



INLAND EMPIRE HEALTH PLAN

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

Drug: Botox®/Botox Cosmetic® [Onabotulinum Toxin A (formerly known as Botulinum Toxin Type A)], Myobloc® (Rimabotulinum Toxin B), Dysport™ (Abobotulinum Toxin A)

Class: Neurotoxin (Botulinum Toxin or BTX)

Formulary Medication: N/A

Effective Date: May 2010

Policy/Criteria:

FDA Approved Indications for Botulinum Toxin (BTX)	BOTULINUM TOXIN TYPE A	BOTULINUM TOXIN TYPE B
Treatment of cervical dystonia (CD) in adults to decrease the severity of abnormal head position and neck pain associated with CD	✓	✓
Treatment of severe primary axillary hyperhidrosis inadequately managed with topical agents	✓	
Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients ≥ 12 years of age	✓	
Treatment of Upper Limb Spasticity in Adult Patients	✓	

Selected off-label indications for Botulinum Toxins (Please see criteria below)
Movement Disorders
Focal point dystonia
Tourette's syndrome
Tardive dyskinesia
Essential tremor
Pain Syndromes
Migraine headache prophylaxis
Chronic daily headache prophylaxis
Genitourinary Disorders
Neurogenic detrusor overactivity incontinence
Idiopathic detrusor overactivity
Gastrointestinal Disorders
Achalasia
Otolaryngological Disorders
Spasmodic dysphonia

Drug	FDA Approved Dosing
Botox®	Blepharospasm - Initial dose: 1.25-2.5 units injected at each site

	<ul style="list-style-type: none"> - Retreatment can be done in 3 months <p>Primary Axillary Hyperhidrosis</p> <ul style="list-style-type: none"> - 50 units given intradermally <p>Strabismus</p> <ul style="list-style-type: none"> - 1.25-5 units (injection should be carried out only with electromyographic guidance) <p>Upper Limb Spasticity</p> <ul style="list-style-type: none"> - Treatment will vary depending on number of muscles involved, severity of spasticity, and patient response - In clinical trials – doses ranged from 75 units to 360 units divided among selected muscles every 12 weeks
Myobloc®	<p>Cervical Dystonia</p> <ul style="list-style-type: none"> - Initial dose: 2,500-5,000 units divided among affected muscles - Retreatment every 12 to 15 weeks or longer as necessary (dosing range 5,000-10,000 units)
Dysport®	<p>Cervical Dystonia</p> <ul style="list-style-type: none"> • Initial dose: 500 units IM in divided dose among affected muscles • Retreatment every 12 to 15 weeks or longer as necessary (dosing range 250-1000 units optimized clinical benefit)

Criteria for FDA Approved Indications:

For FDA approved Indications (excluding Cosmetic Use):

- Prescribed by neurologist, otolaryngologist, ophthalmologist, or physiatrist
- Must be for an approved FDA indication (Excluding Cosmetic Use) and must meet these requirements:
 - Blepharospasm
 - Confirmed diagnosis
 - Must be greater than 12 years of age
 - Cervical Dystonia
 - Confirmed diagnosis
 - Must be greater than 12 years of age
 - Primary Axillary Hyperhidrosis
 - Failure or intolerance to adequate trial of topical prescription strength aluminum chloride (ex. Drysol) and/or other extra strength antiperspirants (e.g., anti-cholinergics, beta-blockers, benzodiazapines)
 - Documentation of significant disruption of professional and/or social life has occurred because of excessive sweating
 - Upper Limb Spasticity
 - Failure of physical and/or occupational therapy
 - Failure or intolerance to formulary muscle relaxer (Baclofen, Tizanidine, Cyclobenzaprine, etc...)
- *Please note:* the FDA does not consider the various BTX products as interchangeable due to differences in concentration/dosing

Criteria for Off-Label Indications:

Movement Disorders:

- Essential Tremor
 - Must be prescribed by neurologist
 - Must try and fail conservative pharmacological therapy first:

- Anticonvulsant (ex. Gabapentin, Primidone, Topiramate)
- Beta Blocker (ex. Atenolol, Nadolol, Propranolol, Sotalol)
- Benzodiazepine (ex. Alprazolam, Clonazepam)

Genitourinary Disorder:

- Must be for indication of detrusor overactivity
- Member must try and fail conservative pharmacological treatment options prior to consideration of BTX:
 - Darfenacin
 - Oxybutynin
 - Solifenacin
 - Tolterodine
 - Trospium

Migraine/Chronic Headache:

- Current available clinical studies indicates that the efficacy of BTX for the use in migraines or chronic headache is not clinically significant compared to placebo
- Both the US Headache Consortium and American Academy of Neurology indicates that the use of BTX is most likely ineffective and is not considered a treatment option
- Requests for BTX will not be approved for these indications

Tardive Dyskinesia (Parkinson's Disease):

- Must be prescribed by neurologist
- Must try and fail conservative pharmacological therapy first (Anti-Parkinsonian Agents):
 - Amantadine
 - Anticholinergic Agents (ex. Benztropine, trihexyphenidyl)
 - Apomorphine
 - Carbidopa/levadopa
 - COMT inhibitor (ex. Entacapone, Tolcapone)
 - Ergo Dopamine Agonist (ex. Bromocriptine, Cabergoline, Pergolide)
 - MAO-B inhibitor (ex. Selegiline)
 - Non-Ergot Dopamine Agonists (ex. Pramipexole, Ropinirole)

Clinical Evidence:

Achalasia

American Gastroenterological Association (AGA) Practice Guideline on the Diagnosis and Management of Achalasia (1999) recommends either laparoscopic myotomy or graded pneumatic dilation (PD) in patients who are good surgical candidates. The choice between the two procedures depends on institutional preference and experience. In patients who are poor candidates for surgery or refuse surgery, initial treatment with BTX is the preferred approach. Available data indicate that BTX is effective in relieving symptoms initially in about 85% of patients; however, symptoms recur in more than 50% of patients within 6 months possibly because of regeneration of the affected receptors. Older patients (> 60 years) and those with vigorous achalasia are more likely to have a sustained response (up to 1.5 years) to BTX injection. In those responding to the first injection, 76% will respond to a second injection with decreasing response to further injections, usually from antibody formation to this foreign protein. Less than 20% of patients failing to respond to the first injection will respond to a second injection. Studies have shown that BTX is less effective than PD long term. Additionally, some reports indicate that cardiomyotomy may be more difficult and less effective in patients who were previously treated with repeated BTX injections, possibly because of submucosal scar formation in the esophagus at the site of injection. The long-term safety of

repeated injections of BTX in achalasia is unknown. Therefore, BTX injection should be reserved for elderly patients or patients who are at high surgical risk or refuse PD and surgical myotomy.

Blepharospasm

Costa et al (2004) conducted a Cochrane review to evaluate the safety and efficacy of BTX-A in the treatment of blepharospasm. Participants of any age with a clinical diagnosis of idiopathic blepharospasm were eligible for inclusion. IM injections given in any administration schedule and by any injection technique, either EMG guided or not, were permitted. Previous therapy with BTX-A was allowed whether patients were still responding or not. The primary outcome measure for the meta-analysis was improvements in symptomatic rating scales (any). Secondary outcomes included changes in subjective evaluation of clinical status both by patients and clinicians, changes in quality of life assessments, adverse reactions (frequency and severity). The analysis included all randomized, controlled, double-blind trials of BTX-A vs. placebo. No suitable randomized, controlled trials fitting the criteria for inclusion in this meta-analysis were identified, and thus, all were excluded. Few controlled trials were found and they were of short duration and enrolled small numbers of patients. However, all of these trials found BTX-A to be superior to placebo as did large case-control and cohort studies, which reported that around 90% of patients benefited. The authors concluded that there are no high-quality, randomized, controlled efficacy data to support the use of BTX-A for blepharospasm. Despite this, other studies suggest that BTX-A is highly effective and safe for treating blepharospasm and support its use.

Hemifacial Spasm

Costa et al (2005) conducted a Cochrane review to evaluate the safety and efficacy of BTX-A for the treatment of hemifacial spasm (HFS). Participants of any age with a clinical diagnosis of HFS were eligible for inclusion. IM injections given in any administration schedule and by any injection technique, either EMG guided or not, were permitted. Previous therapy with BTX-A was allowed whether patients were still responding or not. The primary outcome for the meta-analysis was improvement in objective symptomatic rating scales (any). Secondary outcomes included changes in subjective evaluation of clinical status both by patients and clinicians, changes in QOL assessments, and adverse reactions (frequency and severity). Only one randomized, placebo-controlled trial was found involving 11 patients (3 male, 8 female) naïve to BTX-A therapy. All patients had been treated with medications unsuccessfully and one patient had undergone surgical microvascular decompressive procedures without lasting benefit. This was a cross-over trial during which patients underwent 4 sets of injections, comparing placebo (saline) with 3 different doses of BTX-A (Botox) (low dose [one-half of intermediate dose], intermediate dose, and high dose [twice the intermediate dose]). Injections were given at least one month apart as clinically indicated; participants were not reinjected until any response to the previous injection had been lost. Selection of muscles to inject and dose administered were based on clinical involvement. For each participant, the site of injections was kept constant. The mean dose ranged from 2.5 to 10 units of BTX-A per muscle. The total dose administered at any one time varied between 5 and 90 units. The primary endpoint was subjective patient self-assessment of global improvement on a 10-point analog scale where 5 was the preinjection baseline and values < 5 represented improvement. Secondary outcomes included objective physician assessment of improvement assessed with a categorical 10-point scale to characterize the frequency of spasms (range, 0 to 3), number of muscles involved (range, 0 to 4), and severity of spasms (range, 0 to 3), adverse events, and duration of improvement. All outcomes were assessed one month after injections. For both subjective and objective evaluations, a change of at least 2 points was considered substantial. Duration of benefit was defined as the time for the participant to return to subjective and objective baseline after each injection. One participant withdrew after 2 injections because of concern about facial weakness caused by BTX-A. Two others withdrew for domestic reasons, after one and 3 injection sessions, respectively. The data from these 3 participants were used in the analysis of treatment efficacy and adverse events. Adverse effects were reported for BTX-A, affecting all 11 participants on a combined total of 30 occasions. These included facial weakness (29), bruising (6), diplopia (4), ptosis (2), headache (2) lagophthalmos, blurred vision, tearing, dysphagia, nausea, and flu-like symptoms all in one occasion. The distribution of adverse events between the various treatment groups and doses was not clear. The authors concluded that the findings of this single eligible trial support the results of large, open-label, case-control studies showing a benefit rate between 76% and 100%. Despite the lack of good quality controlled data, the authors concluded that BTX-A is probably effective and safe for treating HFS.

Cervical Dystonia (CD)

BTX-A vs. Placebo

Costa et al (2005) performed a Cochrane review to evaluate the safety and efficacy of IM injections of BTX-A for the treatment of CD. Thirteen randomized, placebo-controlled, blinded trials were included in the analysis. Eight trials enrolling 361 patients used the Botox formulation of BTX-A, while 5 trials enrolling 319 patients used the Dysport formulation. The studies were all short-term, ranging from 6 to 16 weeks in duration. The dose and technique of administration varied significantly between studies. The primary outcome for the meta-analysis was improvement in rating scales (all). For most of the trials, the primary outcome was the change from baseline in the Tsui scale at week 4 to 6. The Tsui scale grades severity of postural deviance (rotatocollis, antecollis, retrocollis, head tilt, and elevation of shoulder), acknowledges the presence or absence of head tremor, as well as whether the movements are continuous or intermittent; the score ranges from 0 to 25. This scale does not assess disability, pain, or other subjective symptoms. The mean change in the Tsui scale score at peak of BTX-A effect was between 2 to 3 points and the odds ratio for any improvement in Tsui scores was 5.47 (95% CI 3.5-8.5). The NNT was 3 (95% CI 3-4). Adverse events were transient and either mild to moderate or intermittent. The number of participants with adverse events was significantly higher with BTX-A than placebo [OR 2.1 (95% CI: 1.3 to 3.4)] and number needed to harm [NNH] 6 (95% CI 4-15). The adverse events included neck weakness, dysphagia, dry mouth/sore throat, voice change/hoarseness, and injection site pain. The authors concluded that a single injection of BTX-A was safe and effective for treating CD. Trials that included patients previously treated with BTX-A suggest that further injection cycles continue to work for most patients. Adverse effects tended to be transient and rarely severe.

BTX-B vs. Placebo

Costa et al (2004) conducted a Cochrane review to evaluate the safety and efficacy of BTX-B for the treatment of CD. The analysis included 3 multicenter, randomized, placebo-controlled, parallel-group trials conducted in the US in the 1990s and included a total of 308 subjects over age 18 (mean age 50). The primary outcome for the meta-analysis was improvement in rating scales (all). All 3 trials used the change in the TWSTRS total score at week 4. The authors concluded that a single injection of BTX-B was safe and effective for treating CD. Long-term uncontrolled studies suggested that further injection cycles continue to work for most patients.

BTX-A vs. Anticholinergics

Costa (2005) conducted a Cochrane review to evaluate the safety and efficacy of BTX-A vs. anticholinergic drugs in the treatment of CD. Only one trial suitable for inclusion was found; thus, no meta-analysis was performed. The trial included in the analysis was a multicenter, double-blind, double-dummy, placebo-controlled, study in which patients were randomized to trihexyphenidyl (Artane[®]) 1 mg orally once daily, increased every 3 days to a maximum of 6 mg four times daily (mean dose 16.25 mg/day, range, 4 to 24) (n = 33) or BTX-A (Dysport) IM injections (mean dose 292 units: range, 38 to 440 units) at baseline and at week 8 (mean dose 262 units: range, 36 to 440). The selection of muscles to inject and the number of injection sites per muscle were based on the investigator criteria. For the primary outcome was the change in TWSTRS disability score. The authors gave the mean change (-4 in the trihexyphenidyl group and +2 in the BTX-A group) and the level of significance for this difference in medians (p = 0.0023 [95% CI: 4 to 12]). The authors commented that more participants in the BTX-A group experienced pain relief, but did not give exact numbers. The mean improvement in TWSTRS pain scale score was 1 point in the trihexyphenidyl group and 3 points in the BTX-A group; the SD for this difference was not provided, but the authors reported that it did not reach statistical significance. There were no serious adverse events. The authors concluded that the available evidence suggests that BTX-A injections provide more objective and subjective benefit than trihexyphenidyl to patients with CD, but no conclusions could be drawn regarding superiority over anticholinergics.

Focal Limb Dystonia

AAN (2008) conducted a meta-analysis to evaluate the safety and efficacy of BTX in the treatment of focal limb dystonia. Two trials met criteria. One randomized placebo-controlled trial (N=40) gave one injection and were offered another injection at 1 month. The primary endpoint was based on patient reported self evaluation. Based on patient response, 70% of those randomized to BTX wished to continue treatment compared to 32% of those receiving placebo (p =0.03). Significant improvement was also found in BTX-injected subjects compared to those receiving placebo in secondary outcome measures including a visual analog scale, symptoms severity scale, writer's

cramp rating scale, and assessment of writing speed, but not in the functional status scale. Temporary weakness and pain at the injection site were the only adverse events reported. Another RCT found was a prospective, double-blind, crossover study of 17 patients with several forms of limb dystonia. Subjects received a series of four injections in random order, including placebo. Using a patient subjective scale, 82% of patients receiving BTX had benefit compared to 6% (one patient) who received placebo. Using physician rating of videotapes, 59% improved with active treatment and 38% with placebo (not significant). There was no dose-response relationship for benefit, and there was a large degree of interobserver variability. BTX has shown some efficacy for the treatment of focal upper extremity limb dystonia, but the data is limited and not well defined.

Hypersecretory Disorders

Primary focal hyperhidrosis is a chronic idiopathic disorder of excessive sweating, which most often affects the axillae, palms, soles, and forehead. Treatment options include topical or systemic pharmacological therapy, iontophoresis, or surgical procedures. In a randomized, placebo-controlled, double-blind study of 320 subjects with axillary hyperhidrosis, 242 patients received BTX and 78 received saline placebo intradermally. Patients receiving BTX had a higher response rate (more than 50% reduction of sweat production compared to baseline sweating) at all time points than those receiving placebo (82% to 95% vs 20% to 37%; $p < 0.001$). In another RCT study of 145 patients with axillary hyperhidrosis, BTX was injected into one axilla and placebo was injected into the other. At week 2, sweat production was reduced in the axilla that had received BoNT as compared with the placebo-injected side ($p < 0.001$).

Migraine

Episodic migraine is a headache that is typically throbbing and often unilateral, usually accompanied by photophobia, phonophobia, nausea, or vomiting. The presence of focal neurological symptoms defines migraine with aura. Pharmacological agents are the mainstay for acute and prophylactic treatment of most forms of headache.

AAN (2008) conducted a meta-analysis to review the safety and efficacy of BTX in the treatment and prevention of episodic migraine. There were a total 11 randomized placebo-controlled studies of BTX included in the analysis. Three RCT studies used a fixed injection site strategy and enrolled patients had two to eight episodic migraines per month. Primary endpoints were the reductions from baseline in migraine frequency, maximum severity, and duration. The results indicate that there was no significant difference between BTX and placebo groups at 1 to 3 months after injection. Another RCT study was comprised of three sequential investigations of 418 patients with re-randomization at each stage and doses ranging from 7.5 to 50 U. All patients had a history of four to eight moderate to severe migraines per month. No statistically significant differences were found. Based on published RCT studies, the efficacy for the treatment of migraine appears to be non-significant. The authors concluded that BTX was probably ineffective for the treatment of episodic migraine.

Gupta (2006) systematically reviewed clinical trials evaluating the use of scalp IM injections of BTX-A for the prophylactic treatment of migraine. Only trials with level of evidence of I and II and a sample size > 20 were included in the analysis. A summary of these studies is provided in the table below.

Level I and II clinical studies of BTX-A in the prophylactic treatment of migraine

Study level of evidence	No. of patients, sex, age	Results
II	106 (95 F; 11 M; 21 - 74 yrs)	51% no attacks for 4.1 months ($p < 0.05$) 38% improvement $\geq 50\%$ for 2.7 months
II	27 (25 F; 2 M; 26 - 61 yrs)	85% improvement for 2 to 6 months 4 patients without improvement
I B	123 (105 F; 3 M; 18 - 65 yrs)	25 units: significant reduction in migraine frequency (month 3, $p < 0.014$) and intensity (month 2, $p \leq 0.008$ and month 3, $p < 0.042$) 75 units: no improvement; increased adverse events
1 B	56	Significant reduction of pain intensity in group 1 (frontal/temporal BTX-A) compared with group 4

		(frontal/temporal placebo) at week 12 ($p < 0.04$); trend to reduction of migraine frequency and duration
I B	30	Significant reduction in migraine frequency at day 30 ($p < 0.02$), day 60 ($p < 0.02$), day 90 ($p < 0.01$); trend to reduction of migraine severity and duration
II	48	58% reported decrease in migraine-associated disability; episodic migraine patients responded better than chronic migraine patients
I B	60 (chronic daily headache, including chronic migraine)	Significantly fewer headache days from weeks 8 to 12 compared with the placebo group ($p < 0.05$). Patients receiving second BTX-A injection at 12 weeks reported fewer headache days at 24 weeks than those receiving one injection ($p < 0.05$)
I B	60 (83 F; 17 M)	No effect on migraine frequency or severity or on psychosocial impact of migraine

IA: Evidence based on meta-analysis of randomized and controlled studies

IB: Evidence based on at least one randomized and controlled study

II: Evidence based on at least one well-designed controlled study without randomization

III: Evidence based on well-designed, nonexperimental, descriptive studies

IV: Evidence based on experiences of expert committees or experts; case reports

The author concluded that responses to BTX-A in migraine patients seen in clinical trials were inconsistent, unpredictable, not dose-dependent, and have not been compared against established therapies. BTX-A-induced direct analgesia independent of skeletal muscle relaxation has not been seen in normal human volunteers. The placebo effect of needling itself has not been excluded in BTX-A studies in migraine patients. Thus, the efficacy of BTX-A in preventing migraine headaches remains controversial.

As of 2000, the US Headache Consortium does not list BTX as a treatment option for the prevention or treatment of migraine headache.

Neurological bladder

Patients with neurogenic bladder suffer from detrusor overactivity (detrusor hyperreflexia), which may be combined with detrusor sphincter dyssynergia (DSD; uncoordinated voiding). Both conditions cause high intravesical pressure and can lead to upper urinary tract damage. Treatment for both DSD and detrusor overactivity include pharmacological therapy, catheterization, and surgery.

Schmid (2006) evaluated the safety and efficacy of BTX-A (unknown formulation) injections in the detrusor muscle to treat patients with idiopathic overactive bladder (IDO) resistant to conventional treatment such as anticholinergics in a multicenter, open-label case series. A total of 100 patients were consecutively injected with BTX-A 100 units into the detrusor muscle at 30 sites. All patients were asked to gradually taper their anticholinergic medication(s) within 1 week after BTX-A administration and to completely discontinue it after that time. Primary endpoints were daytime frequency (DF), nocturia (N), urge incontinence episodes, and the need to change pads per 24 hours, recorded in 3-day voiding diaries, as well as subjective cure of urgency using a 3-point scale (3 = strong urgency; 2 = moderate/greater than 50% decreased urgency; 1 = no urgency). Overall, 88% of patients showed significant improvements in bladder function in regard to subjective symptoms (excellent/very satisfied or improved/satisfied) as well as urodynamic parameters after 4 and 12 weeks ($p < 0.001$). Within 1 to 2 weeks (mean 5 days) after BTX-A injections, urgency completely disappeared in 72 of 100 patients (72%) at the 4-week assessment and in 66% at the 12-week follow-up. Incontinence, which was initially present in 84 patients, completely disappeared in 74% at the 4-week follow-up and in 80% at 12 weeks. This was also reflected in a significant decrease in the median number of pads changed per 24 hours. Mean DF decreased significantly from 13.5 to 7 micturitions daily (-50%) after 4 and 12 weeks ($p < 0.0001$), then minimally increased to 8 micturitions daily after 36 weeks. Mean N decreased from 4 to 1.5 micturitions nightly after 4 and 12 weeks ($p < 0.0001$), then slightly increased to 2.1 micturitions nightly at 36 weeks. The mean duration of effect was 6 months (range, 5 to 9); a slight to moderate decrease in the maximal effect was noted in 20 patients with a complete 9-month follow-up. The same tendency was observed in another 16 patients lacking 9-month urodynamic evaluations. Incontinence was still absent in 7 patients (33%), mild in 10

(50%), and severe in 3 (17%), whereas urgency was moderate in 83% and strong in 17%. QOL assessments at 4 and 12-week follow-ups revealed a statistically significant improvement from baseline in all urge-related items evaluated by KHQ ($p < 0.001$). Ninety percent of patients experienced improvement in ≥ 1 KHQ category, including ability to travel, effect on sleep, participation in social life, accomplishment of household tasks, and general effect on daily life. This positive effect increased at the 3-month follow-up and then decreased somewhat at 9 months. The authors concluded that intradetrusor BTX-A injections may be an efficient and safe treatment option in patients with severe idiopathic overactive bladder resistant to all conventional treatments; improvement in symptoms may be seen for at least 6 months after treatment.

Schurch et al (2005) evaluated the safety and efficacy of BTX-A for the treatment of neurogenic urinary incontinence in a randomized, double-blind, placebo-controlled trial. A total of 59 patients with urinary incontinence caused by neurogenic detrusor overactivity (NDO) (due to spinal cord injury in 53 and multiple sclerosis in 6) requiring clean intermittent self-catheterization (CIC) were randomized to receive a single IM injection into the detrusor muscle of BTX-A 200 units ($n = 19$) or 300 units ($n = 19$) or placebo ($n = 21$). Primary endpoint was change in daily frequency of urinary incontinence episodes monitored using a patient diary. Follow-up visits occurred at weeks 2, 6, 12, 18, and 24. QOL was assessed using the Incontinence Quality of Life (I-QOL) Questionnaire. The results showed that there were significant decreases in incontinence episodes at all time points in the two BTX-A groups, except at weeks 12 and 18 in the BTX-A 200 unit group and there were none in the placebo group. The decreases in the BTX-A groups represented a reduction in incontinence episodes of ~50% and was statistically significant ($P < 0.05$). The authors concluded that IM injections of BTX-A into the detrusor muscle can provide rapid, well tolerated, clinically significant decreases in signs and symptoms of urinary incontinence caused by NDO during a 24-week period.

Spasticity

AAN (2008) A meta-analysis completed by American Academy of Neurology in 2008 found 11 RCT studies in adult upper extremity spasticity (BTX-A =10; BTX-B =1). All but one used measurements of tone as the primary endpoint. All of the studies demonstrated that BTX is safe and reduced tone in a dose dependent manner; however, resistance to passive movement was not shown to correlate with improvement in active function (defined as activities that the subject can voluntarily perform with the spastic limb). For lower extremity spasticity, 3 RCT studies were found. Most studies focused on reduction in muscle tone with demonstrated efficacy, but only few measured changes in gait. One placebo-controlled crossover protocol reported a non-significant 17% increase in walking speed after BoNT injection into calf muscles in spastic hemiparesis. Another placebo-controlled study failed to demonstrate gains in walking speed. Overall, the data appears to be non-significant for lower extremity spasticity. The authors concluded that the recommended doses of BoNT injection into specific muscles have been derived predominantly from expert consensus rather than dose-response studies. BTX has been shown to be effective in the treatment of adult spasticity in the upper limb in reducing muscle tone and improving passive function, while the data related to lower spasticity has not been established. Improvement in active function has not been shown in the data. There are no controlled studies comparing BTX to other treatment modalities for spasticity. Currently, there is a lack of data to determine efficacy of BoNT for spasticity in children.

Wasiak (2004) conducted a Cochrane review to evaluate the safety and efficacy of BTX-A as an adjunct to managing the upper limb in children with spastic cerebral palsy (CP). Participants between 0 and 19 years of age requiring treatment for upper limb spasticity and muscle tone secondary to CP were eligible for inclusion. The analysis included all randomized controlled trials comparing IM BTX-A injections of any dosage into any muscle group of the upper limb compared with either placebo; no other treatment, or other interventions. Only two trials met inclusion criteria and there were no outcome measures in common between the 2 included trials; thus, data could not be combined for a meta-analysis. In the first randomized, controlled, double-blind trial, the effects of BTX-A (either Botox 90 to 250 units at 4 to 7 units/kg or Dysport 160 to 400 units at 8 to 9 units/kg) were compared with placebo (normal saline) on the hemiplegic upper limb in 14 patients with CP (5 male, 9 female, mean age 9 years). The primary endpoints were active range of motion (ROM) of metacarpal phalangeal (MCP); wrist and elbow extension; thumb in palm position for both thumb extension and abduction; Ashworth scale (a widely used 5-point scale used to measure spasticity of central or peripheral origin ranging from 0 to 5, i.e., no increase in tone to limb rigid in flexion or extension) for thumb, wrist, and elbow tone; wrist resonance frequency (tone); grasp and release of an empty capsule scored using a modified Reddihough scale, and the number of transfers of a coin. Median change and range data were provided. The second randomized, controlled, assessor-blind trial compared

BTX-A (Botox 2 to 6 units/kg) in conjunction with occupational therapy with occupational therapy alone in 30 children (20 male, 10 female) aged 2 to 10 years diagnosed with hemiplegic CP and moderate spasticity of the elbow, wrist, or thumb with a modified Ashworth score ≥ 2 ; subjects had full passive range and the ability to initiate voluntary movement of the digits. The primary outcome was the Quality of Upper Extremity Skills Test (QUEST). Secondary endpoints were the Pediatric Evaluation of Disability Inventory (PEDI); sphygmomanometer measurements of grip strength; modified Ashworth scale for elbow, wrist, and thumb extension and forearm supination; and passive elbow and wrist extension, supination, and thumb abduction. Study 1 reported at 12 weeks, the grasp and release score, tone at the wrist, and wrist resonance frequency improved significantly more in the BTX-A group than the placebo group. Study 2 reported at 1 month the QUEST changes score favored better quality of movement in the BTX-A group, the change in PEDI scores were higher in the BTX-A group, and increase in ROM at the elbow and towards supination were greater in the BTX-A group compared to placebo. The grip strength decreased in the BTX-A group at 1 and 3 months and increased at 6 months. There was; however, little consistent difference in change between groups on the modified Ashworth scale. The mean changes for these trends in favor of the BTX-A group were small. The authors concluded that this systematic review did not find sufficient evidence to support or refute the use of IM injections of BTX-A as an adjunct to managing the upper limb in children with spastic cerebral palsy. Only one of the two identified randomized controlled trials reported some promising results in support of reduced muscle tone following BTX-A injections.

Ade-Hall (2000) conducted a Cochrane review to evaluate the safety and efficacy of BTX-A for the treatment of lower limb spasticity in children with CP. Participants between 0 and 19 years of age requiring treatment for lower limb spasticity secondary to CP were eligible for inclusion. Three studies met inclusion criteria, but meta-analysis was not possible because the results were presented in an incompatible form. Where appropriate, a Peto OR with a 95% CI was calculated. Study 1 (n = 12) compared BTX-A to placebo in a double-blind fashion. Outcome measures included a physician rating scale (PRS), Biodex isokinetic computerized dynamometry, physiotherapy evaluations, parent/guardian assessment. Eighty-three percent (5) of children who received BTX-A and 33% (2) who received placebo had an improved gait pattern (PRS) 4 to 6 weeks after the intervention. Statistical significance was not reported. Study 2 and 3 compared BTX-A to plaster casts; however, each trial reported the results in different ways, precluding a pooled statistical analysis of the data. Two children were lost from the BTX-A group following randomization in Study 3. Each study reported statistically significant improvements in gait pattern (PRS) for both the BTX-A group and the cast group at 12 weeks (Study 2) and 6 months (Study 3) following intervention. However, neither study was able to show a significant difference between the groups. Study 3 used the gross motor function measure (GMFM) to measure changes in standing function and dynamic function. There was a significant improvement following administration of BTX-A and of casts, but no significant difference between the improvements of the 2 groups. Study 2 assessed 12 out of 20 children using 3D gait analysis and found the improvement in maximal ankle dorsiflexion and plantar flexion at 12 weeks post intervention to be significantly greater in the children who had received BTX-A compared to those who had worn casts. The other gait parameters did not show any significant differences between the groups. Muscle tone, rated on the Ashworth scale, improved significantly for both groups in Study 3; however, there was no significant difference between the groups. Study 2 found no significant change in muscle tone in either group. Passive range of ankle dorsiflexion was significantly improved for each group in Study 3, but only for the BTX-A group in Study 2. The difference between groups was not significant in either trial. Study 3 questioned parents on their satisfaction with treatment (rather than their perception of how well treatment had worked). All the reported comments from the BTX-A group were positive, as were some from the cast group. The negative comments came from the cast group and included inconvenience and weakness of legs following their removal. The two authors who compared BTX-A with casts also compared the cost of administration of each treatment and concluded that once parental time and travel expenses had been taken into account, the two treatments were cost comparable. The authors concluded that this systematic review did not reveal strong controlled evidence to support or refute the use of BTX-A for the treatment of leg spasticity in CP.

Cardoso et al (2005) performed a meta-analysis evaluating the safety and efficacy of BTX-A in the management of patients with upper limb spasticity following stroke. Five randomized, double-blind, placebo-controlled trials meeting the eligibility criteria were included in the analysis. The study participants had not previously received other pharmacological or surgical treatment for spasticity and all were receiving physiotherapy. The primary efficacy measure in all but one study was muscle tone activity using the modified Ashworth scale (MAS) or Global Assessment Score (GAS). All of the studies described the clinical data referring from the period between the fourth and sixth weeks after BTX-A administration. Clinical improvement at week 4-6 after injection assessed with the MAS was significantly higher in the BTX-A group compared to placebo in all of the included studies (WMD = 0.95,

95% CI: 0.74 to 1.17, $Z = 8.57$, $p < 0.00001$). Mean MAS score was also higher when wrist joint was included at the same endpoint ($Z = 8.44$, $p < 0.00001$). The mean GAS scores improvement was significantly higher in all parameters in the BTX-A group (WMD = 1.11, 95% CI: 0.81 to 1.41, $Z = 7.32$, $p < 0.00001$). Two of the 3 studies assessing GAS did not show statistically significant differences between BTX-A and placebo; however, when all studies were analyzed, BTX-A showed a significantly better therapeutic response compared to placebo (OR = 3.27, 95% CI: 1.38 to 7.74). Although the outcomes showed that BTX-A resulted in significantly greater reduction in muscle tone compared to placebo, the overall effect on functional disability was not fully observed in the majority of studies. Most of the studies did not employ functional or QOL measures. Also, the studied population had different times of post-stroke spasticity and some patients may have adapted to their spasticity. The authors concluded that BTX-A was superior to placebo in reducing upper limb spasticity after stroke and was well tolerated; however, no data is available regarding the long-term use of BTX-A.

Strabismus

Botox Package Insert (2006) describes experience with 667 adults (aged 12 to 90 years) and 356 children (aged 2 months to 12 years) with strabismus treated with one or more injections of BTX-A into the extraocular muscles. Fifty-five percent of patients in the adult group with esotropia ($n = 384$) improved to an alignment of ≤ 10 prism diopters (PD) when evaluated at a follow-up of 6 to 83 months (average 17 months); in those patients with exotropia ($n = 293$), 52% improved to an alignment of ≤ 10 PD. Sixty-five percent of patients in the child group with esotropia ($n = 261$) improved to an alignment of ≤ 10 PD as did 47% with exotropia ($n = 95$) when evaluated at a follow-up of 6 to 65 months (average 27 months).

Sapsmodic Dysphonia

Watts (2004) conducted a Cochrane review to evaluate the safety and efficacy of BTX for the treatment of spasmodic dysphonia (SD). All randomized controlled trials that compared the use of BTX to placebo, no treatment, or alternative treatments in adults with a primary diagnosis of adductor, abductor, or mixed SD were eligible for inclusion in the analysis. Experimental interventions included any unilateral or bilateral injection of BTX into a muscle or muscles of the laryngeal mechanism. There was no restriction on dosage, number of treatments or time to outcome measure. Only one study met the inclusion criteria based on methodological quality and availability of appropriate data for analysis; thus, a meta-analysis was not possible. This was a randomized, double-blind, placebo-controlled, cross-over trial evaluating the effects of BTX-A (Botox) on voice quality (via spectrographic analysis), perceived voice improvement, and acoustic measures in 13 subjects with adductor SD. The results showed that BTX-A produced significantly decreased perturbation and fundamental frequency range compared to placebo. The BTX-A group also showed a significant improvement in ratings of speech quality (spectrographic analysis) and perceived improvements compared to placebo (for both self and independent ratings. Data provided for the Self Rating of Improvement did not allow for a calculation of effect. Outcome measures were assessed at 4 days post treatment and an average improvement lasting 3 months was reported. Breathiness was reported as an adverse effect in 2 subjects. No information was provided with regard to the measurement of vocal production beyond the 4 days. Other studies published in the literature have reported that the effects of BTX typically last between 3 and 12 months. The authors concluded that the randomized controlled trials published in the literature have demonstrated a benefit of BTX treatment in subjective measures of voice production and select acoustic and aerodynamic variables. However, due to the small number of studies available and methodological differences, no firm conclusions can be drawn regarding the efficacy of BTX for all types of SD or for patients with different behavioral or clinical characteristics.

Tremor

AAN (2008) A randomized placebo-controlled study ($N=25$) injecting either 50 units of BTX-A (Botox[®]) or placebo into the wrist flexors and extensors of the dominant limb, found that BTX produced significant improvement on the tremor severity rating scale 4 weeks after injection compared to placebo. Postural accelerometry measurements showed a 30% reduction in amplitude in 9 of 12 BTX-treated subjects and in 1 of 9 placebo-treated subjects ($p < 0.05$). Oral agents still continue to be considered first line therapy (ex. propranolol and primidone). According to American Academy of Neurology 2008, there is presently no data comparing the efficacy of BTX to other treatment modalities and BTX should be reserved as 2nd line treatment.

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