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USE OF BOTULINUM TOXIN-A IN PAIN ASSOCIATED WITH NEUROMUSCULAR DISORDERS

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Executive Summary

The strains of the bacterium Clostridium botulinum produce a group of the most potent biological toxins, which act by preventing synaptic transmission of acetylcholine across the neuromuscular junction. Botulinum toxin (BTX) is classified into eight distinct serologically related neurotoxins, seven of which can cause paralysis. Three of these types A, B and E are also associated with epidemic botulism from food poisonings. The Botulinum toxins are members of a class of drugs and as such show important similarities and differences. BTX-A is the most widely used subtype for medical indications and is injected directly into affected muscles in order to produce chemical denervation of the abnormally functioning muscles by blocking synaptic transmission. Its effects are dose dependent and last for approximately 2 to 6 months. Repeated injections are needed in the majority of cases to maintain the beneficial effects. Pharmacological and surgical approaches for breaking the connection between muscle and nerve have been traditionally used with neuromuscular disorders involving chronic muscle spasm. Chemodenervation by BTX treatment was first used in the 1970s in humans and has been proposed as an alternative to the side effects and questionable efficacy of drug treatment and the possible serious complications associated with surgical interventions.

Spasticity can be defined as a motor disorder characterized by an increase in tonic stretch reflexes with exaggerated tendon jerks and is caused in part by a disturbed processing of peripheral afferent messages at the spinal cord level. Pain, disturbed posture, and permanent contractures may result. Other mechanisms have also been postulated for treatment effects of botulinum toxins on pain including nociception changes. Proof of efficacy of a botulinum toxin depends on accumulation of appropriate clinical information for each pharmaceutical preparation of the toxin. Spasticity can manifest as myofascial pain or tension headache.

Sustained muscle contraction also characterizes a group of disorders known as dystonias. Some of the clinical manifestations of dystonia include: cervical dystonia, which may produce twisting and involuntary muscle contractions of the head and neck; Meige's syndrome, characterized by spasm of the eyelids and oromandibular regions; hand dystonias, which may be induced by repetitive movement such as writing, playing a musical instrument, or typing; blepharospasm, the involuntary closing of the eyelid muscles; and spasmodic dysphonia, a disorder of speech characterized by abnormal control of the laryngeal muscles. This group of muscular disorders can be primary, also termed idiopathic, or they may be secondary to trauma or cerebrovascular accident.

Note: This report evaluates the use of Botulinum toxin type-A in the control of pain associated with neuromuscular disorders and excludes smooth muscle/sphincter disorders.

Findings

There are a large number of clinical studies of BTX and for the purpose of establishing categories among the multiple reports describing the use of BTX in neuromuscular pain, one may divide case studies into the categories based on the predominance of the movement

disorder, primarily the focal dystonias, or the predominance of spasticity, primarily of the central nervous system (CNS) origin. Most of these studies, however, have very small sample sizes. Majority of the studies and the discussion in this report pertains to Botulinum toxin type A.

The efficacy, safety, and appropriate patient selection criteria for BTX treatment of neuromuscular disorders were evaluated based on data published in the peer-reviewed literature. Two studies found positive results in BTX treatment of headache, while a third study found no difference between BTX and placebo. BTX was found to successfully alleviate pain associated with myofascial pain. In four studies using comparison groups, stroke-induced spasticity was treated with BTX, and all four found significant reductions in spasticity relative to the control groups. Eight studies treating cerebral palsy with BTX were examined, and all found improvement in spasticity symptoms, with a ninth study finding BTX-A to be effective in the treatment of pain associated with spasticity caused by adductor surgery. A double-blind placebo-controlled study found a significant reduction in spasticity among a population of multiple sclerosis patients. One case series study found lessening of pain and dystonia in the "off" phase of painful dystonia associated with Parkinson's disease. Another study using a mixed rigidity and spasticity population found a 35.7 percent improvement rate among Parkinson's patients, with an 83.5 percent improvement rate among focal dystonia patients. Among the reviewed studies comparing BTX to conventional medical treatment, one study found that BTX in combination with electrical stimulation produced better results in the treatment of upper-limb post-stroke spasticity than BTX alone. Another study found that BTX produced a greater magnitude of reduction in symptoms of equinovarus calf, and for a longer duration, than casting, and one study found that BTX produced results comparable with pneumatic dilation in the treatment of achalasia.

Four studies examined BTX to treat cervical dystonia: two found that BTX-A significantly outperformed placebo in symptom alleviation; one found that BTX-B outperformed placebo among patients who were BTX-A responsive and in patients not responsive to BTX-A and one found that the efficacy of BTX-A treatment was superior to standard anticholinergic medication and produced fewer side effects. Three studies were performed using BTX-A to treat upper limb dystonias. All found significant improvement on subjective and objective measures, although one study found that writer's cramp patients with joint-wrist deviation benefited significantly more than patients with neutral wrist positions. Two studies were performed where blepharospasm and mixed blepharospasm/cervicocranial dystonia patients were treated with BTX-A. One study used BTX-A and the other BTX-F, and both found significant improvement in the blepharospasm patients however only modest improvement among the mixed blepharospasm/dystonia patients. A double-blind study of BTX-A treatment of adductor spasmodic dysphonia found that the toxin group experienced significantly greater improvement on several measures than the placebo group.

Potential biases in the reviewed studies include baseline differences between toxin and control groups on clinical characteristics, heterogeneous samples, small sample sizes, absence of inferential statistics, brief follow-up periods, and significant loss to follow-up. Complications noted in the reviewed studies included weakness, dysphagia, dry mouth, pain, infection, injection site pain, headache, flu syndrome, nausea, hematoma, tearing, blurred vision, ecchymosis, ptosis, diplopia, vertical deviation, and excessive breathiness. No cardiorespiratory side effects were noted. The FDA has approved BTX-A (Botox - Allergan) for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia. Also, BTX-A is indicated for treatment of strabismus and blepharospasm associated with dystonia. Recently, FDA has approved the use of Botulinum toxin type B (Myobloc - Elan Pharmaceuticals) for the treatment of cervical dystonia. At this time no published information on peer reviewed clinical trials for this product is available except in cervical dystonia.

Introduction

The strains of the bacterium Clostridium botulinum produce a group of the most potent biological toxins that act by preventing synaptic transmission of acetylcholine across the

neuromuscular junction. Botulinum toxin (BTX) is classified into eight distinct serologically related neurotoxins, seven of which can cause paralysis. Three of these types A, B and E are also associated with epidemic botulism from food poisonings. The Botulinum toxins are members of a class of drugs and as such show important similarities and differences.

Although these toxins are antigenically distinct (i.e different serotypes), they possess similar molecular weights, and have a similar subunit structure, though different amino acid sequences. The active toxins have a molecular weight of approximately 150,000 daltons and are composed of a heavy chain (100,000 daltons) that is linked by a disulfide bond to a light chain (50,000 daltons) associated with a single Zinc atom.[1] Botulinum toxin as a class (BTX) exerts its effect at the neuromuscular junction by inhibiting the release of acetylcholine, and this in turn causes flaccid paralysis. Botulinum toxin type A (BTX-A) causes chemical denervation by preventing synaptic transmission and effectively weakening the muscle. BTX-A injected into a muscle binds reversibly to the nerve, where it is internalized into the nerve ending, causing paralysis of the muscle by preventing the release of acetylcholine. BTX-A binds rapidly and with high affinity to the nerve, however, its maximal paralytic effect peaks 4 to 7 days after the injection. Very little toxin reaches the systemic circulation. Muscle paralysis is dose dependent and reversible. Recovery either occurs when new portions of the nerve, called axonal terminals, sprout and reinnervate the muscle or when the original terminal is reactivated. Side effects occur when too much BTX-A is injected, when the drug is not contained in an injected muscle or very rarely when an underlying syndrome that is latent such as Myasthenia Gravis is unmasked by the injection. Clinical effects of BTX-A injections lasts from two to six months or more depending on the dose and condition being treated and repeated treatments are often necessary to control abnormal muscle functioning. Treatment with BTX-A does not cause a return to normal muscle functioning since the underlying cause is still present. BTX-A treatment weakens specific muscles, allowing graded movements, unlike other pharmacological treatments that weaken all muscles.[2]

BTX-A, (in the U.S., manufactured by Allergan under the name Botox) is available in a standard vial that contains 100 U of toxin. The toxin is shipped on dry ice and is stored frozen. The vacuum dried toxin is reconstituted with 0.9 percent nonpreserved sterile saline to various concentrations just before usage, depending on the indication. Preservatives in the saline deactivate the toxin. The injection of the diluent into the vial must be performed according to manufacturers recommendations with gentle mixing after allowing the vacuum in the vial to draw in the injected diluent. The lethal dose for 50 percent (LD/50) of humans is estimated to be 39 units/kg.

Dystonic muscles are located either clinically by visual inspection and palpation or with the use of electromyography (EMG). Injections of BTX-A toxin can be performed with or without EMG guidance. When EMG is not used, BTX-A is injected into the dystonic muscle using either a sterile tuberculin syringe or a 27- to 30-gauge needle. Otherwise, under local anesthesia or light general anesthesia, a Teflon-coated, EMG-guided needle is inserted into the selected muscle, and a diluted solution of BTX-A is injected. BTX-A treatment may involve injections into more than one muscle, and it may be necessary to repeat treatment every 3 to 6 months. The full effect is apparent 4 to 7 days after the injection and can last from 2 to 6 months.[2-4]

There are a burgeoning number of clinical studies of BTX-A. For the purpose of establishing categories among the multiple reports describing the use of BTX-A in musculoskeletal pain, case studies have been divided into these categories based on the predominance of the movement disorder, primarily the focal dystonias, or the predominance of spasticity, primarily of the central nervous system (CNS) origin.

Focal Dystonia with Pain

Normal muscles have a certain amount of inherent tension, or muscle "tone". When there is a malfunction in muscle tone, a condition called dystonia occurs, which is characterized by sustained or spasmodic abnormal movements, contractures, or postures. Repeated, patterned

contractures often cause twisting (e.g., torticollis), flexion or extension (e.g., writer's cramp), and squeezing (e.g., blepharospasm). The underlying cause of dystonic movement is dysfunction within the CNS control mechanisms.[2,5] A rating scale has been developed to assess baseline cramping and therapeutic response to BTX-A in upper limb dystonia.[6]

Population estimates places the prevalence of cervical dystonia at 8 per 100,000.[7-9] Dystonia can develop at any age, and childhood-onset dystonia is particularly common among Ashkenazic Jews, suggesting an underlying genetic predisposition.

One approach used to prevent excessive muscle contractions is to break the connection between the nerve and the muscle, preventing synaptic transmission. This process is called denervation and effectively weakens the muscle. Initially, surgical procedures were used to denervate the abnormally functioning muscles. However, in the early 1970s, investigators observed the value of using microbial proteins such as BTX, to treat muscular disorders.[2,8]

Treatment of pain with BTX-A is effective in various focal dystonias including writer's cramp, multiple sclerosis and Parkinson's disease. Studies indicate that BTX-A is effective in treating pain associated with musculoskeletal hyperactivity. Although control of undesirable movement or muscle spasm is the most common condition for which BTX-A is regularly used, several such conditions are associated with a significant element of pain. BTX-A is used as a therapeutic agent in syndromes having a significant component of pain associated with musculoskeletal hyperactivity.

Definitions:

Cranial-Cervical Dystonia (Spasmodic Torticollis)
Cranial-cervical dystonia, the most common form of dystonia, is an involuntary, sustained contraction of the periorbital, facial, oromandibular, pharyngeal, laryngeal, or cervical muscles. When occurring in the neck muscles, the sustained neck muscle contractions cause the head to deviate from its normal position, thereby causing torticollis when the head twists toward the shoulder. It is termed laterocollis with a tilting of the head towards the shoulder, retrocollis with the extension of the head, and anterocollis with the flexion of the head. Stroke, multiple sclerosis, thalamotomy, neurodegenerative disease, hydrocephalus, and drugs may be responsible for craniofacial dystonia in some patients, although the majority of patients have no specific cause. Various surgical approaches have been used to treat this condition, however, the risk to speech, irreversible damage to neck muscles, and cervical instability has made these options unsatisfactory. With the exception of dopa-responsive dystonia, conventional pharmacotherapy benefits few patients with dystonia.[10-12]

Focal Hand Dystonia
Focal hand dystonia is characterized by involuntary muscle contractions that result in abnormal posturing of the fingers, wrists, or forearms, and impaired motor control during skilled manual tasks. "Writer's cramp" is the most common form of hand dystonia. Hand dystonia can be classified as "simple", where there is difficulty in performing one task only; "dystonic", where the muscle spasms occur with several tasks from the onset; and "progressive", where there is increasing difficulty performing an increasing number of new tasks. Electrophysiological studies have demonstrated a co-contraction of agonist and antagonist muscles, with an overflow of activity to other remote muscles. Beta-blockers, primodine, benzodiazepines and alcohol often suppress the amplitude of tremor, however, functional disability may persist. Patients with hand dystonia may be forced to change their occupation or resign from their jobs because hand cramps prevent them from writing, typing, or performing other occupational activities. Essential tremor involves postural and action tremor of the arms, hands, and sometimes the head, and is produced by alternating or synchronous contractions of agonist and antagonist muscles.[8,13,14]

Blepharospasm
Blepharospasm is a variable, progressive, bilateral, involuntary focal dyskinesia characterized by spasmodic, forceful eyelid closure due to involuntary contraction of the orbicularis oculi

muscles. This disability can be severe and render a patient functionally blind. The disorder may be associated with cranial-cervical dystonia (Meige's Syndrome).[15,16]

Spasmodic dysphonia
Spasmodic dysphonia (SD), also known as laryngeal dystonia, is a neurologic voice disorder that is characterized by jerky, strained, strangled and sometimes unintelligible speech. Intermittent vocal interruptions (vocal spasms) and periods of voice loss may alternate with periods of near normal voice. It is estimated that 20,000 adults in the United States have this disorder. The condition can range from interfering mildly with an individual's ability to communicate, to being socially incapacitating and unemployable. In SD, the muscles of the larynx fail to relax properly, resulting in abnormal function of the vocal cords. The cause is unknown, however, evidence suggests a genetic origin for some cases, and a central neurologic source in most cases.[17]

Diagnosis of laryngeal dystonia, or spasmodic dystonia, depends mainly on clinical symptoms. Two distinct subtypes have been identified, adductor and abductor dysphonia. Patients with adductor dysphonia have a strained, strangled sounding voice with intermittent breaks in speech. These voice irregularities are due to irregular hyperadductions of the vocal folds during phonation, which increase resistance to the phonatory airflow during phonation. The relatively rare abductor type of dysphonia causes a breathy or whispered voice due to intermittent abductions of the vocal folds that provoke a fall in airflow resistance through the glottis. Some patients have a combination of the two.[10]

Parkinson's Disease
Foot dystonia is sometimes observed in untreated Parkinson's disease, but occurs more frequently in the advanced stages in connection with chronic levodopa (L-dopa) treatment. Approximately 1 in 3 Parkinson's disease patients treated with this drug for a period exceeding 3 years will develop this symptom. The foot dystonia is usually related to the timing of the L-dopa intake and is characterized by "on" phases and "off" phases.[18]

Temporomandibular disorders
Temporomandibular disorder (TMD) is a collective term used to describe a group of conditions involving the temporomandibular joint (TMJ), masticatory muscles, and associated structures. The incidence of TMD in North America is estimated at 10%.[19] It often presents as pain and dysfunction specific to the jaws. Associated complaints can include earache, headache, neck pain and facial swelling.[20]

Findings

Cranial-Cervical Dystonia
Four controlled studies have reported using BTX-A to treat cervical dystonia. These studies suggest that patients receiving toxin experienced greater symptom relief, fewer side effects, and subjective and objective improvement from BTX-A for varying patient groups with cranial-cervical dystonia.[11,21-23]

BTX-A may reduce pain independent of its effect on muscle spasms. The use of BTX-A in cervical dystonia patients results in pain relief that exceeds the motor benefit. Acquardo et al.[24] treated two patients with cervical taut bands and trigger points along the trapezius and splenius capitis muscles and reported excellent results.

Focal Hand Dystonia
BTX has been used to treat hand dystonias in three controlled studies. These studies concluded that BTX lessens some of the symptoms of hand dystonias, including writer's cramp, with a correlation between subjective and objective improvement. Side effects included muscle weakness.[25-27]

To improve efficacy and minimize the spread of the toxin into unintended adjacent muscles in

patients with occupational cramping, such as writing or typing-induced dystonia, multiple low-dose injections rather than a single large dose can be employed.[6]

In a sample of long-term recipients of BTX-A treatment for hand dystonia, Karp et al.[95] found that women required lower doses of toxin, had a better outcome, and experienced a longer duration of benefit than men. Women were also more likely to continue the injections.

Blepharospasm
Jankovic and Orman12 report treating a mixed blepharospasm and Meige's disease sample with BTX-A and found significant improvement in the blepharospasm group relative to the placebo group. There was only a modest effect among the Meige's disease patients compared with the placebo recipients. Jankovic et al.[8] found that BTX-A produced significant symptom relief among blepharospasm patients, however, only modest relief in patients who presented with blepharospasm and cranial-cervical dystonia relative to the placebo-treated group. Mezaki et al.[28] demonstrated that BTX-F has equivalent efficacy and side effect profile but shorter duration of action than BTX-A. All blepharospasm patients in their sample showed clinical improvement.

Spasmodic dysphonia
In adductor spasmodic dysphonia, paralysis of the thyroarytenoid muscle helps prevent the development of the high subglottic pressure that is associated with vocal spasms. Recently, impressive relief of symptoms has been reported with injection of BTX-A into the thyroarytenoid muscles.

Parkinson's Disease
In some case studies, BTX-A treatment of essential tremor and tremor associated with Parkinson's disease have produced mixed results. Some patients reporting subjective improvement but lack of objective validation.[29] Pacchetti et al.[18] found that BTX-A reduces the pain and spasticity associated with "Off" dystonia of Parkinson's disease.

Temporomandibular Disorder
Forty-six subjects with temporomandibular disorder were enrolled in an uncontrolled study and treated with 150 U of BTX-A. BTX-A injections produced significant improvements in pain, function, mouth opening and tenderness to palpation. Although the study was an uncontrolled one, results suggest that BTX-A reduced the severity of symptoms.[20] Another report indicates the usefulness of BTX-A treatment in TMJ disorders.[30] Recent reports also indicate the success of BTX-A in treating patients with conditions such as bruxism.[31]

Spastic Disease States with Pain

Spasticity is defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting in hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome. Additional components of spasticity include; abnormal cutaneous and autonomic reflexes, paresis, lack of dexterity, and fatigability. Spasticity of the lower limbs, especially adductor spasm, is a major cause of disability in patients with chronic disorders of the pyramidal tract. Disability can result from impaired quality of movements and postures, painful spasms, interference with ambulation, and, in bedridden individuals, the hampering of nursing care and hygiene maintenance. Spasticity is caused by a disturbed processing of peripheral afferent messages at the spinal cord level as well as release and imbalance of the supraspinal control of reflex pathways.[32] Several rating scales have been developed to assess baseline functioning and therapeutic response to BTX-A treatment for muscle spasticity.

Definitions:

Cerebral Palsy
Cerebral palsy (CP) is a non-progressive neurological disorder of posture and movements caused

by an insult to the developing brain. Although the brain lesion is static, the abnormality in posture is not unchanging and may result in progressive physical deformity. The majority of CP patients are spastic and mixed spastic-dystonic, and are at risk of developing progressive joint stiffness, deformity, and disability.[33]

Multiple Sclerosis
Multiple sclerosis (MS) is a chronic, often disabling disease of the central nervous system. Symptoms may be mild, such as numbness in the limbs, difficulty walking, and slurred speech or severe, such as paralysis or loss of vision. Most people with MS are diagnosed between the ages of 20 and 40, however, the unpredictable physical and emotional effects can be lifelong.[34] Spasticity is also a common finding in patients with multiple sclerosis. In this disease, the spasticity may help to stabilize the lower extremities while the patient stands, however, it may also lead to decreased mobility and may interfere with other functional activities.[36]

Post-Stroke Spasticity
Stroke patients comprise a sizable percentage of the spasticity population. Although the spasticity can occur in the upper limbs, it is the limited ankle dorsiflexion and foot inversion, known as equinovarus foot, which is a main cause of locomotor disability.[35]

Myofascial Pain syndrome
Myofascial pain syndrome (MPS) is one of the most common painful conditions seen in general medical practice.[37] It is characterized by acute or chronic specific pain affecting a small number of muscles and involving single or multiple 'trigger points' that are usually located in tight bands within the affected muscles.38 These trigger points are hypersensitive to pressure and produce a local twitch and referred pain within a defined reference area.[39-40]

Migraine
Migraine headaches are characterized by painful, disabling, and recurring symptoms that have no known cause, definitive treatment, or cure. From 1980 through 1989, the prevalence of chronic migraine headaches in the U. S. increased nearly 60 percent, from 25.8 per 1000 persons to 41.0 per 1000 persons. Most (71%) of the increase occurred among persons less than 45 years of age. In each year, the prevalence of migraine headaches was greater among women than men in each age group. In addition, the rate of change was greater among women; and the prevalence among women less than 45 years of age increased 77 percent, compared with a 64 percent increase among men.[41]

Migraine headaches can be hereditary. If both parents have them, there is a 75 percent chance their children will have them; when only one parent is a migraine sufferer, there is a 50 percent chance the child will be afflicted. If even a distant relative has migraine headaches, a 20 percent chance exists that any offspring will be prone to migraine headaches. Recent research has proven that migraines do have physical causes, and triggers for many sufferers include; diet, stress, menstruation, and environmental changes. The length of a migraine attack can last from several minutes to several days, totally incapacitating the sufferer in the latter case.[42]

Tension-type Headache
Tension-type headache is the most common form of headaches. Approximately 90 percent of all headaches are classified as tension-type headache. The pain is typically generalized all over the head. There appears to be a slightly higher incidence of this type of headache among women, since more females than males seek treatment. There are two types of tension-type headache; those that occur on an episodic basis and those that occur daily. If chronic, this type of headache should be promptly treated to avoid developing an addiction to pain relieving drugs. The daily headache is often caused by depression or other emotional problems. Sufferers usually awaken in the morning with the headache and frequently have an accompanying sleep disorder43, which has a socio-economic impact.[44] Thirty to forty percent of all patients who visit a headache clinic suffer from chronic daily headache.[45] Although the pathophysiology of tension headaches are not well understood, it is probable that the headaches arise from afferent fibers in the pericranial

musculature, and that sustained contractions of the pericranial muscle may causes tension headaches.[46]

Mechanical low back pain
Back pain is the leading cause of disability in the U. S. for people younger than 45 years and is the most expensive health care problem for the 30- to 50-year old age group.[47] Low back pain accounted for 23 percent ($8.8 billion) of total workers' compensation payments in 1995.[48] The Annual Survey of Occupational Injuries and Illnesses conducted by the Bureau of Labor Statistics indicates that in 1998 there were 279,507 back injuries due to overexertion that resulted in lost work days (89% in material-handling).[49]

Whiplash associated with neck-pain
Headache is a common finding associated with neck injuries, such as whiplash. Cervicogenic headache, which is believed to be attributable to injury of the ligaments, muscles, or joints of the cervical spine, is centered in the occipital region with referral to the frontotemporal region. Up to 87 percent of the patients with a whiplash-associated disorder have some degree of muscle spasm that is contributory to both pain and dysfunction.[50]

Findings

Cerebral Palsy
Numerous studies treating cerebral palsy with BTX-A were evaluated. BTX-A was found to effectively reduce muscle spasm and tone, and improve range of motion, gait, and motor function.[33,51-57] Barwood et al.[58] found that BTX-A significantly decreased pain in cerebral palsy patients who underwent adductor-release surgery.

Multiple Sclerosis
Snow et al.[59] found that BTX-A reduces spasticity associated with multiple sclerosis.

Post-stroke Spasticity
BTX-A was found to decrease muscle tone and spasticity[35,60-61] and increase motor function.[35] Smith et al.[62] found that BTX-A provided a reduction in spasticity without any apparent improvement in disability.

Myofascial Pain Syndrome
Porta et al.[63] found BTX-A injections were superior to corticosteroid drugs in reducing pain in patients with myofascial pain. Some reports have shown positive results among selected patients with fibromyalgia-myofascial pain syndrome when injected with BTX-A into local trigger points,[64-66] however, these results are not universal[67].

Migraine
The use of BTX-A for treating chronic muscular and migraine headache also has been reported.[68-72] In a randomized double-blind, vehicle-controlled study, 123 subjects with a history of two to eight moderate to severe migraine attacks per month were randomized to receive single adminstration of vehicle or BTX-A, 25 or 75 U, injected into multiple sites of pericranial muscles at the same visit. Both the 25-U and 75-U BTX-A groups were reported to have significantly fewer migraine attacks per month, a reduced maximum severity of migraines, a reduced number of days using migraine medications, and a reduced incidence of migraine associated vomiting.[73]

Tension-type Headache
BTX-A treatment of tension-type headache was mixed; with one study47 finding pain reductions, while another study74 found no differences between BTX-A and placebo in pain reduction. The mechanism of benefit in tension headache is likely related to a decrease in muscle spasm.

Mechanical Low Back Pain
In a double-blind randomized study, 28 consecutive patients with mechanical low back pain were either injected with 200 U of BTX-A or normal saline. Paravertebral injection of BTX-A in patients with chronic low back pain resulted in significant pain relief in 78 percent (11 out of 14) compared to 28 percent (4 out of 14) in the control group injected with normal saline. However, at eight weeks, 9 out of 14 patients in the BTX group and 2 out of 14 in the control group disclosed significant relief.[75]

In 2001, Foster et. al, reported the results of a randomized, double-blind study in which 31 consecutive patients with chronic low back pain were studied: 15 patients received 200 units of BTX-A (40 units/site at five lumbar paravertebral levels), and 16 patients received normal saline. The authors report that paravertebral adminstration of BTX-A relieved pain and improved function in patients with chronic low back pain.[76]

Whiplash associated with neck-pain
Freund and Schwartz[77] found that BTX-A was effective in reducing pain and increasing range of motion in patients with cervical-related headaches stemming from whiplash injuries.

Patient Selection Criteria

Patient selection criteria in the reviewed research on BTX-A for neuromuscular pain include:

- Chronic tension headache associated with disorder of pericranial muscles
- Chronic headache secondary to cervical whiplash injury
- Demonstrated precipitation of head pain with external pressure over the occipital or cervical region on affected side
- Episodic or chronic tension-type headaches
- Chronic myofascial pain originating in the piriformis, iliopsoas, or scalenus anterior muscles
- Experienced pain on maneuver or stretching, trigger point with associated referred pain
- Moderate to severe spasticity of plantar flexors and foot invertors
- Lack of response to conventional physical and medical therapy
- Stable, chronic multiple sclerosis
- Spastic contraction of adductor muscles
- Stronger agonist than antagonist muscle
- Dynamic spasticity
- Dyskinesia with dystonic spasms
- Mixed picture with spasticity and syntonic posturing
- Nonprogressive cerebral lesion
- Positive dystonic response to dopaminergic challenge with apomorphine.

Exclusion criteria in the reviewed research on BTX treatment for neuromuscular pain include:

- Serious somatic or psychiatric illness
- Anticoagulation therapy
- Myasthenia gravis
- Pregnancy or breast-feeding
- Predominant operating factors such as secondary gain, compensation, disability or psychosocial factors
- Analgesic rebound headache syndrome
- Abdominal cavity tumors
- Abnormal anatomy
- Rheumatoid disease or radiculopathy, need for regular analgesic for severe pain
- Fixed contractures
- Treatment with oral antispastic medication in last 4 weeks
- Poor life expectancy
- Fixed joint deformity

- Previous tendon lengthening

In conclusion, since there are numerous reports about the possible indications for the use of BTX-A, it will be very difficult to pinpoint only a few indications. Additionally, more studies are being conducted to establish the efficacy of BTX-A treatment in many other indications including pain management.

Evaluation of Evidence

Study Design
Potential subjects for double-blind studies may undergo a screening process where enrollment in the controlled study is contingent on a therapeutic response to open-label administration of BTX-A. However, using this methodology can inflate the success rate of the blinded study. Cole et al.[25] used such an approach and noted that since 80 percent of patients responded in the open-label trial, the success rate of the controlled study should be downward adjusted by 20 percent. They cite that there may be disadvantages to using treated subjects, since they lose their naiveté to the drug effect and may no longer be truly "blind". Comparison between studies is difficult, due to variations in dosages, treatment protocols, evaluation methods, injection technique (single versus multiple sites), rating scales, and definitions of improvement.[78,80,81]

Several authors have reported spontaneous remission of conditions for which BTX-A is indicated.[11,12] Friedman and Fahn[82] investigated the characteristic of spontaneous remission among samples of patients (treated with BTX-A) with spasmodic torticollis, and found that it occurs with greater frequency in patients with early onset.

Some authors believe that prior surgery, such as myectomy and neurectomy, prolong the duration of BTX-A injection in the treatment of blepharospasm and Meige's syndrome. While others believe the procedures have little effect. Osako and Keltner2 report that the results from a small case series study showed that patients who had previous surgeries experienced longer treatment response than those who had not.

Measures of Outcome
Objective assessment of treatment outcome of focal hand dystonia can be difficult. Although motor performance outside the specific task may be difficult for the patients, there may not be any other symptoms. Additionally, since some of the symptoms are related to discomfort or awkwardness, the patient may not perform the task poorly. Tasks that trigger dystonia specific to each patient should be tested. Writing, holding a pen, or playing a musical instrument can serve as outcome measures.[25]

Gudex et al.[7] performed a study to assess the impact of BTX-A treatment of dystonia on quality of life. Subjects with non-focal dystonias experienced considerably more problems with usual activities than participants with focal dystonia, and a higher number had problems with mobility and self-care. There were no differences between the two groups on levels of pain and emotional well being. Brans et al.[83] treated a sample of 54 cervical dystonia patients for 12 months. Functional health scores among the 16 percent who dropped out were lower than the remainder of the sample. These differences were not detected by impairment and pain scales, and underscore the importance of using functional health measures to analyze treatment outcome.

Efficacy

BTX-A injections are not a curative treatment. The etiology for the dystonic disorders is a malfunctioning central nervous system control mechanism. BTX-A provides a temporary paralytic effect and requires repeated injections to continue the beneficial effects. The duration of effect is longer with the initial injection and progressively gets shorter with repeated injections for most dystonic disorders. It is not known at this time whether BTX-A can be readministered indefinitely or if the effectiveness will wear off over time.[96] Poewe et al.[87] found a

nonsignificant trend for progressive decrease of cervical dystonia symptoms during a treatment period of 1 year. Systemic drugs remain the best treatment for patients with generalized spasticity in which overall reduction in muscle tone is needed, while BTX-A is potentially more helpful for patients with isolated problematic muscle pain and contractions.[60] Improvement in the symptoms of patients with medically intractable cervical dystonia has been reported in 71-90% of the patients observed.[12,87]

The fact that longer-term spasticity seems to benefit less from toxin injections, and that joint retractions may interfere with its efficacy, suggests that BTX treatment may be of greater benefit shortly after a stroke, before the occurrence of fixed retractions, when it is also likely to facilitate physiotherapy. Later on, when evolution in motor capacities and spasticity are unlikely, other more invasive techniques may be more effective.[97]

When using BTX-A to decrease spasticity of the agonist muscle, the function of the previously weakened antagonist muscles can be facilitated or improved, restoring muscle balance across joints. By doing this, fixed joint deformities or fixed contractures can be prevented.

In conducting clinical trials of BTX-A, several variables can affect measurements of efficacy. Many factors can interfere with walking velocity in the assessment of treatment effect on the ambulation of hemiparetic patients. Some patients may no longer need walking devises after treatment with BTX-A, however, they may walk slowly out of apprehension or caution. A lack of improvement in gait velocity may also reflect a detrimental effect of the toxin, which may produce excessive weakness in plantar flexion.[97] Poor treatment response to BTX-A may be due to other factors, such as the unmasking of contractures. BTX-A treatment response in children with cerebral palsy also depends on the patient's intelligence and motivation, the extent of neurological disability, and the goals of the therapeutic program.[56] Additionally, patients having hemiparesis for a longer duration improved less with BTX-A treatment, suggesting that the degree of benefit may correlate with the duration of the spasticity.[97] Finally, in the treatment of dynamic spasticity, there should be sufficient strength in antagonist muscles to permit functional control after spastic muscles have been weakened by BTX-A, thus BTX-A is not effective with fixed contractures.[55]

Development of Anti-BTX-A Antibodies

Some patients do not respond to repeated BTX-A treatment. Investigators have speculated that these patients have developed anti-BTX-A antibodies that cause clinical resistance to subsequent treatments.[5] At present, it is unclear why some patients develop these antibodies, however, doses in excess of 300 U within a 30-day period and low body weight reportedly increase the risk.[15] One recurring problem in many studies that include testing for the presence of anti-BTX-A antibodies is the failure to test all the patients, preventing accurate interpretation of the data. However, morphological data raises the possibility that increased axonal sprouting and single muscle fibers being innervated by more than one axon after BTX-A treatment is an additional underlying factor.[91]

Greene et al.[92] evaluated the development of resistance to BTX-A in patients with spasmodic torticollis. Of 559 patients treated with BTX-A injections, 24 (4.3%) developed antibodies to BTX-A. Since some patients (number not specified) were lost to follow-up, the authors assert that the actual prevalence of antibodies may be greater than 4 percent. Of these 559 patients, the investigators selected a cohort of 76 patients who were injected with BTX-A over a 2- to 45-month period. In this group, 8 of 76 (10.5%) patients developed resistance to BTX-A. Compared with nonresistant patients, these 8 patients received more frequent injections, received booster injections 2 to 3 weeks following the initial injection, and received higher doses of BTX-A per treatment. The authors recommend extending the time between injections, avoiding booster injections, and using the smallest possible dose.

Sheehan and Lees[93] used BTX-F to treat 6 nonresponders to BTX-A for alleviation of torticollis symptoms. Results showed that the efficacy and side effects were comparable to BTX-A,

however, the duration of action was briefer, with a range of 4 to 6 weeks. Greene and Fahn94 used BTX-F to treat 15 torticollis patients who had developed immunity to BTX-A and found improvement in 10 of the 15. However, the duration of treatment for BTX-F was 1 month, compared with 3 months for BTX-A. BTX-B was used in a sample of patients who were naive to or responsive to BTX-A,[3] BTX-B displayed efficacy and safety similar to that of BTX-A.

In order to reduce the risk of antibody formation and the development of resistance against treatment with BTX-A, the only manufacturer of BTX-A in the United States (BOTOX - Allergan Inc.,) have reformulated the preparation of BTX-A in 1997 and have lowered the protein content of BTX-A from 25 ng/100 I.U. to 5 ng/100 I.U.

Safety

Chronic Treatment
The long-term safety and efficacy of multiple BTX-A treatments on both the injected and distant muscles are presently unknown. There are no chronic toxicity studies in animals that can be used for guidance.[78] The meaning of the abnormalities at distant neuromuscular junction seen in single-fiber EMG after low-dose treatment of BTX-A is unclear.[79] The longitudinal study by Jankovic and Schwartz8 found no decline in benefits with chronic BTX-A treatment for blepharospasm and cervical dystonia and a slight improvement in efficacy with repeated treatment.

There are limited data regarding the use of BTX-A during pregnancy or lactation.[5,54] There is a severe risk (50%) of dysphagia for BTX-A treatment for lingual dystonia. Since it is not a safe treatment for lingual dystonia, this is an appropriate therapy only for those patients who have a tracheostomy tube in place and are given an alternative form of feeding. Recently, a questionable case of respiratory arrest has been reported.[98]

Patient Awareness of Treatment Group
Two of the physical effects seen after BTX-A treatment are muscle atrophy and muscle weakness. Patients can be aware of these differences, creating a confounding factor in controlled studies. In the double blind, placebo-controlled study by Blackie and Lees,[89] neck muscle atrophy was apparent in 12 of 19 patients treated for spasmodic torticollis. In the placebo-controlled blinded study of Yoshimura et al.,[88] patients treated for limb dystonias experienced less focal weakness (13%) in the control group than in the experimental group (53%), raising the possibility that some patients could deduce which injection they had received.

In general, the most common side effects of BTX-A treatment occur within the first week following injection of BTX-A. Localized pain, tenderness and/or bruising may be associated with the injection. Other side effects include muscle cramps, flu-like symptoms, dysphagia, upper respiratory infection, and headache.

The effect of BTX-A may be potentiated by aminoglycoside antibiotics or other drugs that may interfere with neuromuscular transmission.

Cost and Cost-effectiveness

According to Allergan - the manufacturer of BTX-A (BOTOX), the average wholesale price of a 100-unit vial of BTX-A (BOTOX) is $370 (personal communication, April 18, 2001). No information was available in the reviewed research that compared the cost of BTX-A treatment with conventional medical treatment. A 100-unit vial when reconstituted cannot be stored for more than four hours and during this time it should be stored in a refrigerator (2-8 C).

Alternative Treatments

For the treatment of blepharospasm, pharmacologic therapy, such as trihexyphenidyl, benzodiazepines, tetrabenazine, levodopa, and benzhexol have been prescribed with inconsistent results. Two different surgical approaches have been used. One is the myectomy of the orbicularis muscle and adjacent eyebrow muscles, and the other is neurectomy of selected facial nerves. Numbness of the forehead and swelling of the eyelid may result from myectomy, and neurectomy can produce brow droop, lagophthalmos, corneal exposure, and ectropion. Treatments whose efficacy is poorly substantiated include psychotherapy, hypnosis, acupuncture, and biofeedback.[2]

Many approaches have been used to treat hemifacial spasm, including carbamazepine, clonazepam, orphenadrine, nerve blocks, myectomy, and neurosurgical microvascular decompression. Of these, microvascular decompression has been the most successful; however, complications include permanent facial paresis, otitis media, meningitis, intracranial hemorrhage, epilepsy, and death.[2]

Issues of Controversy

Electromyographic Recordings (EMG)
Controversy exists in the literature regarding the use of EMG with BTX-A treatment. Some authors report that there is no evidence that EMG makes injections more effective.[78,84] Others feel that EMG guidance helps localize the dystonic muscles and can verify the belly of the muscle before injection, which avoids injection of the wrong muscle and diffusion of BTX-A into neighboring muscles.[80,83,85-89] In a recently published paper, Brans et al.[83] state that any needle activity greater than 100 μV is the gold standard for the detection of involuntary movement of a muscle in the dystonic posture. These authors compared physical examination with EMG in detecting involved muscles in cervical dystonia and concluded that physical examination failed to detect many active muscles, and that physical examination alone was inadequate for a complete assessment of outcome. These findings remained consistent when a cutoff value of 500 μV was used.

A difference of opinion on the utilization of EMG (i.e., for both localization and injection, for initial injections only, or only in complex cases) also exists among these authors. To reduce patient discomfort, Koman et al.[54] recommend that local anesthetics and EMG not be used in BTX-A treatment of pediatric patients with cerebral palsy. Geenen et al.[13] state that EMG signals can be misleading if the tip of the needle is in a synergist or a fixator muscle, and that physicians treating patients with dystonia or spasticity may be unable to contract a target muscle in isolation, significantly limiting the localizing value of EMG. In a study comparing EMG with local electrical stimulation through a cannula for localizing forearm muscles for treatment, Geenen et al. concluded that both methods have advantages and disadvantages, and that localization is probably at least as good a method for location.

Comella et al.[81] designed a progressive, randomized study of 52 spasmodic torticollis patients to address the issue of EMG guidance. The muscle number and injections per muscle were identical in the clinical evaluation and EMG plus clinical evaluation groups. Based on their definition of improvement, both groups showed similar improvement. However, the number of patients showing marked improvement and the magnitude of improvement was significantly greater in the EMG assisted group. EMG may be more effective because it more accurately identifies the deep cervical muscles.[81]

Future of Procedure

An immunologically distinct serotype of BTX should be developed for use with nonresponders. There is a need for further research into the general properties of BTX, such as mechanisms of action and recovery, antidotes and blocking techniques, increasing specificity and duration of action, and optimum dosage for specific disorders. Future research should further compare BTX with conventional medical treatment using larger samples and longer duration of follow-up. In

June of 2001, the FDA has approved the use of Botulinum type B (Myobloc - Elan Pharmaceuticals) for the treatment of cervical dystonia.

Many clinical applications for the use of BTX-A have been identified and these include tennis elbow, bruxism, temporomandibular joint disorder, apraxia, nystagmus, lagophthalmos, hyperlacrimation, and abductor dysphonia. Although small case series studies have been performed with several of these indications, researches using more rigorous study designs with control groups are needed to provide a greater certainty of efficacy.

At present, the longterm effects of the use of BTX-A are not known.

Conclusions

BTX-A (Botox) has been found to be safe and effective for a number of clinical conditions.

- Presently, BTX-A has been approved by the FDA for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia, and for treatment of strabismus and blepharospasm associated with dystonia.
- Listed below are clinical applications for which BTX-A is not approved by the FDA, but where data exists to support the clinical use of BTX-A:
    - Spasmodic torticollis
    - Writer's cramp with significant wrist-joint deviation
    - Spasmodic dysphonia
    - Dynamic contracture in cerebral palsy patients
    - Post Stroke Spasticity
    - Myofascial pain syndrome
    - Chronic low back pain
- Following are the clinical conditions where insufficient data exists to support the clinical use of BTX-A and none of these are FDA approved indications:
    - "Off" painful dystonia in Parkinson's disease patients
    - Rigidity in Parkinson's disease patients
    - TMJ disorders and Bruxism
    - Fixed contracture in cerebral palsy patients
    - Spasticity associated with Multiple sclerosis
    - Tension headache
    - Migraine
    - Whiplash associated with neck-pain
    - Spasticity associated with Perinatal hypoxia
    - Progressive supranuclear palsy
    - Cortical basal degeneration
    - Extensor hallucis longus dystonia
    - Writer's cramp with neutral wrist position
    - Essential tremor
    - Stenographer's cramp
    - Sixth nerve palsy

BTX-A treatment is potentially a painful procedure. It is contraindicated in the presence of infection at the injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

Individuals with peripheral motor neuropathic diseases or neuromuscular junctional disorders should receive BTX-A treatment with caution. BTX-A should also be used with caution in patients receiving aminoglycosides or other agents interfering with neuromuscular transmission.

Formation of neutralizing antibodies to BTX-A may reduce its effectiveness by inactivating the biological activity of the toxin. The rate of formation of these neutralizing antibodies in patients receiving BTX-A treatment has not been well studied and the critical factors for neutralizing

antibody formation have not been well characterized. The effect of the long term use of BTX-A has not been studied, however, the reformulated BTX-A has a lower protein content that may decrease the risk of antibody formation and the development of resistance.

Appendix I: Methodology

Search Strategy
Evidence in this report was obtained from a search of MEDLINE, Current Contents, and HEALTHSTAR databases spanning the years 1985 to May 2001. Search terms included apraxia, blepharospasm, BOTOX, botulinum toxin, botulism toxin, BTX, cerebral palsy, cramp, diplopia, dysphonia, dystonia, Dysport, esotropia, exotropia, headache, Meige's disease, palsy, Parkinson's, spasm, spasticity, torticollis.

Review of the Literature
The reviewed research included baseline differences between toxin and control groups on clinical characteristics, heterogeneous samples, small sample sizes, absence of inferential statistics, brief follow-up periods, and significant loss to follow-up. Comparison of the reviewed studies in aggregate is difficult due to differences in comparison groups, length of time with the underlying medical condition, and dosages of BTX. Many indications for the use of botulinum toxin were found in the literature, an example being gastrointestinal disorders. However, many of these studies used small sample sizes and uncontrolled designs, and were thereby excluded from evaluation.

Appendix II: Summary of Studies

Key: BTX, botulinum toxin; BTX-A, botulinum toxin type A; CD, cervical dystonia; CGI, clinician global impression; CNS, central nervous system; CP, cerebral palsy; ET, essential tremor; LES, lower esophageal sphincter; mL, milliliter; MPS, methylprednisolone; MS, multiple sclerosis; NS, not significant; OCD, oromandibular-cervical dystonia; PD, Parkinson's disease; PRS, Physician Rating Scale; pt(s), patient(s); TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; tx, treatment; U, units; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, visual analog scale.

Authors and Study Design	Patient Population, Indications, and Dosage	Results	Conclusions/Comments/Complications
Foster et al. (2001) Uniformed Services University, Bethesda MD. Randomized, double-blind study of patients with chronic low back pain.	n=31 Randomized to either BTX-A 200 U (n=15) or normal saline (n=16). Mean age of the treatment group was 47 years and the mean age in the control group was 46.4. Inclusion: Chronic low back pain between L-1 and S-1; Pain duration of more than 6 months;	28 of the patients completed the study. At 3 weeks, 13 of 15 patients (86%) in the BTX-A group and 5 of 16 patients (31%) in the saline group reported some degree of pain relief. At 8 weeks, 9 of the 15	

	pain either unilateral or if bilateral, showing a left or right predominance. Exclusion: Low back pain of less than 6 months duration; age under 18 years; presence of any systemic inflammatory disorder; acute pathology on MRI; known allergy or sensitivity to BTX-A; current or planned pregnancy; disorders of neuromuscular transmission.	patients (60%) in the BTX-A group and 2 of the 16 (12.5%) in the saline group reported pain relief exceeding 50% (p=0.009). Side-effects: No patient had worsening of pain or function after BTX-A treatment.	
Smuts et al. (1999) University of Pretoria, Pretoria, South Africa Randomized, double-blind, placebo-controlled of patients with chronic tension-type headache.	n=37 Randomized to either BTX-A 100 U (n=22) or saline placebo 2 mL (n=15). No age provided. Inclusion: Chronic tension-type headache associated with disorder of the pericranial muscles, history of previous failure of prophylactic drug treatment, no more than 1 migraine attack per month in previous 6 months. Exclusion: Previous exposure to BTX-A, serious somatic or psychiatric illness.	Results at 3 months showed a significant improvement in headache intensity in the BTX-A group compared with baseline (P=0.002); the number of headache-free days was greater than at baseline for BTX-A group (P=0.001). Chronic pain index was lower in BTX-A group than placebo group at 3 months. A number of patients in both treatment groups complained of muscle cramps, flu-	BTX-A may be helpful in the treatment of tension headaches that do not respond to other treatment. Small sample size, 9/22, or 40% of BTX-A subjects did not respond to treatment.

		like symptoms, and feelings of weakness in the neck muscles, with no significant between groups differences.	
Freund and Schwartz (2000) University of Toronto, Toronto, Ontario Randomized, double-blind, placebo trial of patients with cervical-related headache.	n=30 Randomized to receive BTX-A 100 U (n=15) or saline solution 1 mL (n=15). Mean age 46. Inclusion: Chronic headache secondary to cervical whiplash injury, injury occurred 2 years prior to enrollment, demonstrated precipitation of head pain with external pressure over the occipital or cervical region on affected side, restricted ROM, ipsilateral neck pain.	Pre-injection, week 2 and week 4; VAS 3, 3, and 4.5 saline group (NS) vs 6.5, 5, and 3.5 BTX-A group (P<0.01). Pre-injection, week 2, and week 4, median ROM 337, 347, and 325 saline group (NS) vs 312, 317, and 343 BTX-A group (P<0.01). No patient experienced any complications.	BTX-A may reduce chronic headache secondary to whiplash injury. Placebo group began the trial with significantly less pain (P<0.01) than toxin group.
Rollnik et al. (2000) Medical School of Hanover, Hanover, Germany Randomized, double-blind, placebo-controlled of patients with tension-type headaches.	n=21 Includes 10 randomized to saline solution placebo (mean age 35.5) and 11 randomized to BTX-A (mean age 39.2). Dose Dysport 200 MU per person. Inclusion: Episodic or chronic tension-type headaches. Exclusion: Anticoagulation,	Both placebo and BTX-A treated patients displayed declining VAS scores at 4, 8, and 12 weeks follow-up, but there were no between-groups differences. There was slight improvement on the CGI at 4 weeks, with no differences	BTX-A offers no advantage over placebo in the treatment of tension-type headache. Small sample size, possible inadequate dose.

	myasthenia gravis, pregnancy, breast-feeding, predominant operating factors such as secondary gain, compensation, disability, and psychosocial factors, analgesic rebound headache syndrome, and symptomatic or other concomitant headaches.	between groups. The BTX-A groups did not display an advantage over placebo group in any outcome measure. At the end of the study, 8 of 10 placebo patients and 6 of 11 BTX-A patients wished to repeat their treatment. No mention of side effects.	
Porta (1999) Policlinico San Marco, Zingonia/Bergamo, Italy Randomized, single-blind, controlled trial of BTX-A treatment of myofascial pain syndrome and tension-type headache.	n=60 Includes 40 with myofascial pain syndrome (mean age 47.7) randomized to BTX-A (n=20) or to MPS (n=20); and 20 with tension-type headache (mean age 37.7) randomized to receive either BTX-A (n=10) or MSP (n=10). Inclusion for myofascial pain syndrome: Chronic myofascial pain originating in the piriformis, iliopsoas, or scalenus anterior muscles, aged 18-75, experienced pain on maneuver or stretching, and had trigger point with associated referred pain. Exclusion for	In the treatment of myofascial pain syndrome, mean VAS scores differed between BTX-A and MPS at baseline, 30 days, and 60 days by P=0.0060, P=0.5824, and P<0.001, respectively, with mean VAS 2.3 BTX-A vs 4.9 MPS at 60 days. In the treatment of myofascial pain, mean VAS scores differed between BTX-A and MPS at baseline, 30 days, and 60 days by P=0.9366, P=0.6659, and P=0.0003,	BTX-A is useful in treating pain secondary to tension-type headache and myofascial pain syndrome. Small sample size, mean pain VAS significantly greater at baseline in BTX-A among myofascial pain patients.

	myofascial pain syndrome: History of disc or bone disease, previous micro- or macrosurgery for disc disease, abdominal cavity tumors, abnormal anatomy, rheumatoid disease or radiculopathy, need for regular analgesic for severe pain. Inclusion for tension-type headache: Age 18-75, history of 2 or more episodes of headache per month for past 3 months. Exclusion: Required oral analgesic medication more than 3 times per month.	respectively. No adverse events were reported.	
Smith et al. (2000) University of Liverpool, Liverpool, England Randomized, double-blind, placebo-controlled of patients with upper limb spasticity after stroke or head injury.	n=25 Randomized to either placebo (n=6, mean age 45), 500 Mu (n=6, mean age 39), 1000 Mu (n=7, mean age 67), or 1500 Mu (n=6, mean age 54). Inclusion: Problematic spasticity in the upper hemiparetic limb arising from a stroke or traumatic brain injury more than 1 year previously.	6 weeks after treatment, there was significant improvement in combined dose vs placebo on modified Ashworth wrist and finger scale ($P<0.01$ for both), passive range of movement in wrist ($P<0.05$), and resting finger curl ($P<0.01$). 15 patients in combined BTX-A group improved their	BTX-A treatment provides short-term reduction in spasticity without significant improvement in disability. Small sample size. Complications included flu-like symptoms for 2 days (1).

	Exclusion: Fixed contracture at either elbow, wrist, or interphalangeal joints.	global rating scale vs 2 in placebo group (P<0.02). At 12 weeks there were no differences between BTX-A groups and placebo group.	
Hesse et al. (1998) University hospital setting, Berlin, Germany Randomized, double-blind, placebo-controlled.	n=24 Post-stroke pts (mean age 50.35) with upper limb flexor spasticity (6 in Group A, 1000 units BTX-A + electrical stim; 6 in Group B, 1000 units BTX-A; 6 in Group C, placebo + electrical stim; 6 in Group D, placebo). Inclusion: 6 to 12 months after stroke, at least grade 3 on Modified Ashworth Scale, affected extremity nonfunctional with no possibility of any selective movement. Exclusion: Fixed contracture, previous BTX-A, neurolytic, or surgical treatment, severe cognitive or communication impairment. BTX-A 125 or 250 U at several muscle sites; electrical stim 20 Hz, 200 µs, 50-90 mA.	Greatest improvement in muscle tone reduction was measured in Group A (P=0.011). Pairwise comparisons revealed that cleaning the palms differed across groups, with Group A differing from Group B (P=0.007) and Group D (P=0.008), but not from Group C (P=0.071). Combined treatment of BTX-A plus electrical stim was superior in the facilitation of hygiene than toxin or placebo without electricity. Very small number of subjects in each treatment cell. No side effects observed in sample.	

Simpson et al. (1996) Multicenter U.S. study Randomized, double-blind, placebo-controlled	n=37 Post-stroke pts (n=37) with upper limb spasticity (21 women, 16 men; mean age, 59; average time since stroke, 37 months). Inclusion: ≥9 months post-stroke, average elbow and wrist flexor tone of grade 2.5 on Ashworth Scale, ≥2 months stable clinical course prior to study, willing to maintain active spasticity treatment. Exclusion: Fixed contracture, previous BTX-A treatment, neurolytic or surgical treatment of affected limb, neuromuscular disease. Pts randomized to placebo or 75 U, 150 U, or 300 U of BTX-A.	300 U BTX-A produced significant reduction in wrist flexor tone of 1.2 (P=0.028), 1.1 (P=0.044), and 1.2 (P=0.026) points, and elbow flexor tone of 1.2 (P=0.024), 1.2 (P=0.028), and 1.1 (P=0.199) at weeks 2, 4, and 6 post-injection. In placebo group, tone reduction in the wrist was 0.3, 0.2, and 0.0, and the elbow was 0.3, 0.3, and 0.6 at weeks 2, 4, and 6 post-injection. Lower doses produced nonsignificant trends toward improved muscle tone. BTX-A groups reported significant improvement on the physician and patient Global Assessment of Response to Treatment scale at weeks 4 and 6.	300 U BTX-A significantly reduces upper limb spasticity in post-stroke patients. Small number of subjects in each treatment cell. Adverse effects included transient global amnesia, finger twitch, rash, soreness and pain at injection site, and bladder instability. Frequency of side effects not mentioned.
Wissel et al. (1999) Universitatsklink Innsbruck, Innsbruck, Austria Randomized, double-blind, of children and young	n=33 CP pts including 16 randomized to receive high dose BTX-A (200 U per leg) and 17 randomized to low dose BTX-	At 6-8 weeks post-treatment, knee joint spasticity, as measured by the Ashworth, was significantly	Higher dose BTX-A causes improvement in spasticity and motor function in patients with cerebral palsy, but younger children appear to benefit to a greater degree than older children. Small sample size, no placebo group. Complications not mentioned.

adults with cerebral palsy.	A (100 U per leg). Inclusion: Cerebral palsy with spastic gait pattern that interferes with everyday function. Exclusion: Significant contractures of the knee joint (passive extension less than neutral position (0 degrees)) or ankle joint (passive dorsal-extension less than 5 degrees and plantar-flexion less than 20 degrees), concomitant disabling morbidity such as severe retardation or cardiopulmonary dysfunction.	higher in the high dose (P<0.001) and low dose (P<0.05) groups; stride length analysis of gait was improved in the high dose (P<0.01) but not low dose (P=0.47) groups; velocity, as measured by meters/minute, was improved in high dose (P<0.01) but not in low dose (P=0.95) groups. Post-hoc analysis revealed that patients 7 or younger showed greater improvement on the Ashworth (P<0.0001) than patients over 7 (P<0.01), stride length improved more in children 7 or younger (P<0.01) than in children older than 7 (P<0.05), and gait velocity improved more in the younger children (P<0.05) than in older children (P<0.16).	
Barwood et al. (2000) Royal	n=16 CP pts, includes	Results found that the BTX-	BTX-A may play an important role in the management of post-operative pain

Children's Hospital, Victoria, Australia Randomized, double-blind, placebo-controlled of cerebral palsy patients undergoing adductor-release surgery.	8 randomized to saline solution placebo (mean age 5.0 years) and 8 randomized to BTX-A (mean age 4.3 years). Inclusion: Spastic type CP, aged 2-10 years, clinical and radiological evidence of being at risk for dislocation, independently scheduled for isolated adductor release surgery. Exclusion: Lack of informed consent, previous hip surgery, medication for spasticity, injection of BTX-A in previous year.	A group needed less 48 hour combined narcotic dose (P<0.009), less total narcotic dose (P<0.005), lower pain score 24 hours post-op (P<0.002), lower pain score 48 hours post-op (P<0.001), less diazepam requirement (P<0.04), less paracetemol requirement (P<0.002), and shorter length of hospital stay (P<0.003) than did placebo group.	that is wholly or partially caused by muscle spasm. Small sample size No side effects were observed in this trial.
Koman et al. (1994) Medical school setting, Winston-Salem, NC Randomized, double-blind, placebo-controlled	n=12 CP pts, age range 4-11. Inclusion: Nonprogressive lesion (palsy) resulting in spasticity; no other significant health problems; equinovarus or equinovalgus foot deformities associated with dynamic joint contracture unresponsive to physical therapy, orthotics, or other nonoperative modalities. BTX-A dose, 1	Results measured by PRS; 83% of toxin group had gait improvement vs 33% placebo. Blinded physical therapist and parent observations noted improvement in toxin group. Side effects in toxin group included soreness at injection site (3); placebo group had soreness at injection site	BTX-A can be useful in treating spasticity associated with cerebral palsy. Small sample size, no inferential statistics used.

	U/kg body weight; average dose, 50 U.	(1), unsteadiness (2), fatigue (1), headache (1). No systemic or generalized complications noted.	
Corry et al. (1998) General hospital setting, Belfast, Northern Ireland Randomized, prospective.	n=20 CP pts, mean age 4.6 Pts with disease-induced spastic equinovarus calf; 10 randomized to cast, 10 randomized to BTX-A. Inclusion: Dynamic component to calf equinovarus. Botox 80-200 U, Dysport 240-360 U.	Results showed significant changes in dorsiflexion in both groups at week 2; BTX-A group continued significance at 12 weeks and cast group relapsed. Tone significantly reduced in BTX-A but relapsed at 12 weeks; cast group significant at week 2 and nonsignificant at week 12. 12-week relapse significantly greater in cast group than in BTX-A group.	BTX-A produces greater reduction in symptoms of equinovarus calf and for a longer duration than casting. Small sample size. Complications included calf pain after injection in BTX-A group (1) and painful foot (3), calf pain (1), and skin inflammation (2) in cast group.
Snow et al. (1990) University medical setting, Vancouver, British Colombia Double-blind, placebo-controlled, crossover	n=10 MS pts, mean age 40.2; mean duration 18.2 years. Inclusion: Stable, chronic multiple sclerosis; spastic contractions of adductor muscles. BTX-A 400 mU/pt divided into 3 injection sites.	BTX-A produced significant reductions in spasticity at 6 weeks (mean, 7.9-4.7; P=0.009), no difference in placebo; comparison of BTX-A pre- and post-tx with placebo pre- and post-tx showed significant improvement with the toxin	BTX provided significant reduction in spasticity and improvement in the ease of nursing care. No side effects reported.

		(P=0.009). A major contribution to reduction in spasticity score was decrease in muscle tone (2.6-1.4; P=0.008) with a trend in reduction in spasm frequency. Significant improvement in the hygiene score at 6 weeks in BTX-A compared with placebo (P=0.009).	
Grazko et al. (1995) Military hospital, Washington, DC Randomized, double-blind, placebo-controlled, crossover	n=20 Pts with spasticity (n=12) or rigidity (n=8) due to stroke, MS, trauma, perinatal hypoxia, PD, progressive supranuclear palsy, or cortical basal degeneration (mean age 50.2). Mean dose BTX-A, 138 U for spasticity group, 148 U for rigidity group.	As measured by the Ashworth Scale, all spasticity patients had improvement in tone by at least 2 grades. Five patients with severe painful spasm also noted significant decrease in number and intensity of spasms. No placebo effect was found. Side effects included local ecchymosis (1), mild transient weakness in injected forearm. No systemic side effects.	BTX-A is helpful in treating spasticity and rigidity associated with a variety of conditions. Sample heterogeneity, small sample size, no inferential statistics used.
Burbaud et al. (1996) General hospital setting,	n=23 Pts with stroke-induced (n=19)	Subjective improvement significantly	BTX effective in treating foot spasticity in the first year after a stroke. Patients receiving placebo or BTX on day 90

Pessac, France Randomized, double-blind, placebo-controlled, crossover.	or trauma-induced (n=4) hemiparetic spastic foot (16 males, 7 females; mean age, 51.3) randomized to placebo or BTX at day 0 and day 90. Inclusion: At least 3 months moderate to severe spasticity of plantar flexors and foot invertors, lack of response to conventional physical and medical therapy. Exclusion: Fixed joint posture, pregnancy, neuromuscular disease. 200 units BTX at several muscle sites.	greater in BTX group over placebo group (P=0.0014); significant changes in Ashworth score in BTX group vs placebo group for ankle extensors (P<0.0001), invertors (P=0.0002), and active ankle dorsiflexion (P=0.001). Trend among BTX group vs placebo group in increased gait velocity (P=0.0731). BTX less effective in pts with spasticity over 1 year (P=0.008).	may have caused a carryover effect among those first exposed to BTX. No local or systemic side effects.
Lew et al. (1997) Multisite, United States Randomized, double-blind, placebo-controlled	n=122 CD pts (67% female, 33% male) randomized to receive 2500 U, 5000 U, or 10,000 U BTX-B, or placebo. Inclusion: >18 years of age; idiopathic CD; baseline TWSTRS total score ≥20; baseline Severity subscale score ≥10; baseline Disability subscale score ≥3; baseline Pain subscale score ≥1; weight	At week 4 vs placebo, TWSTRS total scores were significant (P=0.0016 for 2500 U, P=0.0005 for 5000 U, P=0.0001 for 10,000 U). Compared with placebo, severity scores significant (P=0.0511 for 2500 U, P=0.0021 for 5000 U, P=0.0007 for 10,000 U); disability scores significant (P=0.0165 for	BTX-B is efficacious in the treatment of cervical dystonia. Duration of therapeutic effect unknown. Side effects occurring in ≥5% of subjects included dry mouth, dysphagia, pain, infection, injection site pain, headache, flu syndrome, and nausea. Authors note that there was a dose-dependent trend in side effects.

	≥46 kg. Exclusion: Primary nonresponder to BTX-A; BTX injection in last 4 mos, had not returned to pre-treatment baseline dystonia status; use of narcotics, muscle relaxants, benzodiazepines, or investigational drugs or devices in last 30 days; pregnant or nursing; pure retrocollis or anterocollis; myotomy or denervation surgery in neck or shoulder region; history of neurological, neuromuscular, cardiovascular, renal, hepatic, gastrointestinal, dermatological, major psychiatric, or hematological illness.	2500 U, P=0.0122 for 5000 U, P=0.0004 for 10,000 U); and pain scores significant (P=0.0019 for 2500 U, P=0.0013 for 5000 U, and P=0.0004 for 10,000 U).	
Brans et al. (1996) Academic medical setting, Amsterdam, The Netherlands Randomized, double-blind, placebo-controlled	n=66 CD pts (mean age, 50.6) randomized to THP and saline injection (n=33), mean dose 16.25 mg, or to BTX-A and placebo (n=33), mean dose 292 mU; THP given for 12 weeks, BTX injected at baseline and 8 weeks; outcome measures taken at 12 weeks.	Changes in TWSTRS Disability scale higher in toxin than THP group (P=0.0097); improvement of at least 3 points on TWSTRS Disability scale seen in 18.8% of THP and 42.8% of toxin group (P=0.059); changes on Tsui scale	BTX superior to THP in alleviation of symptoms, pain, and improving overall sense of wellness in CD patients. THP group reported 76 adverse events, toxin group reported 31 events (P<0.0001). THP side effects included dry mouth (25%), forgetfulness (48%), fatigue (22%). Blurred vision, dizziness, and depression reported in both groups, with an excess in THP group. BTX group reported neck muscle weakness (3) and dysphagia (1).

	Inclusion: Idiopathic CD Exclusion: <18 years of age; pregnant; multifocal or generalized dystonia; other neurologic disease; coagulation disorder; secondary dystonia; duration of illness < 1 year; previous BTX treatment	greater in toxin group than THP group (P=0.0009); trend toward greater pain improvement in toxin group than THP group; toxin group had higher score on a quality-of-life scale than THP group (P=0.0023).	
Jankovic (1988) University medical setting, Houston, Randomized, double-blind, placebo-controlled	n=22 Pts with BL (n=9) or Meige's syndrome (n=13) randomized to placebo (n=4 BL, n=5 Meige's) or 12.5-50 U BTX-A (n=5 BL, n=8 Meige's). Inclusion: Disabling BL, oromandibular, pharyngeal, laryngeal, or cervical dystonia unresponsive to pharmacological or surgical therapy.	None of the 9 placebo pts improved, but 11/13 BTX pts had a 71.6% reduction in severity scores (P<0.01) with a 60.7% reduction in self-assessment scores (P<0.04); 5/8 Meige's syndrome improved with BTX (P=0.05), but with no significant difference in improvement on self-assessment, video, and dystonic rating scales.	BTX provides significant symptom relief for BL but only modest relief for Meige's syndrome. Small sample size. Side effects included blurred vision (6), tearing (5), ecchymosis (4), ptosis (2), and diplopia (1) in toxin group; ecchymosis (1) in saline group.
Tsui et al. (1986) University medical setting, Vancouver, B.C., Canada Randomized, double-blind, placebo-controlled	n=21 Mixed dystonia pts (mean age, 50; mean duration, 9.4 yrs) randomized to receive BTX-A (100 U) or saline, then alternate	Decrease in objective torticollis scores (P<0.05), subjective torticollis scores (P=0.05), and pain (P<0.02)	BTX provides subjective and objective improvement in torticollis. Small sample size. Side effects included mild neck weakness.

	treatment 3 months later. Inclusion: Spasmodic torticollis.	in BTX group. No changes observed in the placebo group.	
Tsui et al. (1993) University medical setting, Vancouver, B.C., Canada Randomized, double blind, placebo-controlled.	n=20 Pts with writer's cramp (mean age, 41.75) randomized to receive 25-50 U BTX-A or saline, then alternate treatment at 3 months. Inclusion: Severe writer's cramp. Exclusion: Significant hand tremor.	Speed and accuracy improved in BTX group (P<0.05) but not in placebo group; speed of completion of Gibson's maze improved in BTX group (P<0.05) but not in placebo; highest response rate in pts with wrist-joint deviation compared with neutral wrist (P=0.001).	BTX lessens writer's cramp symptoms in patients with significant distortion of wrist posture. Small sample size. Side effects included muscle weakness (1).
Truong et al. (1991) University medical setting, Irvine, CA Double-blind, placebo controlled.	n=13 Pts with adductor spasmodic dystonia randomized to receive 5 mU BTX-A or placebo. Inclusion: Voice problems diagnosed as spasmodic dysphonia.	Fundamental frequency measurements and phonation did not differ between groups; decrease in vocal fundamental frequency greater in BTX group (P<0.01); increase in perturbation scores greater in the BTX group than placebo group (P<0.05); spectrographic analysis revealed greater improvement in BTX group than placebo (P<0.05); and	BTX effective in treating many of the symptoms of adductor spasmodic dysphonia. Small sample size. Side effects noted included excessive breathiness (2) and mild bleeding (1) in toxin group, and edema (1) in saline group.

		greater objective improvement in placebo group ($P<0.05$).	

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