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Abbreviated Class Review: Botulinum toxins

Month/Year of Review: May 2014 **End date of literature search:** March 2014
Current PDL Class: None

Drugs included in review

Drug	FDA approved indications*	Evidence available from clinical trials
OnabotulinumtoxinA (Botox®)	Prophylaxis of chronic migraines (≥ 15 days/month) in adults, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, bladder dysfunction (detrusor overactivity associated with a neurologic condition or overactive bladder), blepharospasm, strabismus,	Pharyngoesophageal segment spasm, achalasia
AbobotulinumtoxinA (Dysport®)	Cervical dystonia	Blepharospasm, Neurogenic detrusor overactivity, urinary incontinence, upper limb spasticity, pharyngoesophageal segment spasm
RimabotulinumtoxinB (Myobloc®)	Cervical dystonia	Urinary incontinence, upper limb spasticity
IncobotulinumtoxinA (Xeomin®)	Cervical dystonia, blepharospasm	Upper limb spasticity

***Non-cosmetic indications only**

Research Questions:

- For what indications is there evidence to support the use of botulinum toxin (BoNT)?
- Are there differences in efficacy/effectiveness between the agents and is there evidence to support choosing a specific BoNT based on indication?
- Is BoNT safe for indications with evidence to support its use?
- Are there subpopulations that certain BoNT preparations are more effective or safer than others?

Conclusions:

- There is moderate quality evidence and support from clinical guidelines that BoNT A is recommended first line for cervical dystonias due to increased efficacy compared to standard therapies. [1,2] BoNT B is recommended for BoNT A resistant dystonias. There is low quality evidence of no difference between abobotulinumtoxinA (ABO) and onabotulinumtoxinA (ONA) in the treatment of cervical dystonia.
- There is low quality evidence demonstrating efficacy of BoNT A for the treatment of blepharospasm. However, open-label studies have demonstrated a significant effect size and clinical guidelines recommend BoNT should be a treatment option for blepharospasm.[1] There is low quality evidence of no difference between ABO and ONA and no difference between ABO and incobotulinumtoxinA (INC) in the treatment of blepharospasm.[1]
- There is moderate quality evidence that ABO, ONA and rimabotulinumtoxinB (RIM) reduces muscle tone and improves passive function for upper limb spasticity and low quality evidence for lower limb spasticity.[10,]There is insufficient evidence for an effect on active function.[11]
- There is low quality evidence that unspecified BoNT A products may be associated with benefit in the prophylaxis of chronic migraine headaches (≥15 days a month), but results are inconsistent.[3,4,5] In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headache per month.[3] There is moderate quality evidence of no benefit of prophylaxis with BoNT A in patients with intermittent migraine attacks (less than 15 headache days per month) or chronic tension type headache.[6,5,7]
- There is high quality evidence of no difference between BoNT injections and placebo in neck pain.[8] There is insufficient evidence to support the use of BoNT injections to improve pain or function in patients with lower back pain.[7,9]
- There is low quality and inconsistent evidence for the use of BoNT for increasing healing of anal fissure and appears less effective than sphincterotomy.
- In the treatment of strabismus, there is very low quality evidence, based on a systematic review with limited data that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia, but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus.
- There is low quality evidence of clinical efficacy of BoNT in the treatment of axillary hyperhidrosis and palmar hyperhidrosis. There is insufficient comparative evidence. Aluminum chloride preparations are the most widely used first line agents.
- There is moderate quality evidence that BoNT A injections in the detrusor are the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity that is unresponsive to more conservative therapies
- There is moderate to high quality evidence that pneumatic dilation (PD) and surgical myotomy are more effective on long term remission that BoNT for the treatment of achalasia. BoNT is effective short term, but response diminishes at 2 years. It is a reasonable treatment approach for patients who are not candidates for surgical therapy.
- There is insufficient evidence to make conclusions on the use of BoNT to treat neurogenic dysphagia. A recent systematic review identified no RCTs that met inclusions criteria and an overall lack of evidence to demonstrate efficacy.[10]
- There is insufficient evidence demonstrating long term efficacy of BoNT for the treatment of laryngeal dysphonia or spasmotic dysphonia. [11]

Recommendations:

- Manually review claim profiles for patients not associated with an evidence-supported diagnosis to determine if BoNT was used appropriately.
- Consider implementing prior authorization criteria to limit use to evidence supported diagnoses (Appendix 1).

Background:

There are seven serologically distinct forms of botulinum toxin (BoNT), A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain. [12] All serotypes interfere with neural transmission by blocking acetylcholine release at the neuromuscular junction, causing muscle paralysis.[13] Each neurotoxin works at a distinct site.[12] Botulinum toxins now play a role in the management of a variety of medical conditions. Three distinct serotype A botulinum toxin (BoNT A) products, abobotulinumtoxinA (ABO), incobotulinumtoxinA (INC), onabotulinumtoxinA (ONA), and one serotype B botulinum toxin (BoNT B) product, rimabotulinumtoxinB (RIM), have been approved by the U.S. Food and Drug Administration (FDA). The most recent preparation approved is INC in 2010. Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each BoNT product and cannot be compared or converted into units of another product. In addition, there are no universally accepted safe dose conversion ratios. [12] BoNTs are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, where the goal of therapy is to reduce contraction of striated or smooth muscle. All of the products have a black box warning in their labeling regarding the risk of BoNT spreading beyond the site of injection, resulting in adverse events and death in some cases. BoNT A has become first line therapy for cervical dystonia.[14] Not all patients respond well to BoNT A though, and 5 to 10% become resistant to it.[15] In these cases, BoNT B is an alternative to BoNT A. [14] Head to head studies comparing the efficacy and safety of different BoNT formulations are limited.[16]

The use of BoNT has also been evaluated for prophylaxis treatment of migraines. Prophylactic treatment for migraines is often considered for patients who have two or more migraines with three or more days of disability per month or use of acute medication more than twice per week. Common prophylactic treatments for migraines include beta-blockers, tricyclic antidepressants, calcium channel blockers, antiepileptic drugs, and lifestyle management. The reported range of efficacy for these drugs varies from modest (effect size, 0.5-0.8) for most drugs to large (effect size, >0.8) for amitriptyline and valproate.[3] Due to the lack of proven differences in efficacy between different prophylactic medications, a medication is often selected based potential side effects, the presence of other disorders which may be coexistent with migraine, patient disability, and patient preferences in a given patient. OnabotulinumtoxinA is the only BoNT approved by the FDA for the prophylactic treatment of chronic migraine. None of the BoNT formulations are approved for the prophylactic treatment of chronic tension-type headache.

Methods:

A Medline literature search ending March 2014 for new systematic reviews, clinical guidelines, and head to head randomized controlled trials (RCTs) for all of the BoNT products was conducted. Cosmetic indications were excluded, as they are not covered by the Oregon Health Plan (OHP). The focus of the review is on non-cosmetic indications only. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Cervical Dystonia and Blepharospasm:

Cervical dystonia is the most common form of focal dystonia and also referred to as spasmodic torticollis. It is a neurologic condition that causes abnormal movements and/or postures of the neck.[17] Botulinum toxin is considered first-line therapy for cervical dystonia to decrease the severity of associated abnormal

head position and neck pain.[18] According to DynaMed, there is level 1 evidence that BoNT (6 trials used ONA, 4 trials used abobotulinumtoxinA and 3 trials used RIM) reduced pain in patients with cervical dystonia and is effective and safe. There is level 2 evidence that abobotulinumtoxinA may be more effective than anticholinergic drugs and that unspecified BoNT A may have fewer adverse events than BoNT B with similar efficacy. [18] BoNT B may be useful for patients refractory to BoNT A. Blepharospasm is a focal dystonia involving the periocular muscles. Clinical signs include increased blinking and spasms of involuntary eye closure. BoNT A is the current first line medication therapy for blepharospasm.[19] Other treatments include surgery, psychological support, and biofeedback.

Systematic Reviews:

A Cochrane Collaboration systematic review of all blinded RCTs of BoNT A versus placebo evaluated the effectiveness and safety of BoNT for cervical dystonia.[20] A literature search up to June 2003 identified 13 studies for inclusion; most of which were published in the early 1990s and included only small numbers of participants. Eight trials evaluated ONA and five evaluated abobotulinumtoxinA. Techniques and administration methods varied significantly between the studies. In general, the quality of the studies was good. There was limited data on objective outcomes. Data from 3 studies (n=121) demonstrated a significant improvement of at least one point (OR 8.16; 95% CI 4.03-16.5) and at least 3 points (OR 4.25; 95% CI 2.00-9.05) in the Tsui scale (demonstrating improvement) compared to placebo. The patient subjective assessment of any improvement was also significantly better with treatment than placebo (OR 6.58; 95% CI 4.55-9.54; 11 studies; n=510). Adverse effects were transient and either mild to moderate or intermittent. Events that occurred more frequently with BoNT than placebo were neck weakness, dysphagia, dry mouth, voice changes, and local pain. There did not appear to be any significant differences between ONA and ABO in efficacy or safety.

In addition, the authors of the Cochrane systematic reviews compared the clinical efficacy and safety of BoNT A versus BoNT B in cervical dystonia.[14] However, at the time of the literature search, only two ongoing trials were identified and there were no preliminary results or interim analysis available for them. The authors were able to make any conclusions on the comparative efficacy or safety of BoNT A versus BoNT B. Since this systematic review, two randomized trials have been published comparing BoNT types A and B.[21,22] The first study was a randomized, double-blind, noninferiority trial in patients cervical dystonia who were toxin-naïve (n=111).[21] The primary outcome was change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), which is a summation of motor severity, pain, and disability. Results demonstrated that BoNT B was noninferior to BoNT A in change in baseline in TWSTRS score (mean difference 02.2 points; 90% CI -4.9 to 0.6), with no difference in duration of effect or adverse events. The second trial was a randomized, double-blind, parallel-arm study in subjects with cervical dystonia who had a previous response from BoNT A (n=139).[22] Both serotypes of BoNT were found to be equivalent at week 4 in terms of efficacy. The BoNT B group had an increase in frequency and severity of dysphagia and dry mouth after treatment compared to BoNT A (dysphagia: ONA 19% vs. RIM 48%; dry mouth: ONA 41% vs. RIM 80%). In clinical responders, BoNT A was associated with a slightly longer duration of benefit than BoNT B (ONA 14 weeks, RIM 12.1 weeks; p=0.033). [22]

Another Cochrane systematic review evaluated RCTs to determine how effective and safe BoNT A is for the treatment of blepharospasm.[19] Overall, the authors found no high quality, randomized, controlled efficacy data to support the use of BoNT A for blepharospasm. Because none of the studies met their inclusion criteria, only a descriptive analysis was provided for the trials excluded that were controlled. However, open-label studies demonstrate a significant effect size (90% of patients benefit), making it difficult to justify new placebo-controlled trials and it appears that BoNT A is indeed effective and safe in blepharospasm. Most of the trials evaluated ONA; two trials included ABO.

An evidence-based review and meta-analysis attempted to evaluate which treatments for dystonia have proven efficacy and which of them have unproven results.[23] A literature search was performed through 2003 and all types of articles were comprised, including case reports. A random effects meta-analysis confirmed positive results for BoNTA efficacy in patients with cervical dystonia (RD 0.46; 95% CI 0.25-0.67; p<0.0001; I2=82.1%) based on 6 double-blind,

placebo-controlled trials, all comparing ONA to placebo. Similar results were seen in one RCT evaluating ABO in 75 patients. Two RCTs compared ONA to ABO and one found no differences in degree of improvements between the two preparations, while the second study showed abobotulinumtoxinA to be superior to ONA for impairment and pain, but with a higher incidence if minor side effects. Three double-blind and one single-blind study (n=73) showed a positive effect of BoNT A (nonspecific) on blepharospasm lasting more than 2-3 months (Level A data). A meta-analysis included two placebo controlled studies using BoNT A to treat writer's cramp that resulted in C-level data (RD 0.31; 95% CI 0.10-0.52; p=0.004; I2=0%). The authors concluded that BoNT is possibly effective for writer's cramp. Treatment efficacy was found to be unproven for the following indications: Oromandibular dystonia and laryngeal dystonia. No controlled studies were found in laryngeal dystonia and a single placebo-controlled study showed improvement in only 37.5% of a total of 8 patients with oromandibular dystonia with BoNTA injections.

Clinical Guidelines:

The American Academy of Neurology performed an evidence-based review of the safety and efficacy of BoNT in the treatment of movement disorders.[1] They concluded that BoNT is established as safe and effective for the treatment of cervical dystonia based on seven Class 1 (RCT with masked or objective outcome assessment in a representative population) rated studies. Due to no effective alternative medical therapies, the academy concludes the following:

- BoNT should be offered as a treatment option to patients with cervical dystonia (Level A).
- BoNT is probably more efficacious and better tolerated in patients with cervical dystonia than treatment with trihexyphenidyl (Level B).
- There are no data to compare BoNT with surgical treatment of cervical dystonia.
- From the available evidence there is no proven superiority for a single BoNT product.

Recommendations for additional movement disorders are also included:

- BoNT injection should be considered as a treatment option for blepharospasm (Level B).
    - This is based on two studies demonstrating that BoNT is probably effective with minimal side effects. OnabotulinumtoxinA and INC have been shown to be probably equivalent, and ONA and ABO as possibly equivalent.
- BoNT may be considered as a treatment option for hemifacial spasm (Level C).
- BoNT should be considered as a treatment option for focal upper extremity dystonia (Level B). However, the data are insufficient to provide a recommendation for lower extremity dystonia.
- BoNT should be considered as a treatment option for adductor spasmodic dysphonia (Level B).
- There is insufficient evidence to support or refute the use of BoNT in abductor spasmodic dysphonia (Level U).
- BoNT may be considered as a treatment option for motor tics (Level C). There are insufficient data to determine the effectiveness of BoNT in phonic tics.
- BoNT should be considered as a treatment option for essential hand tremor in those patients who fail treatment with oral agents (Level B).

The European Federation of Neurological Societies also recommend botulin toxin as a treatment option for patients with cervical dystonia.[2] Based on a systematic review from the American Academy of Neurology that established botulinum toxin as an effective treatment for cervical dystonia, blepharospasm, focal upper extremity dystonia, and laryngeal dystonia (probably effective). A lower level of evidence was found for focal lower limb dystonia (possibly effective). The following recommendations are provided:

- BoNT A (or BoNT B if there is resistance to BoNT A) is recommended as first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia (Level A).

- BoNT A is probably effective for adductor-type laryngeal dystonia, but there is insufficient evidence to support efficacy in abductor-type laryngeal dystonia and in muscular tension dysphonia.

Spasticity:

Spasticity results from many etiologies including stroke, trauma, multiple sclerosis, cerebral palsy and neoplasm involving the CNS. Reduction in function is related to at least muscle weakness, soft tissue contracture, and muscle overactivity**.** A recent systematic review and meta-analysis evaluated the efficacy of any preparation of BoNT A for spasticity and pain in adults.[24] Trials including both ONA and ABO were included, although the comparative efficacy and safety of the different BoNT A preparations was not addressed. Specifically, data was evaluated for spasticity and spasticity-related pain in the upper and lower limbs in adults. Results showed that BoNT A may improve spasticity but may not reduce spasticity-related pain in adults.[24] A literature review through April 2013 identified 27 studies and 10 were used for quantitative analysis of pain. Significant heterogeneity was found (I2=83%) for the studies evaluating spasticity-related pain in the upper limb. There was a non-significant effect slightly in favor of BoNT A (standardized mean difference [SMD] 0.44; 95% CI -0.02 to 0.90; p=0.06). Removing the two studies that were thought to cause significant heterogeneity due to different patient populations confirmed a non-significant result (p=0.35). Three studies evaluated pain in the lower limb and also showed no significant effect with BoNT A (RR 1.01; 95% CI 0.19-5.36; p=0.99) with significant heterogeneity (I2=87%). There was moderate quality evidence that BoNT A did demonstrate a statistically significant improvement of spasticity of the upper limb with compared to placebo (RR 1.30; 95% CI 1.11-1.52; p=0.001). There was moderate quality evidence of a significant effect on spasticity in the lower limb as well (RR 2.42; 95% CI 1.60-3.65; p<0.0001).

The American Academy of Neurology also performed an evidence-based review of the safety and efficacy of BoNT (serotypes A and B) in the treatment of adult and childhood spasticity.[25] The review evaluated the use in the following indications: adult spasticity and spasticity in pediatric cerebral palsy. A literature search identified 11 class I efficacy trials in adult upper extremity spasticity, 6 of which used ABO, 4 used ONA and 1 used RIM. All of these studies showed that BoNT is safe and reduced tone in a dose-dependent manner. There was insufficient evidence to evaluate the outcome of active functional gains. Three trials evaluated lower extremity spasticity, most of which focused on reduction in muscle tone with demonstrated efficacy. The authors concluded that BoNT is established as effective in the treatment of adult spasticity in the upper and lower limb in reducing muscle tone and improving passive function. However, few studies examined active function. There were no RCTS comparing BoNT to other treatments for spasticity. In addition, BoNT is established as effective in the treatment of spastic equinus in patients with cerebral palsy. The AAN recommends that:

- BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (level A), and should be considered to improve active function (Level B).
- There is insufficient information to recommend an optimum technique for muscle localization at the time of injection (Level U).
- BoNT injections of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy (level A).
- BoNT should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery (Level B).
- BoNT should be considered as a treatment option in children with upper extremity spasticity (level B).

The Royal College of Physicians developed national guidelines on the management of BoNT in spasticity in adults.[26] The guideline panel notes that local intramuscular injection of BoNT is an established, well-tolerated treatment in the pharmacological management of focal spasticity and there is a strong body of evidence for its effectiveness in the management of upper and lower limb spasticity. The guideline recommends that it be used for focal or multi-focal spasticity in demonstrable muscle overactivity.

The international cerebral palsy institute released a consensus statement for lower limb spasticity in children with cerebral palsy.[27] Based on a literature review and appraisal, the committee recommends the following:

- BoNT A is established as effective in the treatment of spastic equinus to improve gait (level A).
- BoNT A is probably effective to improve goal attainment and function in the management of spastic equinus (level B).
- BoNT A injections to the adductor muscles do not improve gross motor function (level A).
- BoNT A injections to the adductor muscles may delay hip displacement, but does not affect long-term outcomes (level A).
- BoNT A injections to multiple lower limb muscles have inadequate and conflicting data in respect of gait, goal attainment and function (level U).

Migraine:

DynaMed reports that BoNT injections appear ineffective for patients with episode migraine headache (< 15 days/month) based on level 2 evidence, but they may reduce frequency in adults with chronic migraine headache (≥15 days/month).[28]

Systematic Reviews:

A recent draft technology assessment on controversies in migraine management was released by the Institute for Clinical and Economic Review (ICER).[29] Results demonstrated a small clinical improvement with BoNT compared to placebo injections, with a reduction in 2.3 migraine headache days per month. There was also a significant difference in the proportion of patients with at least a 50% reduction in headache frequency (RR 2.2, 95% CI 1.3 to 3.8). However, the authors concluded that the absolute benefit is relatively small compared to the placebo effect and the 2.3 point difference is only minimally significant from a clinical perspective. There are also more adverse events in trials of BoNT, with the most common being muscle weakness, neck pain, neck stiffness, and drooping eyelids. The authors noted that the large difference in adverse events, such as muscle weakness, raises the potential of unblinding of trial participants. Overall, there seems to be consistent and direct evidence that BoNT offers a small but statistically significant benefit in the prevention of chronic migraine compared to placebo and given the adverse events and uncertainty of unblinding, there is moderate certainty that the net health benefits are small, at best. [29]

A systematic review of trials was conducted through 2012 to assess BoNT A (specific products were not reported) for the prophylactic treatment of headaches in adults.[3] Only RCTs that evaluated BoNT A in association with the reduction in frequency or severity of headaches that were at least 4 weeks induration were included. The Cochrane Risk of Bias tool was used to assess study quality and disagreements were resolved by consensus. A total of 27 placebo-controlled RCTs and 4 active comparator trials were included. Among the placebo controlled trials, 10 evaluated episodic migraines, 5 assessed chronic migraines, 8 evaluated patients with chronic tension-type headaches, and 3 studied chronic daily headaches. Different protocols were followed for botulinum injections, including fixed injection plans and follow-the-pain approached. BoNT A was associated with a reduction in headaches per month for both chronic daily headaches (-2.06 headaches per month; 95% CI -3.56 to -0.56; I^2=28.2%; p=0.25) and chronic migraine (-2.30 headaches per month; 95% CI -3.66 to -0.94; I2=32.2%; p=0.21). There was no association of BoNT A with a reduction in the number of episodic migraine headaches per month or chronic tension-type headaches. Eight studies reported on the likelihood of achieving 50% improvement in headache and BoNT A was associated with improvement in chronic migraine headaches (2 studies; RR 2.21; 95% CI 1.30-3.78). Compared with placebo, there was no association of BoNT A with improvement in chronic daily headaches, episodic migraine headaches, or chronic tension-type headaches. [3]

Only 4 trials compared BoNT A with other treatments. In single trials, BoNT A was not associated with a reduction in headache frequency compared with topiramate (1.4 headaches per month; 95% CI -2.5 to 1.3) or amitriptyline (2.1 headaches per month; 95% CI -1.2 to 5.4) for prophylaxis against chronic migraine

headaches. It was also not associated with reduction in headache frequency compared to valproate in patients with chronic and episodic migraines or in patients with episodic migraines. [3] These trials were not designed as equivalence trials and all were underpowered to show even modest differences. Overall, there was moderate heterogeneity between trials and variability in overall study quality. There was also evidence of a favorable improvement in headaches in the placebo-treated groups, with patients reporting a substantial improvement in headaches over time. The authors concluded that there may be an association between BoNT A and improvement in the frequency of chronic migraine and chronic daily headaches, but not with improvement in the frequency of episodic migraine, chronic tension-type headaches, or episodic tension-type headaches. Also, the effect size was small with a reduction seen in number of headaches per month from 19.5 to 17.2 for chronic migraine and from 17.5 to 15.4 for chronic daily headaches. Although there is insufficient direct evidence to make definitive conclusions comparing BoNT A to other medications, it appears that BoNT A may be associated with less benefit than other common prophylactic medications for migraine headaches.

A 2011 systematic review evaluated the evidence from double-blind, RCTs that had at least 100 patients from a literature search through August 2011.[4] Studies including both BoNT A and BoNT B in the treatment of migraine were included in the search criteria; however, all 10 trials identified evaluated BoNT A (eight with ONA and 2 with ABO). One trial compared BoNT A to histamine and the other nine versus placebo. The primary outcome included the difference in the number of headache episodes and the mean change in number of headache days or headache-free days. The largest available study evaluated ONA and found a small but statistically significant decrease in the mean number of headache days per month (-8.4 vs. -6.6; $p<0.001$) and in mean number of migraine days per month (-8.2 versus -6.2, $p<0.001$) in the treatment group. The small effect size suggests that this may not be clinically significant. Eight additional trials reported on migraine frequency. With the exception of one trial, there were no significant differences in migraine medication use or migraine severity or duration in any of these 8 trials. Only one trial compared BoNT A to another active treatment (histamine), and found no statistical difference between the two groups in the number of headache attacks, or in any of the secondary outcome measures. Common adverse events occurred in 20% to 67% of patients, and included muscular weakness, headache, pain, neck rigidity, blepharoptosis, skin tightness, hypertonia, dysphagia, asthenia, and eyelid edema or ptosis. Overall, the evidence for the effectiveness of BoNT A is inconsistent, and suggests that if there is a benefit, it is small and the clinical significance is unknown. In addition, it does not appear effective for improving quality of life. There was insufficient evidence to evaluate if there was a difference in efficacy among serotypes and the various products. In addition, this review combines the results of trials in chronic migraine and episodic migraine.

Another systematic review evaluated BoNT A use in chronic tension-type headache.[4] A literature search identified 9 RCTs with outcome measures including headache severity and/or intensity, headache frequency, medication use, measures of mood, and quality of life. Six trials evaluated ONA and three evaluated ABO. Seven of the nine found no significant difference in most or all headache outcomes compared to placebo. One trial (n=300) found significantly more headache free days in the placebo group compared to the highest dose of ONA (150U), but no differences in any of the lower dose groups (50U-100U). The only trial to show a statistically significant improvement in multiple headache symptoms was small (n=28) and found fewer headache days, lower headache severity, and shorter duration in the treatment group (ONA) compared to placebo. There were no studies comparing BoNT A to another active treatment for chronic tension-type headache. Overall, the evidence suggests that BoNT is ineffective for the use in chronic tension-type headache.

Clinical Guidelines:

The Canadian Headache Society released high quality clinical guidelines for migraine prophylaxis in March 2012 with an overall goal to assist the practitioner in choosing an appropriate prophylactic medication for an individual with episodic migraine (headache on ≤ 14 days a month), based on current evidence and expert consensus.[6] A comprehensive literature search and systematic review was done by the guideline panel to inform the recommendations regarding medications for migraine prophylaxis. The initial review found eight studies on the use of BoNT A for the prophylaxis of migraine and five fair-quality trials were negative with respect to the primary outcome on migraine frequency. The following are the main recommendations included:

Starting and stopping prophylactic therapy (Based on Expert Consensus only)

- Migraine prophylactic therapy should be considered in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management (Expert Consensus)
- Migraine prophylactic therapy should be considered when the frequency of migraine attacks is such that reliance on acute medications alone puts patients at risk of medication overuse headache. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, NSAIDs) on 15 days a month or more (Expert Consensus).
- Migraine prophylaxis should be considered for patients with greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective.
- Migraine prophylaxis may be considered according to patient preference and physician judgment, for example in patients with hemiplegic migraine.
- A prophylactic medication trial should consist of at least two months at the target or optimal dose before it is considered ineffective.
- A prophylactic medication is usually considered effective if migraine attack frequency or the number of days with headache per month is reduced by 50% or more.
- After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the medication in many patients, although others may benefit from a much longer duration of therapy.

Botulinum Toxin Type A

- A strong recommendation based on high quality evidence against BoNT A for the prophylaxis of episodic migraine in patients with less than 15 headache days per month. The evidence indicates that BoNT A is no better than placebo for prophylaxis of migraine in such patients.

Other medications (for the treatment of episodic migraine)

- A strong recommendation based on high quality evidence supports the use of topiramate, propranolol, metoprolol, and amitriptyline for migraine prophylaxis.
- A strong recommendation based on moderate quality evidence supports the use of nadolol, gabapentin, candesartan, and butterbur.
- A strong recommendation based on low quality evidence and minimal side effects for riboflavin, coenzyme Q10, and magnesium citrate.
- A weak recommendation based on high quality evidence for efficacy of divalproex sodium, flunarizine, and pizotifen primarily because of frequent and significant side effects.
- Propranolol, nadolol, and metoprolol are good initial prophylactic drug choices for many patients with migraine. (Expert Consensus)
- Amitriptyline is a good initial drug and may be particularly useful in patients with insomnia or associated tension-type headache. (Expert Consensus)
- Magnesium is considered the safest migraine prophylactic during pregnancy.

The National Institute for Health and Clinical Excellence (NICE) produced a technology appraisal guidance for BoTN A for the prevention of headaches in adults with chronic migraine.[5] Efficacy was established based on a systematic review of RCTs comparing BoTN A with placebo. Although the clinical trial evidence demonstrated statistically significant benefits of BoTN A compared with placebo for a number of outcomes, the absolute numerical differences were small. Further, there was a large placebo effect seen in trials. The guidance includes the following:

- BoTN A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):
    - That has not responded to at least three prior pharmacological prophylaxis therapies
      AND
    - Whose condition is appropriately managed for medication overuse
- Treatment with BoTN A that is recommended should be stopped in people whose condition:
    - Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles)
      OR
    - Has changed to episodic migraine (fewer than 15 headache days per month) for three consecutive months.

The American Academy of Neurology evaluated the evidence for using BoNT in episodic migraine, tension-type headache, and chronic daily headache.[7] Analysis of data resulted in conclusions that BoNT is probably ineffective for episodic migraine and tension-type headache (Grade B Recommendation) and that there is insufficient evidence for use in chronic daily headache. However, this was performed before the FDA approval of ONA for the use of prophylaxis of headaches in adult patients with chronic migraine.

Chronic Neck/Back Pain:
A Cochrane Database systemic review of BoNT A for subacute/chronic neck pain did not find a statistically or clinically difference between BoNT A and placebo injections.[8] Randomized and quasi-randomized controlled trials were included. Nine trials with 503 participants were included; only BoNT type A was used in these studies. High quality evidence showed little or no difference in pain between BoNT A and saline injections at 4 weeks (standardized mean difference [SMD] -0.07; 95% CI -0.36 to 0.21) and six months for chronic neck pain. Very low quality evidence suggests no difference in pain in those with cervicogenic headache (SMD 0.16; 95% CI -0.53 to 0.86; NNT 264). There was also no benefit seen for disability and quality of life at four weeks and six months.

Another Cochrane Database systematic review evaluated BoNT for treating non-specific lower back pain and did not find sufficient evidence to reach a conclusion regarding its effectiveness.[9] Only 3 trials met inclusion criteria, but only one had a low risk of bias and evaluated patients with non-specific lower back pain (N=31). The two other studies examined specific subpopulations. Heterogeneity of the studies prevented meta-analysis. The one study with a low risk of bias did demonstrate that BoNT A injections were significantly better than control injections on pain intensity and improved function. There is no evidence for long-term improvement in pain intensity. The authors concluded that the evidence in favor of BoNT injections is only of low or very low quality and further research is very likely to change the estimate of effect.

The American Academy of Neurology found only one class II study that demonstrated that BoNT is possibly effective for the treatment of chronic predominantly unilateral low back pain.[7] Although they give a Level C recommendation that it may be considered as a treatment option for patients with chronic predominantly unilateral low back pain, it is difficult to diagnose the precise origin of pain.

Hyperhidrosis:
Hyperhidrosis is a chronic idiopathic disorder of excessive sweating which usually affects the axillae, palms, soles, and forehead. Overall, there is a lack of high quality evidence and clinical guidelines to guide management of the disease.[30] Aluminum chloride topical preparations are the most widely used first line agent. When topical agents have not worked, BoNT (most commonly BoNT A) is often recommended. Effects are reported to last for 6 to 9 months with high reported

levels of patient satisfaction.[30] However, treatment is potentially lifelong. A small quasi-randomized trial (n=10) found ONA and ABO to be equally effective in reducing sweat rate and no difference in duration of benefit.[31] Patients were randomized based on date of birth which adds a significant risk of bias. Another double-blind trial compared ONA and INC in 46 patients with axillary hyperhidrosis using patient reported outcomes.[32] Both groups were equally effective, with a total of 89% reported the overall therapeutic effect as excellent. According to DynaMed, BoNT A intradermal injections are effective for up to 16 weeks and for improving quality of life (level 1 evidence) and BoNT B is reported to reduce sweating and improve quality of life based on poor quality evidence (level 3 evidence).[33]

In the American Academy of Neurology (AAN) assessment of BoNT for the treatment of autonomic disorders and pain, a subcommittee recommended that BoNT should be offered as a treatment option to patients with axillary hyperhidrosis (Level A; Established as effective).[7] Two Class I studies were identified in axillary hyperhidrosis. A RCT double-blind study showed that patients receiving BoNT had a higher response rate (more than 50% reduction of sweat production) at all time points than those receiving placebo ($P<0.001$). The panel also recommended it should be considered as a treatment option for palmar hyperhidrosis and drooling (Level B; Probably effective). There are no head to head comparisons of BoNT with other treatment options in hyperhidrosis or drooling.

The Canadian Hyperhidrosis Advisory Committee created guidelines for the treatment of primary focal hyperhidrosis.[34] These guidelines recommend using the Hyperhidrosis Disease Severity Scale (HDSS) to measure disease severity before evaluating for treatment. A HDSS score of 2 is defined as underarm sweating is tolerable but sometimes interferes with daily activities. A score of 3 and 4 correlates with underarm sweating frequently interferes with daily activities to always interferes with daily activities. The following recommendations are provided:

Axillary Hyperhidrosis

HDSS Score of 2:

- For mild or moderate axillary hyperhidrosis, topical aluminum chloride is the first choice of therapy. An initial concentration of 10-2% may be tried to minimize irritation. Euhidrosis may not be achieved until a 35% solution is used.
- If a patient fails to respond to topical therapy after 1 month, intradermal injection of BoNT A may be administered. Treatment is repeated on average every 4 to 6 months when the patient has a change in HDSS score that warrants treatment.

HDSS Score of 3 or 4:

- For severe axillary hyperhidrosis, aluminum chloride or BoNT A is first line therapy.
- If a patient fails to respond, consider using both in combination.

Palmer and Plantar Hyperhidrosis

HDSS Score of 2:

- For mild or moderate axillary hyperhidrosis, aluminum chloride hexahydrate in absolute ethanol or in a salicylic acid gel is the therapy of first choice of therapy.
- If a patient fails to respond to topical therapy, intradermal injection of BoNT A may be administered or iontophoresis therapy initiated.

HDSS Score of 3 or 4:

- For severe palmer hyperhidrosis, aluminum chloride, iontophoresis or BoNT A are considered first line therapy.
- If a patient fails to respond, consider using both in combination.

Neurogenic Bladder Dysfunction and Overactive Bladder Syndrome:

Urinary symptoms can arise due to neurological disease in the brain, the spinal cord, or the peripheral nervous system. Damage within these areas can produce characteristic patterns of bladder and sphincter dysfunction. Conditions such as cerebral palsy, stroke, multiple sclerosis, Parkinson's disease, dementia, spinal cord injury, and peripheral neuropathy can cause dysfunction of the lower urinary tract system. [35] Detrusor overactivity is defined as an urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. Detrusor overactivity is subdivided into idiopathic detrusor overactivity (IDO), or overactive bladder syndrome, and neurogenic detrusor overactivity (NDO). Overactive bladder syndrome is a symptom complex of urgency with or without urge incontinence. Overactive bladder symptoms may occur with or without NDO.[36] There are limited high quality systematic reviews evaluating BoNT for NDO. Oral antimuscarinic agents are recommended as first line treatment for neurogenic bladder dysfunction.[36] There is evidence that ONA reduces urinary incontinence but increases urinary tract infections in patients with NDO. [36,37] A prospective, double-blind study demonstrated that ONA injection was associated with decreased incontinence episodes in patients with NDO due to multiple sclerosis.[38]

A 2011 systematic review from the Cochrane Collaboration evaluated BoNT injections for adults with overactive bladder syndrome, both NDO and IDO.[39] A total of 19 unique studies met the inclusion criteria. The majority of studies included participants with NDO, often due to spinal cord injury or multiple sclerosis (MS). The majority also had symptoms refractory to antimuscarinics or did not tolerate the medication as an inclusion criteria. Two studies used BoNT B and the other 8 used BoNT A (two used ABO). Three studies compared intravesical BoNT A versus placebo in change in urinary frequency. At 4-6 weeks results favored BoNT A in reducing episodes per day (mean difference [MD] -6.50; 95% CI -8.92 to -4.07; $p<0.001$; $I2=0\%$). The meta-analysis for incontinence episodes also favored BoNT A at both 4-6 weeks (MC -1.58; 95% CI -2.16 to -1.01; p=0.00001) and 12 weeks (MD -2.74; 95% CI -4.47 to -1.01; p=0.002) of follow-up. However, the results for post-void residual volume (PVR) favored placebo with an increase of PVR of 10.22 ml (95% CI 30.63 to 109.81) in the BoNT group (p=0.00005). Due to different tools used, no pooling of quality of life data could be performed. There were no trials that looked at if one formulation of BoNT is better than another, but it seems that BoNT A has a more durable effect than BoNT B which seems to be limited to less than 10 weeks. In addition, the optimally safe and effective dose is still undetermined. One small studied suggested that a lower dose may have comparable efficacy to and improved safety over high doses. The authors concluded that BoNT injections appear to have an effective effect on refractory overactive bladder symptoms, but little controlled data exist on benefits and safety compared with other interventions, or with placebo. Further data is needed on long term outcomes, safety, and optimal dose.

Another systematic review evaluated the evidence of ONA and ABO in the treatment of NDO, including IDO, painful bladder syndrome, bladder outflow obstruction and detrusor sphincter dyssynergia.[40] The authors reviewed articles between 1985 and December 2010 and the results were compiled into high level and low level data. High level data were RCTs or well-designed quasi-experimental studies. Low level data included non-experimental, correlation or comparative studies. A total of 43 articles met the inclusion criteria. The authors noted that ONA has been studied more widely than ABO or the other preparations. ONA had high level data to support its use in all 5 conditions included; while ABO only had high level data for use in NDO. The evidence for use in detrusor sphincter dyssynergia is very limited, with most of the data coming from open label studies. There are no head to head comparisons of the two preparations.

Guidelines:

The American Urological Association (AUA) provides guidelines for the diagnosis and treatment of non-neurogenic overactive bladder, or IDO.[41] The primary evidence source was an AHRQ review of the treatment of overactive bladder in women.[42] Studies focusing on males were added to the database. The AUA performed its own analysis of the data. The panel notes that overactive bladder is not a disease but a symptom complex that generally is not life-threatening.

Based on expert opinion, no treatment is an acceptable choice made by some patients and caregivers. Treatment is focused on quality of life and symptom improvements. Further recommendations are as followed:

- First line therapy is behavioral therapies including bladder training, bladder control strategies, pelvic floor muscle training, and fluid management. (Grade B Evidence)
    - The literature indicates that behavioral treatments are generally either equivalent to or superior to medications in reducing incontinence episodes, improving frequency, and improving quality of life
- Oral anti-muscarinics, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium, are recommended as second-line therapy (Grade B Evidence), followed by transdermal oxybutynin (Grade C Evidence)
- If patients experience inadequate symptom control or adverse events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried.
- Third line treatment includes sacral neuromodulation or ONA to the carefully selected patient who has failed behavioral and anti-muscarinic therapy or who is not a candidate for these therapies (Grade C Evidence)
    - If prescribed ONA, the patient must be able and willing to return for frequent PVR evaluation and to perform self-catheterization.

The Obstetricians and Gynecologists of Canada also released guidelines for the treatment of unspecified overactive bladder.[43] These guidelines are consistent with AUA guidelines in recommending behavioral therapy as first line treatment, followed by anti-muscarinics as second line. BoNT A is only recommended for refractory overactive bladder due to the high rate of urinary retention. Studies have shown that up to 43% of patients needed clean intermittent self-catheterization. The guidelines recommend that intravesical BoNT A is a clinically effective option for patients unresponsive to conservative options, anticholinergics, or vaginal estrogen.

The European Association of Urology guidelines on neurogenic lower urinary tract dysfunction recommends that the mainstay of treatment for NDO anticholinergic drug therapy (Grade A recommendation), which is a non-invasive conservative treatment. [44] In regards to minimal invasive treatments, the guidelines state that BoNT injection in the detrusor is most effective minimally invasive treatment to reduce NDO.[44] BoNT causes a long-lasting but reversible chemical denervation that lasts for about 9 months. Generalized muscular weakness is an occasional adverse effect. The Consortium for Spinal Cord Medicine clinical practice guidelines recommend considering ONA injections into detrusor for patients with intermittent catheterization with detrusor overactivity.[45]
A NICE clinical guideline for NDO was published in August 2012 based on the best available evidence.[35] BoNT injections are not included in the recommendations for stress incontinence or for the treatment to improve bladder emptying. The following recommendations are given to improve bladder storage:

- Offer bladder wall injection with BoNT A to adults and consider in children:
    - With spinal cord disease AND
    - Symptoms of an overactive bladder or urodynamic investigations showing impaired bladder storage AND
    - In whom antimuscarinic drugs have proven to be ineffective or poorly tolerated
- Before offering bladder wall injection with BoNT A:
    - Explain that a catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after treatment, AND
    - That they are able and willing to manage such a regimen should urinary retention develop after the treatment.

The American Academy of Neurology evaluated the literature for the treatment of neurogenic bladder from detrusor overactivity and detrusor sphincter dyssynergia with BoNT.[7] The review found that BoNT is established as safe and effective for the treatment of NDO in adults (3 studies) and data on the use of BoNT for detrusor sphincter dyssynergia are conflicting. BoNT is probably safe and effective for the treatment in patients with spinal cord injury. However, one class I study did not show significant benefit in the treatment of detrusor sphincter dyssynergia in patients with MS. The following recommendations are provided:

- BoNT should be offered as a treatment option for NDO (Level A).
- BoNT should be considered for detrusor sphincter dyssynergia in patients with spinal cord injury (Level B).

A NICE clinical guideline for the management of urinary incontinence in women was issued in September 2013.[46] These guidelines recommend injection of BoNT A to women with overactive bladder caused by proven detrusor overactivity that has not responded to conservative management (including drug therapy with antimuscarinics). They also recommend discussing the risk and benefits, including the risk of intermittent catheterization and the increased risk of urinary tract infection. Treatment should only be started in women who have been trained in clean intermittent catheterization and have performed the technique successfully, and are able and willing to perform this on a regular basis for as long as needed. The recommended dose is 200 units of BoNT-A, or 100 units for women who would prefer a lower dose. BoNT-B should not be offered to women with proven NDO

Anal Fissure: Chronic Anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter, and is treated surgically with an internal sphincterotomy. According to DynaMed, BoNT has inconsistent evidence for increasing healing of anal fissure but appears less effective than sphincterotomy**.**[47]

Based on a Cochrane Collaboration systematic review limited by heterogeneity, authors concluded that medical therapy for chronic anal fissure, including topical glyceryl trinitrate, BoNT (unspecified serotype) or topical calcium channel blockers for fissure in children may be applied with a chance of cure that is marginally better than placebo. [48] For chronic fissure in adults, all medical therapies were found to be far less effective than surgery. Glyceryl trinitrate was found to be marginally but significantly better than placebo in healing anal fissure (48.9% vs. 35.5%/ $p<0.0009$). Studies identified showed that BoNT injection was found in combined analysis to be no better or worse than topical glyceryl trinitrate (OR 0.56; 95% CI 0.20-1.57; $p=0.27$; $I2=71\%$), and also no better than placebo (OR 0.29; 95% CI 0.02-3.61; $p=0.34$; $I2=89\%$). BoNT has also not been shown to do as well as surgery in curing fissure (OR 7.20; 95% CI 3.97-13.07; $p<0.001$; $I2=47\%$). There was no difference seen in one study between ONA and ABO in non-healing of fissure (OR 1.36; 95% CI 0.29-6.43; $p=0.70$), and the authors concluded that the type of BoNT has not been found to affect healing rates. Overall, there was high quality evidence of a significantly higher risk of non-healing (persistence or recurrence) in any medical therapy compared to any surgery (OR 0.11; 95% CI 0.06 to 0.23; $p<0.001$; $I2=62\%$).

The American Society of Colon and Rectal Surgeons released practice guidelines for the management of anal fissures based on a literature search and evidence grading.[49] The following recommendations are provided:

- Nonoperative measures including sitz baths, psyllium fiber and bulking agents with or without the addition of topical anesthetics of anti-inflammatory ointments is recommended first line (strong recommendations; moderate quality evidence).
- Topical nitrates may be used, although they are only marginally superior to placebo in regard to healing (strong recommendation; high quality evidence).
- Anal fissures may be treated with topical calcium blockers, which have a lower incidence of adverse effects than topical nitrates. There are insufficient data to conclude whether they are superior to placebo in healing anal fissures (strong recommendation; moderate quality evidence).

- BoNT has been associated with healing rates superior to placebo. There is inadequate consensus on dosage, site of administration, number of injections or efficacy (Strong recommendation; low quality evidence).
- Surgery is consistently superior to medical therapy and may be offered without a pharmacological treatment failure (Strong recommendation; high quality evidence).

Achalasia

Achalasia is enlargement of the esophagus. Treatment is focused on relieving the obstruction in the distal esophagus created by the incompletely relaxed lower esophageal sphincter. Pharmacological therapy, BoNT injection, pneumatic dilatation (PD), and surgical myotomy are the primary treatment strategies in management of achalasia. BoNT injections are recommended for patients who are poor candidates for other more effective treatment options, such as surgery or dilation.[50] BoNT has been shown to be effective in the short term, but has a high rate of relapse and efficacy quickly and dramatically decreases by 2 years.[51] A meta-analysis by Campos et al. evaluated 9 studies utilizing BoNT as the primary form of therapy. The percentage of patients with symptomatic improvement after one session of BoNT injection was 78.7% at 1 month, 7% at 3 months, 53.3% at 6 months, and 40.6% at over 12 months. However, at least a second injection was required in almost half of patients (46.6%).

A 2006 Cochrane Collaboration systematic review identified 6 studies comparing PD to BoNT (unspecified serotype), both endoscopic options, in patients with primary achalasia.[52] Results of a meta-analysis demonstrated no significant difference in remission between PD and BoNT treatment (RR 1.15; 95% CI 0.95 to 1.38; p=0.39). There was also no significant difference in the mean esophageal pressures between the groups. At 6 months, more patients were in remission in the PD group compared to the BoNT group (RR 2.90; 95% CI 1.48 to 5.67; p=0.00), as well as at 12 months (RR 2.67; 95% CI 1.58 to 4.52; p=0.0002). The authors concluded that PD is the more effective endoscopic treatment in the long term for patients with achalasia.

Another systematic review by Wang, et al. evaluated remission and relapse rate of BoNT compared to PD and surgical myotomy for the treatment of achalasia.[53] A total of 17 clinical studies were included in the analysis (n=761). Five of the studies compared unspecified BoNT injection with PD, 2 compared BoNT with myotomy. Results demonstrated significant differences in remission rate between PD and BoNT (65.8% vs. 36%; RR 2.20; 95% CI 1.51-3.20, p<0.0001) and relapse rate (16.7% vs. 50%; RR 0.36; 95% CI 0.22-0.58) favoring BoNT at 12 months. The authors concluded that PD remains more efficacious that BoNT for the treatment of achalasia. They also found that myotomy had superior efficacy to BoNT in remission rate (83.3% vs. 64.9%; RR 1.28; 95% CI 1.02-1.59; p=0.03). However, there were also more adverse events with BoNT compared to PD (4.5% vs. 18.8%). There was insufficient data to perform a meta-analysis on adverse events and withdrawals. The authors concluded that laproscopic myotomy is the preferred method in the management of achalasia and BoNT can offer dysphagia control, but it is temporary and reversible.

The American College of Gastroenterology recommends PD or laparoscopic surgical myotomy as first line therapy (strong recommendation; moderate quality evidence).[54] BoNT (ONA) is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy (strong recommendation, moderate quality evidence). Lastly, pharmacologic therapy (smooth muscle relaxants) is recommended for patients who have failed BoNT therapy. The primary disadvantage with BoNT for this use is that repeat injections after 6 to 12 months are commonly needed, and the long-term efficacy and safety are not well studied beyond 2 years. Although the initial response rate is high (>75%), the effect eventually wears off and repeat injection is required in a significant portion of the patients. Approximately 50% of patients relapse and require repeat treatments at 6-24 month intervals. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) conducted a literature search to also provide guidelines for the treatment of esophageal achalasia.[55] They are consistent that a single injection of BoNT has been shown to be quite effective, but its long term effectiveness remains limited. They recommend that BoNT can

be administered safely, but its effectiveness is limited especially in the long-term. It should be reserved for patients who are poor candidates for other more effective treatment options, such as surgery or dilation (strong recommendation).

Under the rein of the International Society for Diseases of Esophagus, the Kagoshima consensus on esophageal achalasia was released in 2010.[56] The statement discusses that the clinical response at 2 years is only 3%, decreasing from 90% as an initial clinical response. However, the panel noted that because of its safety, it may be a good option for elderly patients with comorbidities, but it also carries an increased risk of subsequent myotomy, due to fibrosis at the injection sites.

A randomized controlled trial compared the efficacy and tolerability of two BoNT formulations in treating achalasia (ONA and ABO).[57] After BoNT injection was given, 90% of the ONA group and 83.5% of the ABO group reported a symptomatic response to the treatment. No differences were seen between the two formulations in any clinical variables and side effects were similar. At the end of the follow-up period, symptom relapse was documented in 12% of ONA patients and 24% of ABO patients. This was reported as non-significant although p values were not provided.

Strabismus:
Strabismus is the misalignment of 2 eyes so that both cannot be directed toward an object. Comitant strabismus occurs in children <6 years old and noncomitant has an onset later in life. A 2012 Cochrane Collaboration systematic review evaluated the efficacy of any BoNT in the treatment of strabismus compared with alternative treatment options.[58] A literature search was done to identify RCTs and a total of 4 met inclusion criteria (3 with ONA and 1 with ABO). Two trials found that there was no difference between BoNT and surgery for infantile esotropia. There was no evidence for a prophylactic effect of BoNT in a treatment trial of acute onset sixth nerve palsy. BoNT had a poorer response than surgery in a trial of patients with horizontal strabismus. Trials included both ONA and ABO and there was insufficient evidence to establish a dose effect. The American Academy of Ophthalmology concludes that there is insufficient evidence to make treatment recommendations for BoNT treatment for exotropia.[59]

Sialorrhea
Sialorrhea is excessive drooling commonly seen in patients with neurological disorders, such as cerebral palsy, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).[60] Treatment approaches include anticholinergics, antireflux medications, radiation and surgery. More recently, BoNT has become a potential treatment option in these patients. Vashishta, et al conducted a meta-analysis on the available evidence for the use of BoNT A and BoNT B in the treatment of sialorrhea. There were eight studies (three utilizing ONA or ABO and five using RIM) with 181 patients that were included in the analysis. Four studies were in children with cerebral palsy, 2 with adults with Parkinson's disease, and 1 in ALS. The use of BoNT was found to significantly decrease the severity of drooling when compared to placebo using an outcome measure of drooling severity and frequency scales. Both BoNT A and BoNT B preparations were effective in productin similarly significant reductions in drooling severity. [60] Advantages over alternate treatments include a more acceptable safety profile than transdermal scopolamine, fewer drug interactions than scopolamine and glycopyrrolate and a safer alternative to systemic anticholinergic therapy.

An international consensus statement was released for the care of patients with drooling as a result of a neurological problem or anatomical abnormality of the jaw. [61] Literature was searched and appraised to make recommendations. Based on expert opinion only, it is recommended that injection of BoNT A into the salivary glands is given under ultrasound guidance. Due to acquired resistance to BoNT therapy, it is recommend that BoNT B be tried after treatment failure with BoNT A.

Tremor

According to a systematic review of the evidence for BTP for essential tremor (Ferreira and Sampaio, 2003), there is evidence of short-term reduction of tremor but no consistent improvement in disability and function. The review noted that BTP injections cause hand weakness, resulting in a "trade off" between benefits and harms. The review concluded that BTP versus placebo found short term improvement of clinical rating scales, but no consistent improvement of motor task performance or functional disability. The AAN concluded that "the effect of BTA on limb tremor in ET [essential tremor] is modest and is associated with dose-dependent hand weakness and may reduce head tremor and voice tremor associated with ET, but data are limited. When used to treat voice tremor, botulinum toxin A may cause breathiness, hoarseness, and swallowing difficulties."

The AAN's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson et al, 2008) stated that botulinum neurotoxin should be considered a treatment option for essential hand tremor in those patients who fail treatment with oral agents. On the other hand, there is insufficient evidence to draw a conclusion on the use of BTP in the treatment of head and voice tremor.

Spasmodic Dysphonia and Laryngeal Spasm

Spasmodic dysphonia is a focal laryngeal dystonia that affects intrinsic laryngeal muscle control during certain tasks. Adductor spasmodic dysphonia is the most common form of laryngeal dystonia.[62] The standard of care is BoNT injection; however, it does not affect the underlying disorder this only provides temporary symptomatic relief. [62]

A 2010 Cochrane systematic review update was done to determine the effectiveness of BoNT for treating spasmodic dysphonia.[11] A literature search for all RCTs that compared the use of BoNT with placebo, no treatment, or alternative treatments was done. Only one RCT (n=13) with spasmodic dysphonia was included in the review.[63] Results from this study showed significant group differences for fundamental frequency (SMD -1.60; 95% CI -2.92 to -0.29), fundamental frequency range (SMD -4.39; 95% CI -6.68 to -2.09), perturbation (SMD -2.36; 95% CI -3.90 to -0.82) and professional rating of improvement (SMD -4.42; 95% CI -6.72 to -2.11) with BoNT compared to saline. Overall, BoNT had a positive effect on both physiological functioning and listener perception, but based on only one study. The authors concluded that the evidence from RCTs does not allow for conclusions to be made about the effectiveness of BoNT for all types of spasmodic dysphonia.

A more recent study compared a surgery procedure to BoNT injection in those with adductor spasmodic dysphonia.[64] Results demonstrated that patients who underwent surgery had significantly improved patient-based measures of vocal function in comparison to patients who received BoNT injections. Expert listeners' ratings of voice quality did not differ between groups. In addition, positive voice outcomes were seen at an average of 7.5 years after surgery, justifying durability of the surgery. However, this trial was not randomized or blinded and patients were approached for voluntary participation.

Dysphagia

A recent Cochrane Collaboration systematic review evaluated the efficacy and safety of BoNT in improving upper esophageal sphincter dysfunction in people with dysphagia associated with neurological disease.[10] Only RCTs were included in this review. No RCTs were identified that met inclusion criteria. Final citations were excluded due to study design. The authors concluded that there is no evidence available to support the routine use of BoNT to treat neurogenic dysphagia. There is a growing use of BoNT to treat neurogenic dysphagia; however, there is no sound evidence to demonstrate the efficacy of this intervention. [10]

Other Indications:

BoNT has been studied in a number of other disorders where this is insufficient evidence to recommend its use. Several open-label studies have evaluated BoNT in gastroparesis and observed mild improvements in gastric emptying and modest improvement in symptoms.[65–67] Two double-blind placebo-controlled trials have showed no difference in improvement in symptoms compared with placebo.[68] BoNT injection into the pylorus is not recommended as a treatment for gastroparesis. BoNT A has also been evaluated for use in restless legs syndrome; however, there is insufficient evidence to support the use, with one double-blind, RCT showing no significant benefit with BoNT A compared to placebo.[69,70] A recent systematic review from the Cochrane Collaboration were unable to identify any controlled clinical trials assessing the efficacy and safety of BoNT for masseter hypertrophy.[71]

Other areas in which larger, well-designed studies are needed to demonstrate effectiveness include cricopharyngeal dysphagia, gustatory epiphora (crocodile tears), Sphincter of Oddi dysfunction,pancreas divisum, anismus, , pelvic floor spasticity, chronic prostaticpain, severe paradoxical vocal cord movement, postparotidectomy sialoceles, severe bruxism,temporomandibular disorders, myofascial pain syndrome, brachial plexus palsy, thyroid associatedophthalmopathy, esophageal spasm, post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia, trismus and stridor in amyotrophic lateral sclerosis, proctalgia fugax, nasal hypersecretion, gastroparesis (including diabetic gastroparesis), Lichen simplex, lateral epicondylitis, Stiff-person syndrome, benign prostatic hyperplasia, traumatic sixth nerve palsy, Tourette's syndrome, and pain and/or wound healing after hemorrhoidectomy. Only small and uncontrolled open-label studies have been performed for these conditions.

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Botulinum Toxins (BoNT)

Goal(s):

- Approve BoNT only for funded OHP diagnoses which are supported by the medical literature (e.g. various dystonias and spasticity associated with certain neurological diseases).

Length of Authorization:

- 90 days up to lifetime

Requires PA:

Use of BoNT without associated dystonia or neurological disease diagnosis in last 12 months (i.e. 333.6x, 333.7x, 333.81, 333.83, 333.89, 340.xx, 341.0, 342.xx, 343.xx, 344.0x, 344.1, 344.2, 344.3x, 344.4x, 344.5, 344.89, 359.0-2, 438.2x-5x or 378.73)

HSN	Generic Drug Name
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)
036477	ABOBOTULINUMTOXINA (DYSPORT)
021869	RIMABOTULINUMTOXINB (MYOBLOC)
036687	INCOBULINUMTOXINA (XEOMIN)

ProcCode	Descriptions
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-9 Code	
2. Does client have diagnosis of certain dystonias or spasticity associated with other neurological diseases that make BoNT a first-line treatment option? Examples: 333.6x (genetic torsion dystonia) 333.7x (acquired torsion dystonia), 333.81 (blepharospasm) 333.83 (spasmodic torticollis) 333.89 (other fragments of torsion dystonia) 438.2x – 432.5x (paralysis associated with CVD) 340.xx (multiple sclerosis) 341.0 (neuromyelitis optica) 342.xx (spastic hemiplegia, other specified hemiplegia), 343.xx (cerebral palsy), 344.0x (quadriplegia and quadraparesis), 344.1 (parapalegia), 344.2 (diplegia of upper limbs) 344.3x (monoplegia of lower limb) 344.4x (monoplegia of upper limb) 344.5 (unspecified monoplegia) 344.89 (other specified paralytic syndrome) 359.0x – 359.2x (muscular dystrophies) 378.73 (strabismus in other neuromuscular disorders)	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3
3. Does client have diagnosis of chronic migraine based on clinical symptoms; at least 15 headache days per month, of which, at least 8 of those days are considered migraine days?	Yes: Go to #6	No: Go to #4

Approval Criteria		
4. Does client have diagnosis of overactive bladder related to neurological causes? Document neurological cause	Yes: Go to #7	No: Go to #5

Approval Criteria		
5. Does client have any of the following diagnoses? <u>Insufficient evidence of benefit:</u> 787.2x (dysphagia) 333.xx (other extrapyramidal disease and abnormal movement disorders excluding 333.6x, 333.7x, 333.81, 333.83, 333.89 and 333.82, 333. 84, 333.94-333.99) 378 excluding 378.73 (other disorders of binocular eye movements (e.g. esotropia, exotropia, mechanical strabismus, sixth nerve palsy) 307.2x (tics) 478.75 (laryngeal spasm), 723.0 and 723.4 (Spinal stenosis in cervical region or Brachial neuritis or radiculitis NOS) 728.85 (spasm of muscle [in absence of neurological diagnoses]), 727.81 (contracture of tendon – sheath [in absence of neurological diagnoses]) 335.20 (amyotrophic sclerosis), 724.00-724.09, 724.4 (clinically significant spinal deformity or disorders of spine with neurological impairment) 600.xx (hyperplasia of prostate), <u>Unfunded OHP condition:</u> 333.82, 333. 84, 333.94-333.99 (neurologic conditions with no or minimally effective treatment or not treatment is necessary) 351.xx (facial nerve disorders), 478.79 (spastic dysphonia) 565.0 (anal fissure), 705.xx (disorders of sweat glands e.g. focal hyperhidrosis), 723.xx except 723.4 (other disorders of cervical region), 705.0-705.1,705.21-705.9,780.8 (disorders of sweat glands) 724.1, 724.2, 724.4-724.6, 727.70-724.9 (acute and chronic disorders of the spine without neurologic impairment) 729.0-729.2 (disorders of soft tissue) 307.81,339.10-339.89,784. (tension headaches) 536.3 (gastroparesis),	Yes: Pass to RPH; Deny (Medical Appropriateness) (Condition not funded by OHP)	No: Go to #8

Approval Criteria		
6. Has the client not responded or are they contraindicated to at least one drug in three of the following drug classes? • B-blocker (metoprolol, atenolol, nadolol, propranolol, timolol) • Tricyclic antidepressant (nortriptyline, amitriptyline) • Anticonvulsant (valproic acid, divalproate, carbamazepine, topiramate, gabapentin) • Calcium Channel Blocker (verapamil, diltiazem, nimodipine)	Yes: Approve for 180 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (www.orpdl.org).
7. Has the client tried or are they contraindicated to at least two of the following urinary incontinence antimuscarinic therapies? (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium)	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (www.orpdl.org).
8. Pass to pharmacist to evaluate for evidence support and OHP funding level.	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.	No: Pass to RPH; Deny (Medical Appropriateness)

P&T / DUR Action: *7/31/2014*
Revision(s):
Initiated: