential confusion in dosage assignment
- Long-term studies to test the comparative proportion of patients who develop secondary non-responsiveness to treatment are needed to explore the hypothesis that the clinical effectiveness of botulinum toxin decays over time [28]
- It is implied that 'neutralizing antibody development' might be an issue in secondary treatment failure in botulinum toxin type A therapy and can be reduced by "using the lowest effective dose, with the longest acceptable interval between injections" [1]
- For overactive bladder
    - The duration of effect of botulinum toxin type A ranges from three to twelve months [22]
    - There is an increased risk of requirement of clean intermittent catheterization (CIC) after botulinum toxin A treatment applications and the patients should be informed about this [22]
    - "At least a few studies mentioned that urinary adverse events (UTIs, urinary retention, hematuria) were dose-related" [30]

Conclusion

Current medical literature on BOTOX® therapy is not convincing for a number of clinical conditions. Studies on adverse events presumably related to long-term use are scarce. There are limited number of studies independent from pharmaceutical industry support and with sound methodological quality. Information gaps exist in safety, optimal dose, duration and best injection techniques. Cost-effectiveness, especially in a workers compensation context, is not clear.

Appendix 1

Flow Diagram (Study Selection)



** **OvidSP Databases searched:** EBM Reviews -Cochrane Database of Systematic Reviews (2005 to Apr 25, 2018), -Health Technology Assessment (4th Quarter 2016), --Cochrane Central Register of Controlled Trials (March 2018), Embase (1974 to 2018) and Ovid MEDLINE(R) (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to Present)*

*** **irrelevant publications:** publications that did not meet the inclusion criteria, and the ones with full text not available in English*

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