AHM Botulinum Toxin: Botox

Clinical Indications

- **OnabotulinumtoxinA (Botulinum Toxin Type A)** may be indicated for **1 or more** of the following:
    - Strabismus for deviations less that 50 prism diopters, including gaze palsies accompanying diseases, such as **1 or more** of the following [A]
        - Neuromyelitis optica
        - Schilders disease
    - Blepharospasm, characterized by intermittent or sustained closure of the eyelids caused by involuntary contractions of the orbicularis oculi muscle
    - Post-facial (7th cranial) nerve palsy synkinesis (hemifacial spasms), characterized by sudden, unilateral, synchronous contractions of muscles innervated by the facial nerve
    - Laryngeal spasm
    - Cervical dystonia (spasmodic torticollis) of moderate or greater severity when **ALL** of the following criteria are met
        - There are clonic and/or tonic involuntary contractions of multiple neck muscles (e.g., sternocleidomastoid, splenius, trapezius and/or posterior cervical muscles)
        - There is sustained head torsion and/or tilt with limited range of motion in the neck
        - The duration of the condition is greater than 6 months
        - Alternative causes of the patients symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures, or other neuromuscular disorders [B]
    - Focal hand dystonias (i.e., organic writers cramp), when **ALL** of the following criteria are met:
        - Documentation that abnormal muscle tone is causing persistent pain and/or interfering with functional ability, and
        - Documented failure on conservative medical therapy
    - Focal dystonias, including **1 or more** of the following
        - Adductor laryngeal dystonia
        - Focal dystonias in corticobasilar degeneration
        - Jaw-closing oromandibular dystonia, characterized by dystonic movements involving the jaw, tongue, and lower facial muscles
        - Lingual dystonia
        - Symptomatic torsion dystonia (not including lumbar torsion dystonia)
    - Limb spasticity. Must meet **ALL** of the following - One from the conditions and all of the documentation requirements:
        - Pt. must have **1 or more** of the following conditions:
            - Equinus varus deformity in children with cerebral palsy
            - Hereditary spastic paraplegia
            - Limb spasticity due to multiple sclerosis

- Limb spasticity due to other demyelinating diseases of the central nervous system (including adductor spasticity and pain control in children undergoing adductor-lengthening surgery as well as children with upper extremity spasticity)
- Spastic hemiplegia, such as due to stroke or brain injury

▪ When **ALL** of the following criteria are met:
- Documentation that abnormal muscle tone is either interfering with functional ability, or is expected to result in joint contracture with future growth
- Documented failure to standard medical treatments
- Surgical intervention is considered to be the last option
- Treatment is being requested to enhance function or allow additional therapeutic modalities to be employed

o Esophageal achalasia, for individuals who have **1 or more** of the following
▪ Are at high risk of complications of pneumatic dilation or surgical myotomy
▪ Have failed conventional therapy
▪ Have failed a prior myotomy or dilation
▪ Have had a previous dilation-induced perforation
▪ Have an epiphrenic diverticulum or hiatal hernia, both of which increase the risk of dilation-induced perforation

o Chronic anal fissure unresponsive to conservative therapeutic measures (e.g., nitroglycerin ointment)

o Intractable, disabling focal primary hyperhydrosis, when **ALL** of the following are met
▪ Patient is unresponsive or unable to tolerate pharmacotherapy prescribed for excessive sweating (e.g., anticholinergics, beta-blockers, or benzodiazepines) if sweating is episodic
▪ Significant disruption of professional and/or social life has occurred because of excessive sweating
▪ Topical aluminum chloride or other extra-strength antiperspirants are ineffective or result in a severe rash

o Ptyalism / sialorrhea (excessive secretion of saliva, drooling) that meets **ALL** of the following criteria:
▪ Refractory to pharmacotherapy (including anticholinergics)
▪ Documentation of medically significant complications of sialorrhea, such as chronic skin maceration or infections that cannot be controlled with topical treatments or hygiene.

o Facial myokymia and trismus associated with post-radiation myokymia

o Hirschsprungs disease with internal sphincter achalasia following endorectal pull-through

o Medically refractory upper extremity tremor that interferes with activities of daily living (ADLs). (Additional botulinum toxin injections are considered

medically necessary if response to a trial of botulinum toxin enables ADLs or communication
    - Detrusor-sphincter dyssynergia after spinal cord injury
    - Neurogenic detrusor (bladder) overactivity resulting from a neurologic condition (e.g., multiple sclerosis or spinal cord injury), **ALL** of the following criteria are met:
        - Documentation of detrusor overactivity confirmed by urodynamic testing
        - Documented failure of behavioral therapy
        - Documented failure/intolerance to at least one adequately titrated anticholinergic medication (e.g., oxybutynin, tolterodine, trospium, darifenacin, fesoterodine, solifenacin)
    - Overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who meet **ALL** of the following criteria:
        - Documented failure of behavioral therapy
        - Documented failure or intolerance to at least three adequately titrated overactive bladder medications (e.g., oxybutynin (Ditropan), trospium (Sanctura), tolterodine (Detrol), darifenacin (Enablex), fesoterodine (Toviaz), mirabegron (Myrbetriq), solifenacin (Vesicare), duloxetine (Cymbalta))
    - Frey s syndrome
    - Orofacial tardive dyskinesia when conventional therapies had been tried and failed (e.g., benzodiazepines, clozapine, and tetrabenazine).
    - Migraines -- for prevention of chronic (more than 14 days per month with headaches lasting 4 hours a day or longer) migraine headaches (see appendix for diagnostic criteria) in adults who have tried and failed trials of at least 3 classes of migraine headache prophylaxis medications of at least 2 months (60 days) duration for each medication: Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (e.g., losartan, valsartan, lisinopril); Anti-depressants (e.g., amitriptyline, clomipramine, doxepin, mirtazapine, nortryptiline, protriptyline);Anti-epileptic drugs (e.g., gabapentin, topiramate, valproic acid);Beta blockers (e.g., atenolol, metoprolol, nadolol, propranolol, timolol); Calcium channel blockers (e.g., diltiazem, nifedipine, nimodipine, verapamil). [C]
        - Botulinum toxin is considered experimental and investigational for migraines that do not meet the above-listed criteria.
    - Painful bruxism
- **RimabotulinumtoxinB (Myobloc Brand of Botulinum Toxin Type B)** is considered medically necessary for the treatment of **1 or more** of the following conditions
    - Individuals with cervical dystonia (spasmodic torticollis) of moderate or greater severity when **ALL** of the following are met
        - Alternative causes of the patients symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures; or other neuromuscular disorders
        - There is sustained head torsion and/or tilt with limited range of motion in the neck
        - The duration of the condition is greater than 6 months

        - There are clonic and/or tonic involuntary contractions of multiple neck muscles (e.g., sternocleidomastoid, splenius, trapezius and/or posterior cervical muscles [D]
    - Ptyalism/sialorrhea (excessive secretion of saliva, drooling) that meets **ALL** of the following criteria:
        - Refractory to pharmacotherapy (including anticholinergics)
        - Documentation of medically significant complications of sialorrhea, such as chronic skin maceration or infections that cannot be controlled with topical treatments or hygiene
    - Intractable, disabling focal primary hyperhydrosis, when **ALL** of the following are met
        - Member is unresponsive or unable to tolerate pharmacotherapy prescribed for excessive sweating (e.g., anticholinergics, beta-blockers, or benzodiazepines) if sweating is episodic
        - Significant disruption of professional and/or social life has occurred because of excessive sweating
        - Topical aluminum chloride or other extra-strength antiperspirants are ineffective or result in a severe rash
- **AbobotulinumtoxinA (Dysport Brand of Botulinum Toxin Type A)** is considered medically necessary for the treatment of **1 or more** of the following
    - Blepharospasm, characterized by intermittent or sustained closure of the eyelids caused by involuntary contractions of the orbicularis oculi muscle
    - Cervical dystonia, (spasmodic torticollis) of moderate or greater severity when **ALL** of the following criteria are met
        - Alternative causes of the members symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures, or other neuromuscular disorders
        - There is sustained head torsion and/or tilt with limited range of motion in the neck
        - The duration of the condition is greater than 6 months
        - There are clonic and/or tonic involuntary contractions of multiple neck muscles (e.g., sternocleidomastoid, splenius, trapezius and/or posterior cervical muscles) [E]
    - Limb spasticity- Must meet **ALL** of the following - One from the conditions and all of the documentation requirements:
        - Pt. must have **1 or more** of the following conditions:
            - Equinus varus deformity in children with cerebral palsy
            - Hereditary spastic paraplegia
            - Limb spasticity due to multiple sclerosis
            - Limb spasticity due to other demyelinating diseases of the central nervous system (including adductor spasticity and pain control in children undergoing adductor-lengthening surgery as well as children with upper extremity spasticity)
            - Spastic hemiplegia, such as due to stroke or brain injury
        - When **ALL** of the following criteria are met:

- Documentation that abnormal muscle tone is either interfering with functional ability, or is expected to result in joint contracture with future growth
- Documented failure to standard medical treatments
- Surgical intervention is considered to be the last option
- Treatment is being requested to enhance function or allow additional therapeutic modalities to be employed.

- **IncobotulinumtoxinA (Xeomin Brand of Botulinum Toxin Type A)** is considered medically necessary for the treatment of **1 or more** of the following indications
    - Blepharospasm, characterized by intermittent or sustained closure of the eyelids caused by involuntary contractions of the orbicularis oculi muscle
    - Cervical dystonia, (spasmodic torticollis) of moderate or greater severity when **ALL** of the following
        - Alternative causes of the members symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures, or other neuromuscular disorders
        - There is sustained head torsion and/or tilt with limited range of motion in the neck
        - The duration of the condition is greater than 6 months
        - There are clonic and/or tonic involuntary contractions of multiple neck muscles (e.g., sternocleidomastoid, splenius, trapezius and/or posterior cervical muscles) [F]
    - Post-stroke spasticity of the upper limb
- **Repeat Injections** are considered medically necessary if **ALL** of the following are met:
    - Physician progress notes document the patients response to treatment (patients functional improvement, degree of spasticity)
    - Physician progress notes document the physical examination and the return of clinical signs and symptoms of the disorder for which Botox was used to treat.
    - Treatment plan provides documentation of expected therapeutic goals (short- and long-term), the distribution of muscle groups injected, any co-existing complications, outcome measures and functional scales to be employed [G]
- **State Step Therapy Exception:** For Fully Insured in states: **CO, GA, IA, LA, NY, OH, OK, SD, VA, WA** Turnaround time other than are standard: **GA** (urgent 24 hrs, non-urgent- 2 business days; **LA** (urgent -24 hrs from receipt of all info. or 72 hrs from request if no info received. Non urgent requests- 72 hrs of receipt of all info. or 15 calendar days from request if no info. was received); **NY** (72 hrs or 24 hrs for expedited-life threatening); **OH** (48 hrs - urgent or 10 calendar days for non-urgent); **OK** (Urgent 24 hrs. Non-urgent 72 hrs); **TX** (TAT's for TX- 24 hours); **VA** (Non- Urgent requests 2 business from rec. of info or 15 calendar days from request). **WA** (Urgent- 1 business day from receipt of info, or 48 hours from request whichever is earlier. Non urgent request- 3 business days of receipt of info or 5 calendar days from request whichever is earlier). Carriers must approve step therapy override exception requests if **1 or more** of the following circumstances apply:
    - Cause an adverse reaction or is contraindicated based on the FDA prescribing information.

- Decrease a covered person's ability to achieve or maintain reasonable functional ability in performing daily activities
- Cause physical or mental harm to the covered person
- Cause a significant barrier to the adherence to or compliance with the plan of care
- It is expected to be ineffective based on the known clinical characteristics of the patient and the known characteristics of the prescription drug regimen such as **1 or more** of the following scenarios:
    - The patient previously stopped taking the drug required under the step therapy protocol, or another drug in the same pharmacological class or with the same mechanism of action, because the drug was not effective, had a diminished effect, or because of an adverse event.
    - The drug that is subject to the step therapy protocol was previously prescribed for the patient's condition, the patient received benefits for the drug under a health benefit plan. The patient is stable on the drug, and the change in the patient's drug regimen required by the step therapy protocol is expected to be ineffective or cause harm to the patient (based on the known clinical characteristics of the patient and the known characteristics of the required drug regimen).
    - Arizona: the prescription drug required by the step therapy protocol is not in the best interest of the patient based on medical necessity because the patient's use of the prescription drug is expected to cause **1 or more** of the following
        - A barrier to the patient's adherence to or compliance with the patient's plan of care.
        - A negative impact on the patient's comorbid conditions.
        - A clinically predictable negative drug interaction.
        - A decrease in the patient's ability to achieve or maintain a reasonably functional ability in performing daily activities for which the patient has experienced a positive therapeutic outcome.
        - The patient has experienced a positive therapeutic outcome on a prescribed drug selected by the patient's health care provider for the medical condition under consideration while on the patient's current or previous health care plan. A health care provider may not use a pharmaceutical sample for the purpose of qualifying for an exception to step therapy.
    - South Dakota, Virginia-The patient is currently receiving a positive therapeutic outcome on a prescription drug recommended by his provider for the medical condition under consideration while on a current or the immediately preceding health benefit plan.

- **State Step Therapy Exception: Oregon.** Carriers must approve a request for an exception to step therapy if the entity determines that the evidence submitted by the prescribing practitioner is sufficient to establish **1 or more** of the following
    - Cause an adverse reaction or is contraindicated based on the FDA prescribing information
    - The prescription drug required by the step therapy is expected to be ineffective based on the known clinical characteristics of the beneficiary and the known characteristics of the prescription drug regimen
    - The patient previously stopped taking the drug required under the step therapy protocol, or another drug in the same pharmacological class or with the same mechanism of action, because the drug was not effective, had a diminished effect, or because of an adverse event.
    - For a period of at least 90 days the beneficiary has experienced a positive therapeutic outcome from the drug for which the exception is requested while enrolled in the current or immediately preceding health care coverage and changing to the drug required by the step therapy may cause a clinically predictable adverse reaction or physical or mental harm to the beneficiary; or
    - The prescription drug required by the step therapy is not in the best interest of the beneficiary based on medical necessity.

Investigational Indications

- The use of Botulinum treatment for the following conditions is considered investigational. (this is not an inclusive list)
    - Anal sphincter dysfunction
    - Animus (pelvic floor dyssynergia)
    - Bells palsy
    - Benign prostatic hypertrophy
    - Biliary dyskinesia
    - Brachial plexus injury (also known as brachial palsy in newborns and Erbs palsy)
    - Carpal tunnel syndrome
    - Cervicalgia
    - Chronic constipation
    - Chronic low back pain
    - Chronic neck pain
    - Chronic pelvic pain
    - Chronic quadratus lumborum strain
    - Clenched fist syndrome
    - Clubfoot
    - Complex regional pain syndrome
    - Congenital hypertonia
    - Contracture of hip secondary to Legg-Perthe-Calves disease
    - Cranial-facial pain of unknown etiology
    - Cricopharyngeal/oropharyngeal dysphagia
    - Depression
    - Detrusor-sphincter dyssynergia associated with multiple sclerosis

- Diabetic neuropathic pain
- Dyspareunia
- Dsyphagia
- Esophageal stricture
- Fibromyalgia
- Fibromyositis
- Focal lower limb dystonia
- Gastroparesis
- Graves ophthalmopathy
- Gustatory sweating
- Head and voice tremor
- Headache, including cervicogenic, cluster, or tension-type or chronic daily headache
- Hyper-lacrimation
- Injection of the pylorus during esophago-gastrectomy
- Interstitial cystitis
- Irritable colon
- Intra-operative relaxation of the anal sphincter during hemorrhoidectomy
- Keratoconjunctivitis
- Knee flexion contracture
- Lateral epicondylitis (tennis elbow)
- Lumbar torsion dystonia
- Masseter hypertrophy
- Morton neuroma
- Motor tics
- Myofascial pain
- Notalgia paresthetica
- Nystagmus
- Obturator internus syndrome
- Orofacial tardive dyskinesia
- Pain from muscle trigger points
- Painful cramps
- Palatal myoclonus
- Parkinson's disease
- Parotitis
- Pelvic floor tension myalgia (also known as coccygodynia, diaphragma pelvis spastica, levator ani syndrome, levator spasm syndrome, spastic and pelvic floor syndrome),
- Phantom limb pain
- Phonic tics
- Piriformis syndrome
- Post-hemorrhoidectomy pain
- Post-herpetic neuralgia
- Pudendal neuralgia
- Pylorospasm
- Raynaud's phenomenon/Raynaud's scleroderma
- Reduction of mucin secretion
- Reduction of muscle tension after hamstring avulsion repair
- Restless legs syndrome

- Schwalbe-Ziehen-Oppenheim disease
- Shoulder pain
- Sciatica
- Scoliosis
- Sotos syndrome
- Spasm of the pectoralis muscle after breast reconstruction
- Stiff person syndrome
- Stuttering
- Temporomandibular joint disorders
- Tendon contracture
- Testicular pain (cremasteric synkinesia)
- Thoracic outlet syndrome
- Tinnitus
- Tourettes syndrome
- Trigeminal neuralgia
- Ulcers
- Vaginismus
- Vulvodynia
- Whiplash-related disorders
- Neutralizing Antibodies to Botulinum Toxin: testing for neutralizing antibodies to botulinum toxin is considered experimental and investigational.

Cosmetic Indications

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- **Botulinum toxin is considered cosmetic** for any of the following indications:
  - Aging neck
  - Blepharoplasty (eyelid lift)
  - Wrinkles, frown lines
  - Glabellar lines

Evidence Summary

- **Background**
- Local injections of onabotulinumtoxinA (Botox) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of strabismus, essential blepharospasm, and hemifacial spasm. In patients with congenital strabismus who have compromised or absent binocular vision, treatment is cosmetic as ocular realignment is not capable of restoring binocular vision
- Clinical studies indicate that Botox can also provide symptomatic relief in a variety of other conditions characterized by involuntary spasm of certain muscle groups, notably in cervical dystonia (spasmodic torticollis) and spasmodic dysphonia. Ninety percent of spasmodic torticollis patients show some improvement of pain relief, head position, and disability, and botulinum toxin is now the treatment of choice for this condition. Botox has been shown to result in normal or near normal voice in patients with adductor type (strained or strangled voice) laryngeal dystonia and to be of considerable benefit in patients with abductor type (breathy, whispery voice) laryngeal dystonia

- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson, et al., 2008b) stated that while botulinum neurotoxin is probably effective for the treatment of adductor type laryngeal dystonia, there is insufficient evidence to support a conclusion of effectiveness for botulinum neurotoxin in patients with abductor type of laryngeal dystonia. The assessment also stated that while many clinicians utilize electromyographic targeting for laryngeal injections, the utility of this technique is not established in comparative trials
- Botox has been evaluated in various spastic disorders. Botox can be used to reduce spasticity or excessive muscular contractions to relieve pain; to assist in posturing and walking; to allow better range of motion; to permit better physical therapy; and to reduce severe spasm in order to provide adequate perineal hygiene
- Botox has been shown to improve gait patterns in patients with cerebral palsy with progressive dynamic equinovarus or equinovalgus foot deformities. Treatment of children with cerebral palsy during the early years when functional skills in walking are being developed improves the outcome and may help to avoid surgery for contracture and bony torsion. In multiple sclerosis, Botox can relieve contractions of thigh adductors that interfere with sitting, positioning, cleaning, and urethral catheterization.
- Moore, et al. (2008) examined the durability of effect of Botox in spasticity in cerebral palsy. The investigators stated that the controlled evidence favoring Botox in the treatment for spasticity in cerebral palsy (CP) is based on short-term studies. These researchers conducted a randomized, double-blind, placebo-controlled, parallel-group study of Botox for leg spasticity in 64 children with CP. For 2 years, the children received trial injections of up to 30 mu/kg every 3 months if clinically indicated. For the primary endpoints of Gross Motor Function Measure (GMFM) and Pediatric Evaluation of Disability Index (PEDI) scaled scores at 2 years (trough rather than peak effect), there were no differences between the mean change scores of each group. For the GMFM total score, the 95% CI of -4.81 to 1.90 excluded a 5-point difference in either direction, and a 2-point benefit with 95% confidence. There were no differences in adverse events.
- The authors concluded that there was no evidence of cumulative or persisting benefit from repeated Botox at the injection cycle troughs at 1 year or 2 years. The dose was not enough to change spasticity measures and thus GMFM in this heterogeneous group. Ceiling effects in GMFM and PEDI may have reduced responsiveness. This finding does not deny the value, individually, of single injection cycles or prove that repeating them is unhelpful. In this regard, Botox therapy can be viewed in the same light as other temporary measures to relieve spasticity, such as oral or intra-thecal agents: there is no evidence of continuing benefit if the treatment ceases. The study provided long-term, fully controlled adverse event data and has not revealed any long-term adverse effects.
- Treatment with Botox has been shown to be safe and effective in the jaw-closing variant of oromandibular dystonia. Injections of Botox into the masseter, temporalis, and internal pterygoid muscles result in reduction in the oromandibular and lingual spasms and an improvement in chewing and speech. Symptoms are reduced in about 70% of patients, and treatment may prevent dental complications and temporomandibular joint dysfunction. Treatment with Botox has been shown to be safe and effective for writer's cramp (local and segmental limb dystonia). This dystonia can be incapacitating and has been exceptionally resistant to treatment with oral medications. Other occupational cramps, such as musician s cramp, respond less well to injections as they require very sophisticated neuromuscular performance
- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Naumann, et al., 2008) stated that while many

clinicians advocate electromyography or nerve stimulation guidance to optimize needle localization for injection, further data are needed to establish this recommendation

- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Naumann, et al., 2008) stated that while many clinicians advocate electromyography or nerve stimulation guidance to optimize needle localization for injection, further data are needed to establish this recommendation
- Some autonomic disorders resulting in hypersecretion of glands such as hyperhydrosis and sialism (ptyalism) respond well to Botox
- Botox has been shown to be a promising alternative to sphincterotomy in patients with chronic anal fissures
- An early randomized controlled single-center study that found benefits of onabotulinumtoxinA in the treatment of migraine; however, no firm conclusions could be drawn from this early study because of the marginal statistical significance of the results, the lack of an expected dose-response relationship, and the lack of a valid scientific explanation for treatment effects. 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 administration of placebo vehicle or onabotulinumtoxinA 25 or 75 U, injected into multiple sites of pericranial muscles at the same visit. Study subjects were assessed at 1, 2 and 3 months.
- For the 25-U onabotulinumtoxinA group, reduction in migraine frequency barely reached statistical significance ($p = 0.46$) at the 3-month assessment, but did not reach statistical significance at the 1- or 2-month assessments. The 75-U botulinum toxin group had no statistically significant reduction in migraine frequency at any assessment (Silberstein, et al., 2000).A commentary on this study (Bandolier, 2001) noted that, because of significant flaws in the design of the study by Silberstein, et al., "[t]he trial would score 2 out of a possible 5 points on a common quality scoring scale in which trials scoring 2 or less may be subject to bias." The commentary also noted the marginal statistical significance of results and the lack of an expected dose-response relationship.
- "The simple fact is that with one or two patients giving different responses, this would have been declared a negative trial. It does not inspire confidence, especially as this is the only randomised controlled trial for this intervention in this indication and the quality of reporting allows for the possibility of bias, as well as it being financed by the manufacturer." These results need to be replicated in a longer-term, multicenter randomized clinical study before conclusions about the effectiveness of botulinum toxin in migraine can be drawn.
- A subsequent randomized controlled clinical trial found no benefit to onabotulinumtoxinA in preventing migraine headaches (Evers, et al., 2004). Researchers evaluated 60 migraine patients for a three month period, participants received injections of either a high or low dose of botulinum toxin or placebo in muscles in the neck and or forehead. During the course of the study, migraine frequency was halved for 30% of the participants in the botulinum toxin groups and for 25% of those in the placebo group. Researchers also found that there were no significant differences among the three groups regarding the number of days participants had the migraine or the amount of drugs needed to treat the headaches. The researchers concluded that their findings did not support the hypothesis that Botox is an effective treatment for migraines.
- A study by Dodick, et al. (2005) presented a secondary analysis of data from a randomized controlled clinical trial of botulinum toxin A in the treatment of chronic daily headache, examining outcomes for a subgroup of subjects who were not receiving prophylactic medications. This was a secondary analysis of data from a study in which the overall cohort had no significant benefit from botulinum toxin (Mathew, et al., 2005). In addition, the largest

study of botulinum toxin for chronic daily headache showed no overall benefit (Silberstein, et al., 2005) (see below). These inconsistent results among studies lead the American Academy of Neurology to conclude that there is insufficient evidence to support or refute a benefit of botulinum toxin for chronic daily headache (Naumann, et al., 2008).

- In a phase II clinical trial (n = 702), Silberstein, et al. (2005) assessed the safety and effectiveness of three different doses of onabotulinumtoxinA as prophylactic treatment of chronic daily headache (CDH). Eligible patients were injected with Botox at 225 U, 150 U, 75 U, or placebo and returned for additional masked treatments at day 90 and day 180. Patients were assessed every 30 days for 9 months. The primary efficacy end point was the mean change from baseline in the frequency of headache-free days at day 180 for the placebo non-responder group. The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed in the placebo non-responder group treated with Botox at 225 U, 150 U, 75 U, or placebo, respectively (p = 0.44).
- An a priori-defined analysis of headache frequency revealed that Botox at 225 U or 150 U had significantly greater least squares mean changes from baseline than placebo at day 240 (-8.4, -8.6, and -6.4, respectively, p = 0.03 analysis of covariance). Only 27 of 702 patients (3.8%) withdrew from the study because of adverse events, which generally were transient and mild to moderate. These investigators concluded that although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240. The placebo response was higher than expected. The authors stated that onabotulinumtoxinA was safe and well tolerated. The authors noted that further study of Botox prophylactic treatment of CDH appears warranted.
- The findings of this study were in agreement with those of Mathews, et al. (2005). A review in Clinical Evidence (Silver, 2005) concluded that botulinum toxin for chronic tension-type headache was likely to be ineffective or harmful.
- An assessment on use of botulinum toxin in pain associated with neuromuscular disorders, prepared for the Minnesota Health Technology Advisory Committee (2001), concluded that there is insufficient evidence to support the use of botulinum toxin in the treatment of migraine. A review of the literature on treatments for migraine concluded that "botulinum toxin A ha[s] recently been suggested to be effective [for treatment of migraine]; however, at present, there are insufficient rigorous and reliable controlled data on these drugs for them to be indicated for such use" (Krymchantowski, et al., 2002).
- A structured evidence review by the BlueCross BlueShield Association Technology Evaluation Center (2002) concluded The available evidence does not permit conclusions regarding the prophylactic or abortive effect of [botulinum toxin A] or any other botulinum toxin type on chronic primary headache syndromes, including migraine, chronic tension, and cluster headache syndromes. The BlueCross BlueShield Association Technology Evaluation Center reevaluated the use of botulinum toxin for primary headache disorders (BCBSA, 2004) and concluded that this does not meet the TEC criteria.
- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann, et al., 2008) stated that botulinum neurotoxin is probably ineffective in episodic migraine and chronic tension-type headache. Also, there is currently no consistent evidence or strong evidence to allow drawing conclusions on the effectiveness of botulinum neurotoxin in chronic daily headache. The assessment also noted that the evidence for botulinum neurotoxin in gustatory sweating is suboptimal

- In a meta-analysis, Shuhendler, et al. (2009) evaluated the effectiveness of botulinum toxin type A in lowering the frequency of migraine headaches in patients with episodic migraines. A total of 1601 patients with a history of episodic migraine headaches classified as those experiencing headaches fewer than 15 times/month over a 3-month period were included in the analysis. PubMed, Google Scholar, and the Cochrane Library were searched from inception to October 2007 in order to locate randomized, double-blind, placebo-controlled trials that compared the effectiveness of peri-cranial botulinum toxin A injections with placebo in the prevention of migraines in patients with a history of episodic migraine headaches. The primary outcome of interest was change from baseline to end point in migraine frequency (number of migraines/month).
- A random effects model was used to combine study results, and the standardized mean difference (Cohen's d) in migraine frequency between the placebo and botulinum toxin A groups was reported. Effect sizes (d) less than 0.2 were considered small. Quality assessment was performed by using the Downs and Black scale. Eight randomized, double-blind, placebo-controlled clinical trials (1601 patients) presented a quantitative assessment of the effectiveness of botulinum toxin A versus placebo. The overall treatment effect size of botulinum toxin A over placebo for 30, 60, and 90 days after injection was d -0.06 (95 % confidence interval [CI] - 0.14 to 0.03, z = 1.33, p = 0.18), d -0.05 (95 % CI -0.14 to 0.03, z = 1.22, p = 0.22), and d -0.05 (95 % CI -0.13 to 0.04, z = 1.07, p = 0.28), respectively.
- Even after controlling for a high placebo effect, and after dose stratification, no significant effect of botulinum toxin A in reducing migraine frequency/month was seen over placebo. The authors concluded that botulinum toxin A for the prophylactic treatment of episodic migraine headaches was not significantly different from placebo, both from a clinical and statistical perspective.
- Magalhaes et al (2010) compared the effects of Botox with those of amitriptyline on the treatment of chronic daily migraines. Chronic migraine sufferers were randomized into two groups and treated with 25 or 50 mg/day of amitriptyline or 250 U of Botox. A reduction of at least 50 % in the number of pain episodes, in the intensity of pain, and in the number of drug doses for pain and reports of improvement by the patient or by the examiner were the main end points. A total of 72 subjects were enrolled in the study. A reduction of at least 50 % in the number of days of pain was recorded in 67.8 % of the patients in the Botox group and 72 % (n = 23) of the patients in the amitriptyline group (p = 0.78, risk ratio [RR] = 0.94, CI = 0.11 to 8).
- The reduction in the intensity of pain, as assessed using the VAS, was 50 % in the Botox group and 55.6 % in the amitriptyline group (p = 0.79, RR = 1.11; CI = 0.32 to 3.8). The reduction in the number of pain drug doses was 77 % for the Botox group and 71 % for the amitriptyline group (p = 0.76; RR = 0.92, CI = 0.45 to 1.88). The authors concluded that Botox was as effective as amitriptyline for the prophylactic treatment of chronic daily migraines.
- Aurora and colleagues (2010) evaluated the safety, effectiveness, and tolerability of Botox as headache prophylaxis in adults with chronic migraine. The Phase III REsearch Evaluating Migraine Prophylaxis Therapy 1 (PREEMPT 1) is a phase III study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Subjects were randomized (1:1) to injections every 12 weeks of Botox (155 U to 195 U; n = 341) or placebo (n = 338) (2 cycles). The primary end point was mean change from baseline in headache episode frequency at week 24. No significant between-group difference for Botox versus placebo was observed for the primary end point, headache episodes (-5.2 versus -5.3; p = 0.344).

- Large within-group decreases from baseline were observed for all efficacy variables. Significant between-group differences for Botox were observed for the secondary end points, headache days (p = 0.006) and migraine days (p = 0.002). Botox was safe and well-tolerated, with few treatment-related adverse events. Few subjects discontinued due to adverse events. The authors concluded that there was no between-group difference for the primary end point, headache episodes. However, significant reductions from baseline were observed for Botox for headache and migraine days, cumulative hours of headache on headache days and frequency of moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling chronic migraine.
- Dodick et al (2010) evaluated the efficacy, safety, and tolerability of Botox as headache prophylaxis in adults with chronic migraine. The 2 multi-center, pivotal trials in the PREEMPT clinical program each included a 24-week randomized, double-blind phase followed by a 32-week open-label phase. Qualified patients were randomized (1:1) to Botox (155 U to 195 U) or placebo injections every 12 weeks. Study visits occurred every 4 weeks. These studies were identical in design (e.g., inclusion/exclusion criteria, randomization, visits, double-blind phase, open-label phase, safety assessments, treatment), with the only exception being the designation of the primary and secondary endpoints.Thus, the pre-defined pooling of the results was justified and performed to provide a complete overview of between-group differences in efficacy, safety, and tolerability that may not have been evident in individual studies.
- The primary end point for the pooled analysis was mean change from baseline in frequency of headache days at 24 weeks. Secondary end points were mean change from baseline to week 24 in frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes, frequency of migraine/probable migraine episodes, frequency of acute headache pain medication intakes, and the proportion of patients with severe (greater than or equal to 60) Headache Impact Test-6 score at week 24. A total of 1,384 adults were randomized to Botox (n = 688) or placebo (n = 696). Pooled analyses demonstrated a decrease from baseline in mean frequency of headache days, with statistically significant between-group differences favoring Botox over placebo at week 24 (-8.4 versus -6.6; p < 0.001) and at all other time points.
- Significant differences favoring Botox were also observed for all secondary efficacy variables at all time points, with the exception of frequency of acute headache pain medication intakes. Adverse events occurred in 62.4 % of Botox patients and 51.7 % of placebo patients. Most patients reported adverse events that were mild-to-moderate in severity and few discontinued (Botox, 3.8 %; placebo, 1.2 %) due to adverse events. No unexpected treatment-related adverse events were identified. The authors concluded that the pooled PREEMPT results demonstrate that Botox is an effective prophylactic treatment for chronic migraine. Botox (onabotulinumtoxinA) resulted in significant improvements compared with placebo in multiple headache symptom measures, and significantly reduced headache-related disability and improved functioning, vitality, and overall health-related quality of life. Repeat treatments with Botox were safe and well-tolerated.
- Cady (2010) stated that Botox has been studied as a migraine preventive in numerous clinical trials and in a variety of sub-populations with migraine. Overall, results from the clinical trials are mixed. However, the largest and most recent parallel studies (n = 1,330) conducted on subjects with chronic migraine achieved statistically significant efficacy on numerous end points including the primary end point of reduction of headache days. The author reviewed several clinical studies using Botox in migraine prevention and highlighted some of the inherent difficulties defining study end points and outcomes that are relevant to

clinician, patients, and regulatory agencies. The author concluded that clinical trials utilizing Botox as a preventive therapy for migraine has revealed mixed results.

- In part this reflects the inherent difficulties in study design such as defining different sub-populations of migraine sufferers and trial end points that are meaningful to patient populations. Recent studies of subjects with chronic migraine appear to have positive results. If confirmed this would be the first preventive medication indicated specifically for chronic migraine. In October 2010, the FDA approved Botox injection (onabotulinumtoxinA) to prevent headaches in adult patients with chronic migraine (more than 14 days per month with headaches lasting 4 hours a day or longer). To treat chronic migraines, Botox is given approximately every 12 weeks as multiple injections - a total of 31 injections into 7 specific head and neck sites for a total of 155 U per treatment session. Botox has not been shown to work for the treatment of migraine headaches that occur 14 days or less per month, or for other forms of headache.
- The most common adverse reactions reported by patients being treated for chronic migraine were neck pain and headache
- Botox has been shown to reduce muscle tone and increase range of movement in upper extremity spasticity or in spastic foot drop after stroke. However, whether this translates into functional improvement has yet to be substantiated
- Unit dosing of onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and rimabotulinumtoxinB (Myobloc) or other botulinum toxin serotypes are not interchangeable. According to the U.S. Food and Drug Administration (FDA), "[u]nits of biologic activity of Botox cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other assay method."
- If concomitant neuromuscular disorders, such as myasthenia gravis and certain myopathies exist, Botox may be harmful. Thus, diagnosis is crucial before undertaking botulinum toxin type A injections. Botox is not indicated in patients receiving aminoglycosides, which may interfere with neuromuscular transmission
- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of spasticity (Simpson, et al., 2008a) recommended botulinum neurotoxin as a treatment option to reduce muscle tone and improve passive function in adults with spasticity. The assessment also recommended botulinum neurotoxin for equinus varus deformity in children with cerebral palsy, adductor spasticity and pain control in children undergoing adductor-lengthening surgery, and children with upper extremity spasticity. Furthermore, the assessment stated that there is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection. It noted that further studies on injection methodology including the use of electromyographic guidance, ultrasonography, and electrical stimulation are needed to optimize treatment technique
- The American Academy of Neurologys assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson, et al., 2008b) stated that the role of electromyography has not been established for cervical dystonia. It also stated that while a few patients in one Class II study suggested that botulinum neurotoxin may be effective for lower extremity dystonia, the data are inadequate to provide a recommendation. A randomized controlled clinical trial (n = 16) demonstrated significant reductions in sialorrhea without compromising dysphagia in persons with Parkinsons disease and problematic sialorrhea (Ondo, et al., 2004).
- According to a systematic review of the evidence for botulinum toxin for essential tremor (Ferreira & Sampaio, 2003), there is evidence of short-term reduction of tremor but no consistent improvement in disability and function. The review noted that botulinum toxin injections cause hand weakness, resulting in a "trade off" between benefits and harms. The

review concluded that "RCTs [randomized controlled clinical trials] comparing botulinum A toxin-haemagglutinin complex versus placebo found short term improvement of clinical rating scales, but no consistent improvement of motor task performance or functional disability. Hand weakness, which is dose dependent and transient, is a frequent adverse effect." The American Academy of Neurology (Zesiewicz, et al,, 2005) has stated that botulinum toxin A injections for limb, head, and voice tremor associated with essential tremor may be considered in medically refractory cases.

- This recommendation was categorized as Level C, given the limited strength of the available evidence. The American Academy of Neurology concluded that [t]he effect of botulinum toxin A [botulinum toxin A] on limb tremor in ET [essential tremor] is modest and is associated with dose-dependent hand weakness. botulinum toxin A may reduce head tremor and voice tremor associated with ET, but data are limited. When used to treat voice tremor, botulinum toxin A may cause breathiness, hoarseness, and swallowing difficulties.
- The American Academy of Neurology s assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson et al, 2008b) stated that botulinum neurotoxin should be considered a treatment option for essential hand tremor in those patients who fail treatment with oral agents. On the other hand, there is insufficient evidence to draw a conclusion on the use of botulinum neurotoxin in the treatment of head and voice tremor.
- The evidence of botulinum toxin in the treatment of piriformis syndrome is limited to a small, controlled short-term study and a small pilot cross-over study reporting on the impact of botulinum toxin on pain, but not on disability and function (Fishman, et al., 2002; Childers, et al., 2002). In addition, the placebo-controlled study had a significant drop-out rate. The existence of piriformis syndrome as a clinical entity is controversial (NHS, 2002).
- Several studies have tested the effects of pyloric injection of botulinum toxin in patients with diabetic and idiopathic gastroparesis (Parkman, et al., 2004). These studies have all been unblinded with small numbers of patients from single centers and have observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Moreover, the American Gastroenterological Association (2004) has concluded that double-blind controlled studies are needed to support the efficacy of this treatment (Parkman, et al., 2004).
- Bromer, et al. (2005) reviewed the use of Botox in the treatment of patients with gastroparesis. Response was defined as improvement or resolution of the patient's major symptom and/or two minor symptoms for 4 weeks. Of 115 patients treated, 63 patients met the study criteria. There were 53 women, 10 men, mean age 42 years. Most patients (56%) had idiopathic gastroparesis. Twenty-seven of 63 (43%) patients experienced a symptomatic response to treatment. By stepwise logistic regression, male gender was associated with response to treatment (OR 3.27: 95% CI[1.31, 8.13], p = 0.01). Vomiting as a major symptom was associated with a lack of response (OR 0.16: 95% CI[0.04, 0.67], p = 0.01). Despite the association of male gender with response, the mean duration of response for those patients responding, with a minimum of 3 months' follow-up was 4.9 months (+/- 2.7 months) for women and 3.5 months (+/- 0.71 months) for men (p = 0.59).
- The corresponding medians and inter-quartile ranges (IQR) were 5 (IQR 3 - 6) for females and 3.5 (IQR 3 - 4) for males. The authors concluded that of the patients, 43% had a response to Botox treatment that lasted a mean of approximately 5 months. Male gender was associated with a response to this therapy; however, durability of response was unrelated to gender. Vomiting as a major symptom predicted no response. The major drawbacks of this study were: (i) it was a retrospective study, (ii) the lack of a validated symptom questionnaire or a visual analog scale before for pre- and post-injection estimation

of improvement, (iii) subjects were not prescribed a standardized diet and/or medication regimen for gastroparesis following Botox injection, (iv) a high number of patients (n = 27) were lost to follow-up that may have influenced the response rate, (v) issues with experimental design -- selection bias as well as recall bias.

- Ezzeddine, et al. (2002) reported their findings of pyloric injection of Botox for the treatment of diabetic gastroparesis. A total of 6 patients with diabetic gastroparesis and an abnormal solid phase gastric emptying study underwent upper endoscopy during which 100 units of Botox were injected into the pyloric sphincter. Gastric emptying studies were obtained at 48 hours and 6 weeks after injection. Patients were questioned about symptoms of gastroparesis, and a symptom score was obtained at baseline and at 2 weeks and 6 weeks after injection. There was a mean improvement in the subjective symptom score at 2 weeks of 55% (range of 14 to 80 %). This improvement was maintained at 6 weeks. There was a 52 % improvement in gastric emptying at 2 and 6 weeks.
- The authors concluded that pyloric injection of Botox can improve symptoms and gastric emptying in patients with diabetic gastroparesis. They stated that further evaluation of pyloric injection of Botox as a treatment for diabetic gastroparesis is warranted
- Gupta and Rao (2002) noted that well-designed, prospective, double-blinded, placebo-controlled studies are needed to establish the role of Botox in selected patients with diabetic gastroparesis.
- Yeh and Triadafilopoulos (2006) reviewed injection therapies for non-bleeding disorders of the gastrointestinal tract. With regards to the use of Botox for the treatment of gastroparesis, the authors noted that data from a randomized, sham-controlled study are needed to draw firm conclusion on the utility of this treatment
- Reddymasu, et al. (2007) examined the use of endoscopic pyloric injection of Botox in the treatment of patients with post vagotomy gastroparesis (n = 11). The authors concluded that this approach appears to be safe; but randomized trials are needed
- Friedenberg and colleagues (2008) noted that observational data suggest that intra-pyloric injection of Botox reduces symptoms and accelerates gastric emptying in idiopathic and diabetic gastroparesis. These researchers examined if Botox would improve symptoms to a significantly greater extent than placebo. An additional objective was to ascertain if there is an acceleration of gastric emptying after injection. A single-institution, randomized, double-blind, placebo-controlled study was carried out. Eligible patients had a Gastroparesis Cardinal Symptom Index score greater than or equal to 27 with randomization to intra-pyloric botulinum toxin, 200 units, or saline placebo. Re-assessment of symptoms and repeat gastric emptying scan at 1-month follow-up were done.
- A total of 32 patients were randomized to botulinum toxin (n = 16) and placebo (n = 16). At 1-month follow-up, 37.5% randomized to Botox and 56.3% randomized to placebo achieved improvement as defined by this study. There were no identifiable clinical predictors of response. The Botox group reported improvement in gastric emptying; however, this was not superior to placebo. No serious adverse events were attributable to Botox. The authors concluded that intra-pyloric injection of Botox improves gastric emptying in patients with gastroparesis, although this benefit was not superior to placebo at 1 month. Also, in comparison to placebo, symptoms do not improve significantly by 1 month after injection. These investigators stated that they could not recommend Botox for widespread use in the treatment of delayed gastric emptying until more data are available.
- There is insufficient evidence to support the use of botulinum toxin for treatment of constipation. Lembo and Camilleri (2003) do not recommend botulinum injection for the management of patients with chronic constipation. Furthermore, Talley (2004) stated that a novel approach for the management of chronic constipation is injection of Botox into the

puborectalis muscle of patients with pelvic floor dysfunction. However, there is insufficient evidence to support the effectiveness of this approach

- Botulinum toxin is currently being studied for the management of patients with lower urinary tract dysfunctions such as detrusor-sphincter dyssynergia and detrusor overactivity. Botulinum toxin is injected into the external urethral sphincter to treat detrusor sphincter dyssynergia, while intra-detrusal injections of botulinum toxin is employed in treating detrusor overactivity and symptoms of the overactive bladder (OAB). In a single treatment, randomized, placebo-controlled study (n = 59), Schurch, et al., (2005) found that intramuscular injections of Botox into the detrusor can provide rapid, well-tolerated, clinically significant decreases in the signs and symptoms of urinary incontinence caused by neurogenic detrusor overactivity during a 24-week study period. These researchers noted that Botox is a potential candidate for the management of neurogenic urinary incontinence
- In a randomized, double-blind, placebo-controlled crossover clinical trial, Ghei and colleagues (2005) examined the safety and effectiveness of rimabotulinumtoxinB for the treatment of OAB. A total of 20 patients 18 to 80 years old with detrusor overactivity unresponsive to oral anti-muscarinic agents participated in the study. They were injected with either placebo (20 ml normal saline) or rimabotulinumtoxinB (5,000 IU diluted up to 20 ml) intravesically in a day case setting. After 6 weeks the treatments were crossed over without washout in line with previous findings. The primary outcome was the paired difference in change in average voided volumes. Frequency, incontinence episodes and paired differences in quality of life measured by the King's Health Questionnaire were the secondary outcome measures. Little carryover was noted in the second arm placebo and the placebo data from both arms were included in analysis.
- There were clinically statistically significant paired differences in the change in average voided volume, urinary frequency and episodes of incontinence between active treatment and placebo. There were similarly significant paired differences in the change in quality of life affecting 5 domains of the King's Health Questionnaire. These investigators concluded that the findings of this study provided evidence of the efficacy of rimabotuoinumtoxnB in the treatment of OAB. Autonomic side effects were observed in 4 patients. Moreover, they noted that the short duration of action will presumably limit the use to patients who have experienced tachyphylaxis with Botox.
- In an editorial that accompanied the study by Ghei, et al., Chancellor (2005) stated that one undesirable feature of the study was that the hypothesis was tested on a mixed population of patients (patients with mixed etiologies of detrusor overactivity, 3 neurogenic and 17 nonneurogenic with detrusor overactivity). This limits the generalizability of the findings. The authors made a strong argument why a crossover design was appropriate and their data were valid. However, since almost all studies have shown that botulinum toxin A has a duration of efficacy of approximately 6 months, most experts in the field would still question the merit of a crossover at 6 weeks as not all the patients returned to pre-injection clinical and urodynamic values done at 6 weeks. Most experts would submit that a washout period after the crossover may have been appropriate. Since there are limited experiences with botulinum toxin-B in the bladder, assessment of duration of response would be valuable.
- Chancellor was surprised how short the duration of effectiveness attained by rimabotulinumtoxinB was. Moreover, it is unclear how useful rimabotulinumtoxinB will be in urology since there are suggestions that rimabotulinumtoxinB has a more systemic effect that Botox.
- In a multi-center, randomized, placebo-controlled trial (n = 86), Gallien, et al., (2005) assessed the safety and effectiveness of Botox in the treatment of detrusor sphincter dyssynergia in patients with multiple sclerosis (MS). Individuals with chronic urinary

retention were included if they had post-voiding residual urine volume between 100 and 500 ml. They received a single transperineal injection of either Botox (100 U) or placebo in the sphincter and also 5 mg slow release alfuzosin twice daily over 4 months. Main endpoint was post-voiding residual urine volume assessed 1 month after injection. Follow-up duration was 4 months. The study was stopped after the 4th analysis (placebo = 41, Botox = 45). At inclusion, there was no significant difference between groups whichever variable was considered.

- Mean (standard deviation) post-voiding residual urine volume was 217 (96) and 220 (99) ml in placebo and Botox groups, respectively. One month later, post-voiding residual urine volume was 206 (145) and 186 (158) ml (p = 0.45) in placebo and Botox groups, respectively. However, compared to placebo, Botox significantly increased voiding volume (+54%, p = 0.02) and reduced pre-micturition (-29%, p = 0.02) and maximal (-21 %, p = 0.02) detrusor pressures. Other secondary urodynamic endpoints and tolerance were similar in the two groups.
- These investigators concluded that in MS patients with detrusor sphincter dyssynergia, a single injection of Botox (100 U) does not decrease post-voiding residual urine volume. Also, De Laet and Wyndaele (2005) noted that generalized side effects after Botox injection for voiding disorders are rare but they can be very disabling for patients with spinal cord injury. Although no long-term side effects are reported so far, urologists should be aware that these effects of Botox injections are unknown
- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann, et al., 2008) reported that botulinum neurotoxin is safe and effective for the treatment of neurogenic detrusor overactivity in adults. On the other hand, data on the use of botulinum neurotoxin for detrusor-sphincter dyssynergia (DSD) are conflicting. The AAN concluded that botulinum neurotoxin is probably safe and effective for the treatment of DSD in patients with spinal cord injury and should be considered for use in these patients. However, it does not provide significant benefit for the treatment of DSD in patients with multiple sclerosis
- Other than detrusor-sphincter dyssynergia after spinal cord injury, the role of botulinum toxin in the treatment of lower urinary tract dysfunctions has yet to be established. Sahai, et al., (2005) stated that application of botulinum toxin in the lower urinary tract has produced promising results in treating lower urinary tract dysfunction, which needs further evaluation with randomized, placebo-controlled trials. This is in agreement with the observations of Schurch and Corcos (2005) as well as Grise, et al., (2005).
- Schurch and Corcos noted that Botox appears to be a reasonable alternative to surgery in the management of intractable OAB in children. However, studies of the delivery method, site of injection, dose and long-term follow-up are needed to confirm the good safety profile/clinical benefit of this new, minimally invasive approach. In a review on the use and mechanism of botulinum toxin in the treatment of OAB, Grise and colleagues stated that further studies remain necessary regarding the dosage of Botox, selection of patients, combination with anti-cholinergic treatment, as well as effects of repeated injections.
- The Vanderbilt Evidence-based Practice Center systematically reviewed evidence on treatment of OAB, UI, and related symptoms (Hartmann et al, 2009. These investigators focused on prevalence and incidence, treatment outcomes, comparisons of treatments, modifiers of outcomes, and costs. They searched PubMed, MEDLINE, EMBASE, and CINAHL. They included studies published in English from January 1966 to October 2008; excluded studies with fewer than 50 participants, fewer than 75 % women, or lack of relevance to OAB. Of 232 included publications, 20 were good quality, 145 were fair, and 67 poor. These researchers calculated weighted averages of outcome effects and conducted a

mixed-effects meta-analysis to investigate outcomes of pharmacological treatments across studies. Overactive bladder affects more than 10 to 15 % of adult women, with 5 to 10 % experiencing UI monthly or more often.

- Six available medications are effective in short-term studies: estimates from meta-analysis models suggest extended release forms (taken once-daily) reduce UI by 1.78 (95 % CI: 1.61 to 1.94) episodes per day, and voids by 2.24 (95 % CI: 2.03 to 2.46) per day. Immediate release forms (taken twice or more a day) reduce UI by 1.46 (95 % CI: 1.28 to 1.64), and voids by 2.17 (95 % CI: 1.81 to 2.54). As context, placebo reduces UI episodes by 1.08 (95 % CI: 0.86 to 1.30), and voids by 1.48 (95 % CI: 1.19 to 1.71) per day. No one drug was definitively superior to others, including comparison of newer more selective agents to older anti-muscarinics. Current evidence is insufficient to guide choice of other therapies including sacral neuromodulation, instillation of oxybutynin, and injections of botulinum toxin. Acupuncture was the sole complementary and alternative medicine treatment, among reflexology and hypnosis, with early evidence of benefit.
- The strength of the evidence is insufficient to fully inform choice of these treatments. Select behavioral interventions were associated with symptom improvements comparable to medications. Limited evidence suggests no clear benefit from adding behavioral interventions at the time of initiation of pharmacological treatment. The authors concluded that OAB and associated symptoms are common. Treatment effects are modest. Quality of life and treatment satisfaction measures suggest such improvements can be important to women. The amount of high quality literature available is meager for helping guide women's choices. Gaps include weak or absent data about long-term follow-up, poorly characterized and potentially concerning harms, information about best choices to minimize side effects, and study of how combinations of approaches may best be used. This is problematic since the condition is chronic and a single treatment modality is unlikely to fully resolve symptoms for most women.
- Brubaker et al (2008) compared 200 U intradetrusor botulinum toxin A versus placebo in women with refractory idiopathic urge incontinence (UI). This institutional review board approved, multi-center registered trial randomized women with refractory UI, detrusor overactivity incontinence and 6 or greater UI episodes in 3 days to botulinum toxin A or placebo at a 2:1 ratio. Refractory was defined as inadequate symptom control after 2 or more attempts at pharmacotherapy and 1 or more other first line therapies for detrusor overactivity incontinence. The primary outcome measure was time to failure, as evidenced by a Patient Global Impression of Improvement score of 4 or greater at least 2 months after injection, or changes in treatment (initiation or increase) at any time after injection. Safety data, including increased post-void residual volume, defined as more than 200 ml irrespective of symptoms, was obtained at specified time points.
- Approximately 60 % of the women who received botulinum toxin A had a clinical response based on the Patient Global Impression of Improvement. The median duration of their responses was 373 days, significantly longer than the 62 days or less for placebo ($p < 0.0001$). In the botulinum toxin A group increased post-void residual urine (12 of 28 women or 43 %) and urinary tract infection in those with increased post-void residual urine (9 of 12 or 75 %) exceeded expected ranges. Further injections were stopped after 43 patients were randomized, including 28 to botulinum toxin A and 15 to placebo. The authors concluded that local injection of 200 U botulinum toxin A was an effective and durable treatment for refractory overactive bladder (OAB). However, a transient post-void residual urine increase was experienced in 43 % of patients. The authors noted that botulinum toxin A for idiopathic overactive bladder is still under investigation.

- Chuang, et al. (2003) stated that botulinum toxin type A treatment inhibits afferent-nerve-mediated bladder contraction. This analgesic effect may expand the application of botulinum toxin type A in the localized genitourinary tract pain syndrome, such as interstitial cystitis and prostatodynia. The authors concluded that application of botulinum toxin type A is a promising treatment for lower urinary tract dysfunction with profound basic and clinical implications. Chancellor and Yoshimura (2004) noted that among the potentially effective new treatment modalities for interstitial cystitis currently under investigation are suplatast tosilate, resiniferatoxin, botulinum toxin, and gene therapy to modulate the pain response
- There is insufficient evidence to support the use of botulinum toxin for interstitial cystitis. Kuo (2005) evaluated the clinical effectiveness of sub-urothelial injection of botulinum toxin A in patients with chronic interstitial cystitis (n = 10). Eight women and 2 men with chronic interstitial cystitis who had failed conventional treatments were enrolled in this study. In 5 patients, 100 units of botulinum toxin A was injected sub-urothelially into 20 sites, and an additional 100 units was injected into the trigone in the other 5 patients. Therapeutic outcome including functional bladder capacity, number of daily urinations, bladder pain, and urodynamic changes were compared between baseline and 3 months after treatment. In 2 patients bladder pain and urinary frequency were improved 3 months after treatment. Mild difficulty in urination was reported by 7 patients.
- Functional bladder capacity recorded in a voiding diary was significantly increased (155 + - 26.3 versus. 77 + - 27.1 ml, $p < 0.001$), and the frequency of daily urinations (18 +- 7.7 versus. 24.2 + - 10.3, $p = 0.025$) and the pain score (2.4 +- 1.6 versus. 3.2 + - 1.1, $p = 0.003$) were mildly but significantly reduced after treatment. Only the cystometric capacity improved significantly (287 +- 115 versus. 210 +- 63.8 ml, $p = 0.05$) in urodynamic results. Trigonal injection had no therapeutic effect on symptom or urodynamic improvement. No adverse effect was reported. The author concluded that the clinical result of sub-urothelial botulinum toxin A injection was disappointing. None of the patients was symptom-free and only a limited improvement in bladder capacity and pain score was achieved in 2 patients.
- Toft and Nording (2006) reviewed the recently published literature on intravesical therapy strategies in painful bladder syndrome interstitial cystitis. Bladder irrigation with different agents has been used during years in an attempt to treat painful bladder syndrome/interstitial cystitis. The 'traditional' agent for glycosaminoglycan substitution is hyaluronic acid. Often used are heparin and dimethyl sulfoxide, the actions of which are not quite clear but supposedly on an anti-inflammatory basis. Other agents for intravesical treatment are Bacillus Calmette-Guerin vaccine and botulinum toxin, and some recent studies have pointed to resiniferatoxin and RDP58.
- The authors concluded that painful bladder syndrome/interstitial cystitis persists as a challenging syndrome in urology. Intravesical instillation therapy has basically not changed during the last few years, although some studies have disconfirmed some regimens. Intensive research may hopefully result in more effective treatments in the future.
- Botulinum toxin has been studied as a treatment for flexion contractures. Shah, et al. (2005) described the development of a flexion contracture in a patient with Parkinson's disease after total knee arthroplasty. This contracture was successfully treated with manipulation under anesthesia and injections of botulinum toxin A into the hamstring and gastrocnemius muscles, in conjunction with a static progressive extension orthosis and rigorous physical therapy. This was a case study; and the clinical benefit of botulinum toxin, if any, is confounded by the multiple therapies used in this patient
- There is little evidence to support the use of botulinum toxin for tinnitus. In a prospective, double-blinded study, Stidham, et al. (2005) assessed the potential benefit botulinum toxin A in the treatment of tinnitus. A total of 30 patients with tinnitus were randomly placed into 1

of 2 treatment arms. Patients either received botulinum toxin A (20 to 50 units) or saline injection at the first treatment, and the opposite treatment 4 months later. Prospective data including tinnitus matching test, tinnitus handicap inventory (THI), tinnitus rating scale (TRS), and patient questionnaires were obtained over a 4-month period after each injection. Twenty-six patients completed both injections and follow-up and were included in data analysis. After botulinum toxin A, subjective tinnitus changes included 7 patients improved, 3 worsened, and 16 unchanged.

- Following placebo, 2 patients were improved, 7 worsened, and 17 unchanged. Comparison of the treatment and placebo groups was statistically significant ($p < 0.005$) when including better, worse, and same effects. A significant decrease in THI scores between pretreatment and 4 month post-botulinum toxin A injection ($p = 0.0422$) was recorded. None of the other comparisons of pre-treatment to 1 month, or pre-treatment to 4 months were significantly different. This study found improvement in THI scores and patient subjective results after botulinum toxin- A injection compared with placebo, suggesting a possible benefit of botulinum toxin- A in tinnitus management. The authors noted that larger studies need to be completed to further evaluate potential benefits of botulinum toxin- A in treatment of this difficult problem
- Results of studies of botulinum toxin for lateral epicondylitis have had mixed results. In a randomized, double-blind, placebo controlled study (n = 60), Wong, et al. (2005) examined if an injection of botulinum toxin is more effective than placebo for reducing pain in adults with lateral epicondylitis (tennis elbow). The primary outcome was change in subjective pain as measured by a 100-mm visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain ever) at 4 weeks and 12 weeks. All patients completed post-treatment follow-up. Mean VAS scores for the botulinum toxin group at baseline and at 4 weeks were 65.5 mm and 25.3 mm, respectively; respective scores for the placebo group were 66.2 mm and 50.5 mm (between-group difference of changes, 24.4 mm [95% CI, 13.0 to 35.8 mm] $p < 0.001$).
- At week 12, mean VAS scores were 23.5 mm for the botulinum toxin group and 43.5 mm for the placebo group (between-group difference of changes, 19.3 mm [CI, 5.6 to 32.9 mm]; $p = 0.006$). Grip strength was not statistically significantly different between groups at any time. Mild paresis of the fingers occurred in 4 patients in the botulinum toxin group at 4 weeks. One patient's symptoms persisted until week 12, whereas none of the patients receiving placebo had the same complaint. At 4 weeks, 10 patients in the botulinum toxin group and 6 patients in the placebo group experienced weak finger extension on the same side as the injection site. The study was small, and most subjects were women. The blinding protocol may have been ineffective because the 4 participants who experienced paresis of the fingers could have correctly assumed that they received an active treatment.
- This positive finding is in contrast to that of Hayton et al (2005) who performed a double-blind, randomized, controlled, pilot trial comparing injections of botulinum toxin- A with those of a placebo (normal saline solution) in the treatment of chronic tennis elbow. A total of 40 patients with a history of chronic tennis elbow for which all conservative treatment measures, including steroid injection, had failed were randomized into two groups: (i) half the patients received 50 units of botulinum toxin- A, and (ii) the remainder received normal saline solution. The intramuscular injections were performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. The two solutions used for the injections were identical in appearance and temperature.
- The results of a quality-of-life assessment with the Short Form-12 (SF-12), the pain score on a VAS, and the grip strength measured with a validated Jamar dynamometer were recorded before and 3 months after the injection. Three months following the injections, there was no significant difference between the two groups with regard to grip strength, pain, or quality of

life. The authors reported that with the numbers studied, they failed to find a significant difference between the two groups. Therefore, they concluded that there is no evidence of a benefit from botulinum toxin injection in the treatment of chronic tennis elbow.

- Monnier, et al. (2006) stated that musculoskeletal pain in patients with rheumatic disorders is among the emerging indications for botulinum toxin therapy. Preliminary data have been obtained in patients with cervical or thoracolumbar myofascial pain syndrome, chronic low back pain, piriformis muscle syndrome, tennis elbow, and stiff person syndrome. At present, the effects of botulinum toxin and its use for pain relief remain controversial. Carefully designed prospective studies are needed to ascertain the safety and effectiveness of botulinum toxin in pain disorders
- A randomized study found no effect of botulinum toxin on pain from muscle trigger points. In a double-blind, randomized, placebo-controlled, parallel clinical trial, Qerama, et al. (2006) studied the effect of botulinum toxin A on pain from muscle trigger points and on EMG activity at rest and during voluntary contraction. Thirty patients with trigger points in the infra-spinatus muscles received either 50 units/0.25 mL of botulinum toxin A or 0.25 mL of isotonic saline. Baseline measures were determined during a run-in period of 1 week. Outcome measures including local and referred spontaneous pain, pain detection and tolerance thresholds to mechanical pressure, and shoulder movement were assessed at 3 and 28 days after injection.
- The interference pattern of the EMG during maximal voluntary effort of infra-spinatus muscle was recorded and a standardized search for spontaneous electrical motor endplate activity at the trigger points was performed before and 28 days after botulinum toxin A or saline injection. Botulinum injection reduced motor endplate activity and the interference pattern of EMG significantly but had no effect on either pain (spontaneous or referred) or pain thresholds compared with isotonic saline. The authors concluded that their findings do not support a specific anti-nociceptive and analgesic effect of botulinum toxin A.
- The findings from Qerama, et al. (2006) are in agreement with that of Ojala, et al. (2006) who, in a double-blind, randomized, controlled cross-over study (n = 31) found that there was no difference between the effect of small doses of botulinum toxin A and those of physiological saline in the treatment of myofascial pain syndrome as well as that of Ferrante, et al. (2005) who, in randomized, double-blind, placebo-controlled study (n = 132) reported that injection of botulinum toxin A directly into trigger points did not improve cervico-thoracic myofascial pain
- A number of studies have evaluated the effectiveness of botulinum toxin in the treatment of back and neck pain. However, there is currently insufficient scientific evidence of the effectiveness of botulinum toxin in the treatment of back pain. Two early small double blind studies (Foster, et al., 2000; Foster, et al., 2001) of botulinum toxin for back pain were published, one involving 28 patients, and another involving 31 patients. However, both of these studies were small and from a single investigator, raising questions about the generalization of the findings. In addition, both of the studies were short term, with no comparisons to other treatments for back pain
- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann et al, 2008) found that botulinum neurotoxin is possibly effective for the treatment of chronic predominantly unilateral low back pain. This was based on a single Class II study. The authors stated that the evaluation and treatment of low back pain (LBP) is complicated by its diverse potential causes. In most clinical settings, it is difficult to diagnose the precise origin of pain. This creates challenges in study design, especially in the selection of homogeneous subject populations. The

assessment also noted that there is insufficient evidence to support the effectiveness of botulinum neurotoxin in hyper-lacrimation.

- In a review of the evidence for non-surgical interventional therapies for LBP for the American Pain Society, Chou and colleagues (2009) concluded that there is insufficient (poor) evidence from randomized controlled trials (conflicting trials, sparse and lower quality data, or no randomized trials) to reliably evaluate botulinum toxin injection
- There is emerging evidence for the use of botulinum toxin in painful bruxism. In a controlled placebo pilot study with a 6-month follow-up period, Guarda-Nardini and associates (2008) examined the effectiveness botulinum toxin in treating myofascial pain in bruxers. A total of 20 patients (10 males, 10 females; age range of 25 to 45 years) with a clinical diagnosis of bruxism and myofascial pain of the masticatory muscles were randomly assigned to either a treatment group (10 subjects treated with botulinum toxin injections- botulinum toxin A) or a control group (10 subjects treated with saline placebo injections).
- A number of objective and subjective clinical parameters (pain at rest and during chewing; mastication efficiency; maximum nonassisted and assisted mouth opening, protrusive and laterotrusive movements; functional limitation during usual jaw movements, subjective efficacy of the treatment, tolerance of the treatment) were assessed at baseline time and at 1 week, 1 month, and 6 months follow-up appointments.
- Descriptive analysis showed that improvements in both objective (range of mandibular movements) and subjective (pain at rest; pain during chewing) clinical outcome variables were higher in the botulinum toxin-treated group than in the placebo-treated subjects. Patients treated with botulinum toxin A had a higher subjective improvement in their perception of treatment efficacy than the placebo subjects. Differences were not significant in some cases due to the small sample size. Results from the present study supported the efficacy of botulinum toxin A to reduce myofascial pain symptoms in bruxers, and provided pilot data which need to be confirmed by further research using larger samples.
- There is limited evidence for the use of botulinum toxin in chronic pelvic pain. In a double-blind, randomized, placebo- controlled trial (n = 60), Abbott, et al. (2006) examined if botulinum toxin A is more effective than placebo at reducing pain and pelvic floor pressure in women with chronic pelvic pain and pelvic floor muscle spasm. Subjects had chronic pelvic pain of more than 2 years duration and evidence of pelvic floor muscle spasm. Thirty women had 80 units of botulinum toxin A injected into the pelvic floor muscles, and 30 women received saline. Dysmenorrhea, dyspareunia, dyschezia, and non-menstrual pelvic pain were assessed by VAS at baseline and then monthly for 6 months. Pelvic floor pressures were measured by vaginal manometry.
- There was significant change from baseline in the botulinum toxin- A group for dyspareunia (VAS score 66 versus 12; chi2 = 25.78, $p < 0.001$) and non-menstrual pelvic pain (VAS score 51 versus 22; chi2 = 16.98, $p = 0.009$). In the placebo group only dyspareunia was significantly reduced from baseline (64 versus 27, chi2 = 2.98, $p = 0.043$). There was a significant reduction in pelvic floor pressure (centimeters of water) in the botulinum toxin- A group from baseline (49 versus 32; chi2 = 39.53, $p < 0.001$), with the placebo group also having lower pelvic floor muscle pressures (44 versus 39; chi2 = 19.85, $p = 0.003$). The authors concluded that objective reduction of pelvic floor spasm reduces some types of pelvic pain.
- Injection of botulinum toxin- A reduces pressure in the pelvic floor muscles more than placebo; it may be a useful agent in women with pelvic floor muscle spasm and chronic pelvic pain who do not respond to conservative physical therapy. There were no significant inter-group differences reported in this study between botulinum toxin A and placebo for

pain scores. These investigators noted that more research in this area is essential to further define this tool in the treatment of chronic pelvic pain.

- There is insufficient evidence for the use of botulinum toxin in motor or phonic tics. Awaard (1999) reported that the combination of baclofen/botulinum toxin type A are very effective, safe, and reliable in the treatment of tics/Tourette's syndrome. The author opined that it is worthwhile considering this treatment approach in patients with tics/Tourette's syndrome in order to reduce or avoid the side effects of other medications. Moreover, the author concluded that further studies are needed
- Marras, et al. (2001) discussed the use of botulinum toxin for simple motor tics (n = 18). The authors concluded that botulinum toxin reduced treated tic frequency and the urge associated with the treated tic. Despite these changes, patients did not report an overall benefit from the treatment.
- The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson, et al., 2008b) stated that botulinum neurotoxin is possibly effective for the treatment of motor tics (based on one Class II study). On the other hand, there is insufficient data to ascertain the effectiveness of botulinum neurotoxin in patients with phonic tics.
- Botulinum toxin is the only known treatment for painful dystonia accompanying rare corticobasilar degeneration (CBD). Dystonia, often accompanied by painful rigidity and fixed contractures, is one of the most disabling features of CBD. Vanek and Janovic (2001) found that dystonia is a common manifestation of CBD; of 66 patients with CBD, 39 (59.0%) had dystonia. The investigators noted that there is no effective treatment for this relentless disorder, except for temporary relief of dystonia and pain, with local botulinum toxin injections
- Botulinum toxin has also been studied for its use in treating brachial plexus injury. However, there is currently insufficient evidence to support it use for this indication. Heise, et al. (2005) reported their preliminary experience with the use of botulinum toxin A for the treatment of biceps-triceps muscle co-contraction. A total of 8 children were treated with 2 to 3 U/Kg of botulinum toxin injected in the triceps (4 patients) and biceps (4 patients) muscle, divided in 2 or 3 sites. All patients submitted to triceps injections showed a long-lasting improvement of active elbow flexion and none required new injections, after a follow-up of 3 to 18 months. Three of the patients submitted to biceps injections showed some improvement of elbow extension, but none developed anti-gravitational strength for elbow extension and the effect lasted only 3 to 5 months. One patient showed no response to triceps injections.
- The authors stated that their findings suggested that botulinum toxin can be useful in some children that have persistent disability secondary to obstetrical brachial plexopathy
- DeMatteo, et al. (2006) noted that following obstetrical brachial plexus injury, infants are unable to learn specific patterns of movement due to the disruption of neural pathways. Even with successful re-innervation (spontaneously or post-surgical reconstruction), function can be suboptimal due to over-activity in antagonist muscles preventing movement of re-innervated muscles. Botulinum toxin type A was used to temporarily weaken antagonistic muscles early in the re-innervation process following brachial plexus injury, with the aim of facilitating functional improvement.
- These researchers reported a case series of 8 children (5 females, 3 males; mean age of 12.5 months [SD 6.43]; range of 5 to 22 months) with significant muscle imbalances but evidence of re-innervation who were given botulinum toxin A injections into the triceps, pectoralis major, and/or latissimus dorsi muscles. After a single injection, all parents reported improvement in function. Active Movement Scale total score changed significantly

between pre botulinum toxin A and 1 month (p = 0.014), and 4 months (p = 0.022) post botulinum toxin A injection. The authors proposed that botulinum toxin A facilitated motor learning through improved voluntary relaxation of antagonist muscles while allowing increased activity in re-innervated muscles

- Price, et al. (2007) retrospectively reviewed 26 patients who underwent reconstruction of the shoulder for a medial rotation contracture after birth injury of the brachial plexus. Of these, 13 patients with a mean age of 5.8 years (2.8 to 12.9) received an injection of botulinum toxin A into the pectoralis major as a surgical adjunct. They were matched with 13 patients with a mean age of 4.0 years (1.9 to 7.2) who underwent an identical operation before the introduction of botulinum toxin therapy to these investigators' unit. Pre-operatively, there was no significant difference (p = 0.093) in the modified Gilbert shoulder scores for the 2 groups. Post-operatively, patients who received the botulinum toxin had significantly better Gilbert shoulder scores (p = 0.012) at a mean follow-up of 3 years (1.5 to 9.8).
- It appears that botulinum toxin A produces benefits which are sustained beyond the period for which the toxin is recognized to be active. The authors suggested that by temporarily weakening some of the power of medial rotation, afferent signals to the brain are reduced and cortical recruitment for the injured nerves is improved.
- Botulinum toxin has been investigated for use in restless legs syndrome; however, there is insufficient evidence to support its use for this indication. A small randomized controlled trial found no effect of botulinum toxin on restless leg syndrome; however, this study may have been underpowered to detect clinically significant benefits. In a double-blind, placebo-controlled, pilot trial (n = 6), Nahab and colleagues (2008) examined the effects of botulinum toxin A in the treatment of adults with restless legs syndrome (RLS). Patients were randomized to receive botulinum toxin A or saline, with a maximum dose of 90 mU per leg. At week 12, patients received the alternate compound with continued monitoring. These researchers used the IRLS and the Clinical Global Improvement scale (CGI) to assess efficacy (Nahab, et al., 2008).
- To monitor adverse effects (AEs), patients were asked to rate from 0 (no symptoms) to 10 (severe symptoms) the presence of weakness, pain, swelling, and redness based on the preceding 2 weeks. Ratings were completed at baseline (weeks 0 and 12), and 2 and 4 weeks post-injections. The primary outcome measure was mean change in IRLS from baseline at 4 weeks post-injection. Secondary outcomes included mean IRLS change from baseline at 2 weeks post-injection, mean CGI scores at weeks 2 and 4, and reported AEs. At week 2, placebo-treated patients noted a 5.0 + - 5.1 point improvement on the IRLS versus a 1.0 + -3.5 point improvement in the botulinum toxin arm (p = 0.06). At week 4, placebo-treated patients maintained only a 2.7 + - 5.9 point improvement from baseline, whereas botulinum toxin-treated patients showed a 5.0 + - 6.0 point improvement (p = 0.24).
- The CGI showed similar findings for the botulinum toxin arm with scores of 4.3 +- 0.8 at week 2 (p = 0.01) and 3.7 +- 1.4 at week 4 (p = 0.74), compared to placebo-arm scores of 2.8 +- 1.2 at week 2 and 3.8+- 1.7 at week 4. These researchers compared baseline scores at week 0 and week 12 to assess for any carry-over effect in the botulinum toxin-arm and found no differences (p = 0.55). Reported AEs were similar between groups, with mean placebo AE scores of 1.5 +- 2.5 at baseline, 3.2 +-5.4 at week 2, and 5 +- 7.4 at week 4, while botulinum toxin A scores were 1.8 +- 3.3 at baseline, 6.3 +-7.1 at week 2, and 4.5 +- 5.6 at week 4. Two patients reported mild weakness following both placebo and botulinum toxin A injections.
- This study showed no significant improvement in IRLS and CGI at week 4 for botulinum toxin A. A statistically significant benefit was noted on the CGI secondary endpoint for the placebo group at week 2. Adverse events were similar between the groups. The authors

stated that any future studies should be powered to account for the significant placebo response while exploring higher doses without unmasking controls.

- A small single-blind randomized controlled trial found a nonsignificant reduction in orofacial tardive dyskinesia with botulinum toxin A. Slotema and colleagues (2008) stated that orofacial tardive dyskinesia (OTD) is difficult to treat and botulinium toxin A may be an option. In a single-blind (raters were blind) study (n = 12, duration 33 weeks), OTD was treated with botulinum toxin A in 3 consecutive sessions with increasing dosages. The severity was measured with the Abnormal Involuntary Movement Scale (AIMS). Overall, there was a non-significant reduction in the severity of OTD (p = 0.15). However, in patients with no change in their anti-psychotic medication (n = 8) the reduction was significant (p = 0.035). After the study, 50% of the patients preferred to continue the treatment with botulinum toxin A. The authors concluded that botulinum toxin A was well-tolerated and showed a non-significant improvement for OTD. They stated that a larger double-blind study is warranted.
- Botulinum toxin is being investigated as a treatment for dyspareunia. Park and Paraiso (2009) stated that refractory dyspareunia presents a challenging therapeutic dilemma. These researchers presented the case of a woman with defecatory dysfunction and dyspareunia presented with stage 2 prolapse. She underwent laparoscopic and vaginal pelvic floor reconstruction with excision of endometriosis. The patient experienced increased dyspareunia and de novo vaginismus post-operatively that were refractory to trigger point injections, physical therapy, and medical and surgical management. She underwent botulinum toxin type A (BoNT A) injections into her levator ani muscles, which allowed her to have sexual intercourse again after 2 years of apareunia with no recurrence of pain for 12 months. The authors concluded that injecting botulinum toxin into the levator ani muscles shows promise for post-operative patients who develop vaginismus and do not respond to conservative therapy.
- A pilot study suggests that botulinum toxin may be useful in treating painful diabetic neuropathy. Yuan, et al. (2009) noted that diabetic neuropathy is a common complication in diabetes, with patients typically experiencing diverse sensory symptoms including dysesthesias in the feet and usually accompanied by sleep disturbance. There is still no comprehensive understanding of the underlying biologic processes responsible for diabetic neuropathic pain. Thus, the current symptomatic therapy remains unsatisfactory. Recent experimental evidence suggested that botulinum toxin A may not only inhibit the release of acetylcholine at the neuromuscular junctions, but also modulate afferent sensory fiber firing, thereby relieving neuropathic pain. These investigators performed a double-blind cross-over trial of intradermal botulinum toxin A for diabetic neuropathic pain in 18 patients.
- They found significant reduction in VAS of pain by 0.83 + - 1.11 at 1 week, 2.22 + - 2.24 at 4 weeks, 2.33 + - 2.56 at 8 weeks, and 2.53 + - 2.48 at 12 weeks after injection in the botulinum toxin group, as compared to the respective findings for a placebo group of 0.39 + - 1.18, -0.11 + - 2.04, 0.42 + - 1.62, and 0.53 + - 1.57 at the same time-points ($p < 0.05$). Within the botulinum toxin group, 44.4% of subjects experienced a reduction of VAS greater than or equal to 3 within 3 months after injection, whereas there was no similar response in the placebo group. At the 4-week post-injection stage, improvement in sleep quality was measured using the Chinese version of the Pittsburgh Sleep Quality Index. The authors concluded that the findings of this pilot study showed that botulinum toxin type A significantly reduced diabetic neuropathic pain and transiently improved sleep quality.
- They stated that further large-scaled study is warranted. In an editorial that accompanied the afore-mentioned study, Apfel (2009) stated that larger, carefully designed, multi-center, clinical trials with longer periods of observation are needed to ascertain the clinical value of

botulinum toxin for neuropathic pain. The author also noted that it will be essential in future studies to examine the effectiveness and tolerability of multiple dosing.

- There is insufficient evidence for the use of botulinum toxin for Raynaud's phenomenon. Fregene et al (2009) performed a retrospective chart review on the use of botulinum toxin type A (botulinum toxin A) for the treatment of digital ischemia in patients with Raynaud's phenomenon. All patients presented with a diagnosis of Raynaud's phenomenon with worsening pain, discoloration, or non-healing wound of the hand. Patients received botulinum toxin A injections into the peri-neurovascular tissue of the wrist or the distal palm, or along the digit. Outcomes measured included pain rating, digit color and appearance, transcutaneous oxygen saturation, and healing of chronic ulcers.
- A total of 26 patients were treated, with a total of 55 treatment encounters. Patients were observed for an average of 18 months. Statistically significant improvements were noted for pain score and digit transcutaneous oxygen saturation measurements after treatment ($p < 0.05$). These investigators found smokers and women were more likely to have improved coloration and appearance after injections. Complications included localized injection-related pain and transient intrinsic muscle weakness. The authors concluded that botulinum toxin A significantly improves pain and improves healing in Raynaud's patients with few complications. Botulinum toxin type A was found to be a safe and useful treatment option for vasospastic digital ischemia.
- Moreover, the authors stated that none of the studied demographic data was a significant predictor of improved response to botulinum toxin A. They noted that further investigation is underway to determine the risk factors that respond best to peri-vascular botulinum toxin A therapy.
- Neumeister and colleagues (2009) performed a retrospective study focused on patient outcomes on 19 patients diagnosed with Raynaud's phenomenon. Patients suffered from chronic ischemic hand pain. All patients had vascular studies to rule out occlusive disease. Fifty to 100 units of Botox were injected into the palm around each involved neurovascular bundle. Pre-injection and post-injection laser Doppler scanning was performed on most patients to measure blood flow. Sixteen of 19 patients (84 %) reported pain reduction at rest. Thirteen patients reported immediate relief; 3 reported more gradual pain reduction over 1 to 2 months. Three patients had no or minimal pain relief. Tissue perfusion results demonstrated a marked change in blood flow (-48.15 % to 425 %) to the digits.
- All patients with chronic finger ulcers healed within 60 days. Most patients (n = 12 [63 %]) remained pain-free (13 to 59 months) with a single-injection schedule. Four patients (21 %) required repeated injections because of recurrent pain. The authors concluded that vascular function is abnormal in patients with Raynaud's phenomenon. Although its mechanism is unknown, Botox yielded a distinct improvement in perfusion and reduction in pain in patients failing conservative management. They stated that continued research may lead to more specific and reliable treatment for Raynaud's patients.
- The drawbacks of this study by Neumeister and colleagues (2009) include (i) this was a non-controlled case series without a placebo group, (ii) various confounding factors may be important in the findings, including ambient room temperature, patient core temperature, time of year injected, and (iii) small sample size, broad inclusion criteria, as well as lack of a subjective or objective pain scale. The authors stated that randomized, controlled, prospective studies are needed to address these issues and to define the true benefits of Botox injections in patients with ischemic digits.
- Restivo et al (2006) stated that no specific treatment for oropharyngeal dysphagia related to diabetic neuropathy has been described to date. Chemical myotomy of the cricopharyngeus (CP) muscle by botulinum toxin A has been effective in reducing or abolishing dysphagia

associated with upper esophageal sphincter (UES) hyperactivity of different etiologies. In the present study, these researchers evaluated the effectiveness of botulinum toxin A injections into the CP muscle in diabetic patients with severe oropharyngeal dysphagia associated with diabetic autonomic and/or somatic peripheral neuropathy. A total of 12 type-2 diabetic patients with severe dysphagia for both solid and liquid foods associated with autonomic and/or peripheral somatic neuropathy were investigated. Swallowing function was evaluated by clinical examination, videofluoroscopy (VDF), and simultaneous needle EMG of the CP and pharyngeal inferior constrictor (IC) muscles.

- Clinical evaluation using a 4-level dysphagia severity score was performed every other day for the 1st week and thereafter every other week until week 24. Videofluoroscopy and EMG follow-up were carried out at week 1, 4, 12, 16, 18, and 24 after botulinum toxin A injection. botulinum toxin A was injected percutaneously into the CP muscle under EMG control. botulinum toxin A induced the complete recovery of dysphagia in 10 patients and had a significant ($p = 0.0001$, ANOVA) improvement in 2 patients within 4 +/- 1.1 days (range of 3 to 7). Clinical improvement was confirmed by VDF and EMG. The authors concluded that these findings suggested a potential benefit from botulinum toxin A treatment in dysphagia associated with diabetic neuropathy. They stated that RCTs are needed to confirm this observation.
- In a prospective pilot study, Terre et al (2008) evaluated the effectiveness of botulinum toxin A injection in the CP muscle in patients with neurological dysphagia caused by alteration in the UES opening and with preserved pharyngeal contraction. A total of 10 patients (7 brain lesions and 3 cervical spinal cord injuries), with a minimum time-lapse of 6 months from neurological lesion to botulinum toxin A injection were included in this study. Dysfunction of the UES opening and the presence of pharyngeal contraction were diagnosed by VDF and esophageal manometry (EM). The botulinum toxin A (100 U) injection was guided by endoscopy. Clinical, VDF, and EM follow-ups were carried out at 3 weeks, 3 and 6 months, and at 1 year post-injection. Prior to treatment, 6 patients were fed by nasogastric tube. Videofluoroscopy showed impairment of the UES opening, residue in pyriform sinuses, and aspiration in all cases.
- During follow-up, there was a decrease in the number of patients that had aspiration: 3 patients at 1 year. During swallowing, EM showed a mean UES relaxation of 90 % (range of 74.5 to 100 %), residual pressure 3.2 mmHg (range of 0 to 13 mmHg) and pharyngeal amplitude 52 mmHg (range of 25 to 80 mmHg). At follow-up, a significant improvement in UES relaxation (98 % [89 to 100 %]) and pharyngeal contraction (97 mmHg [35 to 165 mmHg]) was observed. At 3 months, 6 patients were eating exclusively by mouth. The authors concluded that 1 single injection of botulinum toxin A in the UES has long-lasting effectiveness in patients with neurological dysphagia caused by alteration in the UES opening and with pharyngeal contraction. They stated that nevertheless, a RCT should be done to confirm these results and rule out the effect of potential spontaneous improvement of neurological injury.
- There is emerging evidence that injection of the pylorus with botulinum toxin may be an alternative to pyloroplasty or pyloromyotomy for esophagogastrectomy. Cerfolio et al (2009) performed a retrospective study with a prospective database on patients with esophageal cancer or high-grade dysplasia who underwent Ivor-Lewis esophago-gastrectomy. All had 1 surgeon and similar stomach tubularization, hand-sewn anastomoses, nasogastric tube duration, and post-operative prokinetic agents. Outcomes of post-operative gastric emptying, aspiration, and swallowing symptoms were compared. Between January 1997 and June 2008, there were 221 patients. Seventy-one patients had a pyloromyotomy, and gastric emptying judged on post-operative day 4 was delayed in 93 % (52 % had any

morbidity and 14 % had respiratory morbidity). Fifty-four patients had no drainage procedure, and gastric emptying was delayed in 96 % (59 % had any morbidity and 22 % had respiratory morbidity).

- Twenty-eight patients underwent pyloroplasty, and 96 % had delayed gastric emptying (50 % had any morbidity and 32 % had respiratory morbidity). Sixty-eight patients had botulinum toxin injection into the pylorus. Gastric emptying was delayed in only 59 % ($p = 0.002$, 44 % had any morbidity and 13 % had respiratory morbidity). Hospital length of stay ($p = 0.015$) and operative times ($p = 0.037$) were shorter in the botulinum toxin group. Follow-up (mean of 40 months) showed symptoms of biliary reflux to be lowest in the botulinum toxin group ($p = 0.024$). The authors concluded that injection of the pylorus with botulinum toxin at the time of esophago-gastrectomy is safe and decreases operative time when compared with pyloroplasty or pyloromyotomy. In addition, it can improve early gastric emptying, decrease respiratory complications, shorten hospital stay, and reduce late bile reflux. They stated that a prospective multi-institutional RCT is needed.
- A pilot study found no significant effect of botulinum toxin on complex regional pain syndrome. Safarpour and colleagues (2010) examined the effectiveness and tolerability of botulinum toxin A in allodynia of patients with complex regional pain syndrome (CRPS). A total of 14 patients were studied: 8 were subjects of a randomized, prospective, double-blind, placebo-controlled protocol, 6 were studied prospectively in an open-label protocol. Patients were rated at baseline and at 3 weeks and 2 months after botulinum toxin A administration. Ratings included brief pain inventory, McGill pain questionnaire, clinical pain impact questionnaire, quantitative skin sensory test, sleep satisfaction scale, and patient global satisfaction scale. Botulinum toxin A was injected intradermally and subcutaneously, 5 units/site into the allodynic area (total dose 40 to 200 units).
- None of the patients with allodynia showed a significant response following treatment. The treatment was painful and poorly tolerated. The authors concluded that intrademal and subcutaneous administration of botulinum toxin A into the allodynic skin of the patients with CRPS failed to improve pain and was poorly-tolerated.
- A Cochrane systematic evidence review found that botulinum toxin may have a role in certain types of shoulder pain. In a Cochrane review, Singh and Fitzgerald (2010) compared the safety and effectiveness of botulinum toxin in comparison to placebo or other treatment options for shoulder pain. These investigators selected RCTs comparing botulinum toxin with placebo or active treatment in people with shoulder pain. For continuous measures, they calculated mean difference (MD), and for categorical measures risk ratio (RR) (with 95 % CI). A total of 6 RCTs with 164 patients were included. Five RCTs in participants with post-stroke shoulder pain indicated that compared with placebo, a single intramuscular injection of botulinum toxin A significantly reduced pain at 3 to 6 months post-injection (MD -1.2 points, 95 % CI: -2.4 to -0.07; 0 to 10 point scale) but not at 1 month (MD -1.1 points, 95 % CI: -2.9 to 0.7).
- Shoulder external rotation was increased at 1 month (MD 9.8 degrees , 95 % CI: 0.2 to 19.4) but not at 3 to 6 months. Shoulder abduction, external rotation or spasticity did not differ between groups, nor did the number of adverse events (RR 1.46, 95 % CI: 0.6 to 24.3). One RCT in arthritis-related shoulder pain indicated that botulinum toxin reduced pain severity (MD -2.0, 95 % CI: -3.7 to -0.3; 10 point scale) and shoulder disability with a reduction in Shoulder Pain and Disability Index score (MD -13.4, 95 % CI: -24.9 to -1.9; 100 point scale) when compared with placebo. Shoulder abduction was improved (MD 13.8 degrees, 95 % CI: 3.2 to 44.0). Serious adverse events did not differ between groups (RR 0.35, 95 % CI: 0.11 to 1.12). The authors concluded that these findings should be interpreted with caution due to few studies with small sample sizes and high risk of bias.

- Botulinum toxin-A injections seem to reduce pain severity and improve shoulder function and range of motion when compared with placebo in patients with shoulder pain due to spastic hemiplegia or arthritis. It is unclear if the benefit of pain relief in post-stroke shoulder pain at 3 to 6 months but not at 1 month is due to limitations of the evidence, which includes small sample sizes with imprecise estimates, or a delayed onset of action. The authors stated that more studies with safety data are needed.
- Botulinum toxin is being investigated as a treatment for depression. Beer (2010) noted that the standard of care for the treatment of depression entails pharmacotherapy with selective serotonin reuptake inhibitors. Cognitive therapy is typically utilized in addition to a pharmacological intervention. However, the benefits of the drugs used may be marginal compared with placebo yet the costs associated with their use continue to increase. One potential treatment for depression utilizes botulinum toxins. Currently, there is a small body of evidence supporting their use for depression, the potential efficacy and cost effectiveness of this treatment requires more research including head-to-head clinical trials.
- In a review on airway mucus function and dysfunction, Fahy and Dickey (2010) listed botulinum neurotoxins as one of the agents in development for reducing mucin secretion.
- RimabotulinumtoxinB (Myobloc) was approved by the Food and Drug Administration for symptomatic treatment of patients with cervical dystonia (i.e., spasmodic torticollis) to reduce the severity of abnormal head position and neck associated with cervical dystonia. RimabotulinumtoxinB is antigenically distinct and has a different mechanism of action than botulinum toxin type A. Although the U.S. Pharmacopeial Convention (2004) has stated that treatment of spasticity caused by stroke or brain injury is an accepted off-label indication for rimabotulinumtoxinB, based in part on the positive results of an uncontrolled prospective study of rimabotulinumtoxinB (Bradshear, et al., 2003), a subsequently published randomized controlled clinical trial by the same investigator group failed to demonstrate a statistically significant effect of rimabotulinumtoxinB (Bradshear, et al., 2004), perhaps due to the small size of the study.
- Both Botox and Myobloc are neurotoxins produced by fermentation of the bacterium Clostridium botulinum. They interfere with neuromuscular transmission, temporarily paralyzing the affected muscle. Clostridium botulinum is a gram-positive, spore-forming obligate anaerobe that is widely distributed in nature and frequently found in soil, marine environments, and agricultural products. Each strain produces one of eight antigenically distinct toxins designated A through H. Human disease is caused by types A, B, E, and (rarely) F. After repeated use of high doses, antibodies can develop in some individuals, making further treatment ineffective indefinitely. Because of Myobloc unique mechanism of action and antigenicity, Myobloc may be effective in patients with cervical dystonia who have developed antibodies to or who have not responded to Botox.
- There is evidence to support the use of rimabotulinumB in axillary hyperhidrosis. Baumann, et al. (2005) reported on the results of a pilot study of rimabotulinumtoxinB for axillary hyperhidrosis. Twenty patients were randomly assigned to rimabotulinumtoxinB (n = 15) or to placebo injection (n = 5). The investigators explained that this trial was initially conceived as a placebo-controlled study; however, owing to the insufficient size of the placebo group (one placebo subject failed to return for follow up and one responded to placebo injections), the placebo arm of this trial was dropped during data analysis. The investigators reported a significant difference in subject and physician assessed measures of treatment response at one month in the participants receiving Myobloc injections. Duration of action ranged from 2.2 to 8.1 months (mean 5.0 months).

- Nelson, et al. (2005) reported on the results of rimabotulinumtoxinB injections in 13 patients with axillary hyperhidrosis. The investigators reported a significant reduction in hyperhidrosis at 4-week, 8-week, and 12-week follow-up compared to baseline.
- Dressler, et al. (2002) reported on a self-controlled study comparing the efficacy of onabotulinumtoxinA and rimabotulinumtoxinB in persons with bilateral axillary hyperhidrosis. Nineteen subjects with axillary hyperhidrosis received rimabotulinumtoxinB in one axilla and onabotulinumtoxinA in the other axilla. The investigators reported that all subjects except one reported excellent improvement in hyperhidrosis in both axillae, and that none of the subjects had residual hyperhidrosis on clinical examination. The duration of effect was not statistically significantly different between onabotulinumtoxinA and rimabotulinumtoxinB.
- Baumann and Halem (2004) reported on a randomized controlled clinical study of rimabotulinumtoxinB in palmar hyperhidrosis. Twenty persons with hyperhidrosis were randomly assigned to injection with rimabotulinumtoxinB (n = 15) or placebo (n = 5). The investigators reported a significant difference in treatment response (as determined by participant assessment) between the subjects injected with rimabotulinumtoxinB and placebo. The duration of cessation of palmar sweating ranged from 2.3 months to 4.9 months, with a mean duration of 3.8 months. The investigators reported, however, that 18 of 20 participants reported dry mouth/throat, 60 % reported indigestion/heartburn, 60 % reported muscle weakness, and 50 % reported decreased grip strength. The investigators concluded that rimabotulinumtoxinB was safe and effective in treating bilateral palmar hyperhidrosis. However, the side effect profile was substantial.
- The FDA has approved incobotulinumtoxinA (Xeomin, Merz USA), a botulinum toxin type A, for the treatment of adults with cervical dystonia or blepharospasm. The FDA approval of incobotulinumtoxinA was based on the results of 2 pivotal U.S. clinical trials involving adult patients diagnosed with either cervical dystonia or blepharospasm.
- A randomized, double-blind, placebo-controlled study examined the efficacy of incobotulinumtoxinA in 233 patients with cervical dystonia. Patients were randomized (1:1:1) to receive a single administration of incobotulinumtoxinA 240 Units (n = 81), incobotulinumtoxinA 120 Units (n = 78), or placebo (n = 74). The primary efficacy endpoint was the change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score from baseline to week 4 post-injection. The difference between the incobotulinumtoxinA 240 Unit group and the placebo group in the change of the TWSTRS total score from baseline to week 4 was -9.0 points (95 % CI: -12.0 to -5.9 points).
- The difference between the incobotulinumtoxinA 120 Unit group and the placebo group in the change of the TWSTRS total score from baseline to week 4 was -7.5 points (95 % CI: -10.4 to -4.6 points). Initial inobotulinumtoxinA doses of 120 Units and 240 Units demonstrated no significant difference in effectiveness between the doses. The efficacy of incobotulinumtoxinA was similar in patients who were botulinum toxin naive and those who had received botulinum toxin prior to this study. Examination of age and gender subgroups did not identify differences in response to incobotulinumtoxinA among these subgroups.
- Incobotulinumtoxin A has been investigated in a randomized, double-blind, placebo-controlled trial in a total of 109 patients with blepharospasm. Patients were randomized (2:1) to receive a single administration of incobotulinumtoxinA (n = 75) or placebo (n = 34). The primary efficacy endpoint was the change in the Jankovic Rating Scale (JRS) Severity subscore from baseline to week 6 post-injection. The difference between the incobotulinumtoxinA group and the placebo group in the change of the JRS Severity subscore from baseline to week 6 was -1.0 (95 % CI: -1.4 to -0.5) points. Comparison of the incobotulinumA group to the placebo group was statistically significant at $p < 0.001$.

Examination of age and gender subgroups did not identify substantial differences in response to incobotulinumtoxinA among these subgroups.

- In addition, there is randomized controlled clinical study evidence of the efficacy of incobotulinumtoxinA in the treatment of post-stroke spasticity of the upper limb. Kanovsky et al (2009) reported on the results of a randomized controlled clinical trial of incobotulinumtoxinA on muscle tone, functional disability, and caregiver burden in patients with post-stroke upper limb spasticity. The investigators found that incobotulinumtoxinA led to statistically significant improvements in muscle tone and disability and was well-tolerated in patients with poststroke upper limb spasticity. A total of 148 patients with an Ashworth Scale for Spasticity score (a quantitative measure of hypertonia) of 2 or higher for wrist and finger flexors and at least moderate disability in their principal therapeutic target of the Disability Assessment Scale (a measure of functional impairment) were treated either with incobotulinumtoxinA (median, 320 U) or placebo and followed up for up to 20 weeks
- The investigators reported that a significantly higher proportion of patients treated with incobotulinumtoxinA were responders (improvement of 1 point or more in the Ashworth Scale score), as observed in comparison to placebo 4 weeks after treatment in wrist flexors (odds ratio, 3.97; 95 % CI: 1.9 to 8.3) by intention-to-treat analysis. For all treated flexor muscle groups, statistically significant odds ratios in favor of incobotulinumtoxinA were observed at week 4 ($p < 0.009$). Statistically significant results in favor of incobotulinumtoxinA were observed at all post-injection visits until week 12 in the principal therapeutic target ($p < 0.005$), in the global assessment of efficacy ($p < 0.001$), and in some tasks of the Caregiver Burden Scale ($p < 0.05$). Similar numbers of patients in each group experienced at least 1 adverse event (incobotulinumtoxinA, n = 21; placebo, n = 20). The investigators noted that none of the study subjects developed neutralizing antibodies.
- In clinical studies of incobotulinumtoxinA for cervical dystonia submitted to the FDA, the most commonly observed adverse reactions were dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain. In clinical studies of incobotulinumtoxinA for blepharospasm, the most commonly observed adverse reactions were eyelid ptosis, dry eye, dry mouth, diarrhea, headache, visual impairment, dyspnea, nasopharyngitis, and respiratory tract infection.
- The potency units of incobotulinumtoxinA are not interchangeable with other preparations of botulinum toxin products. Therefore, units of biological activity of incobotulinumtoxinA can not be compared to or converted into units of any other botulinum toxin products. IncobotulinumtoxinA is the only botulinum toxin that does not require refrigeration prior to reconstitution.
- Abobotulinumtoxin A (Dysport) is an acetylcholine release inhibitor and a non-depolarizing neuromuscular blocking agent. It has been shown in European studies to be a safe and effective treatment for cervical dystonia. In a multi-center, double-blind, randomized, controlled trial, Truong and colleagues (2005) evaluated the safety and effectiveness of Dysport in cervical dystonia patients in the United States. A total of 80 patients were randomly assigned to receive one treatment with Dysport (500 units) or placebo. Participants were followed up for 4 to 20 weeks, until they needed further treatment. They were assessed at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment. Dysport was significantly more effective than placebo at weeks 4, 8, and 12 as assessed by the Toronto Western Spasmodic Torticollis Rating Scale (10-point versus 3.8-point
- reduction in total score, respectively, at week 4; $p <$ or $= 0.013$). Of participants in the Dysport group, 38 % showed positive treatment response, compared to 16 % in the placebo group (95 % CI: 0.02 to 0.41). The median duration of response to Dysport was 18.5 weeks. Side effects were generally similar in the two treatment groups; only blurred vision and

weakness occurred significantly more often with Dysport. No participants in the Dysport group converted from negative to positive antibodies after treatment. These results confirmed previous reports that Dysport (500 units) is safe, effective, and well-tolerated in patients with cervical dystonia.

- In a prospective, randomized, double-blind, placebo-controlled, dose-ranging study, Bakheit et al (2000) ought to define a safe and effective dose of Dysport for the treatment of upper limb muscle spasticity due to stroke. Patients received either a placebo or 1 of 3 doses of Dysport (500, 1000, 1,500 units) into 5 muscles of the affected arm. Effectiveness was assessed periodically by the Modified Ashworth Scale and a battery of functional outcome measures. A total of 83 patients were recruited, and 82 completed the study. The 4 study groups were comparable at baseline with respect to their demographic characteristics and severity of spasticity. All doses of Dysport studied showed a significant reduction from baseline of muscle tone compared with placebo.
- However, the effect on functional disability was not statistically significant and was best at a dose of 1,000 units. There were no statistically significant differences between the groups in the incidence of adverse events. The authors concluded that these findings suggested that treatment with Dysport reduces muscle tone in patients with post-stroke upper limb spasticity. Treatment was effective at doses of Dysport of 500, 1000, and 1,500 units. The optimal dose for treatment of patients with residual voluntary movements in the upper limb appears to be 1,000 units.
- Hyman et al (2000) defined a safe and effective dose of Dysport for treating hip adductor spasticity in patients with multiple sclerosis. Patients with definite or probable multiple sclerosis, and disabling spasticity affecting the hip adductor muscles of both legs, were randomized to one of four treatment groups. Dysport (500, 1000, or 1,500 units), or placebo was administered by intra-muscular injection to 3 muscles. Patients were assessed at entry, and 2, 4 (primary analysis time-point), 8, and 12 weeks post-treatment. A total of 74 patients were recruited. Treatment groups were generally well- matched at entry. The primary efficacy variables -- passive hip abduction and distance between the knees -- improved for all groups.
- The improvement in distance between the knees for the 1,500-unit group was significantly greater than placebo ($p = 0.02$). Spasm frequency was reduced in all groups, but muscle tone was reduced in the Dysport groups only. Pain was reduced in all groups, but improvements in hygiene scores were evident only in the 1,000-unit and 1,500-unit groups. Duration of benefit was significantly longer than placebo for all Dysport-treated groups ($p < 0.05$). Adverse events were reported by 32/58 (55 %) Dysport-treated patients, and by 10/16 (63 %) placebo patients. Compared with the 2 lower dose groups, twice as many adverse events were reported by the 1,500-unit group (2.7/patient). The incidence of muscle weakness was higher for the 1,500-unit group (36 %) than for placebo (6 %).
- The response to treatment was considered positive by 2/3 of the patients in the 500-unit group, and by about 50 % the patients in the other groups. The authors concluded that Dysport reduced the degree of hip adductor spasticity associated with multiple sclerosis, and this benefit was evident despite the concomitant use of oral anti-spasticity medication and analgesics. Although evidence for a dose response effect was not statistically significant, there was a clear trend towards greater efficacy and duration of effect with higher doses of Dysport. Dysport treatment was well-tolerated, with no major side effects seen at doses up to 1,500 units. The optimal dose for hip adductor spasticity seems to be 500 to 1,000 units, divided between both legs.
- In a prospective, multi-center, double-blind, placebo-controlled, dose-ranging study, Pittock et al (2003) evaluated the effects of Dysport in post-stroke calf spasticity. Dysport was

administered at 500, 1,000 or 1,500 units in 234 stroke patients. They were assessed at 4-week intervals over 12 weeks. The primary outcome measure, 2-min walking distance and stepping rate increased significantly in each group ($p < 0.05$, paired test), but there was no significant difference between groups (including placebo). Following Dysport treatment, there were small but significant ($p = 0.0002$ to 0.0188) improvements in calf spasticity, limb pain, and a reduction in the use of walking aids, compared to placebo. Investigators' and patients' assessments of overall benefit suggested an advantage for Dysport over placebo, but this was not significant.

- A total of 68 patients reported 130 adverse events, with similar numbers in each group. The few severe events recorded were not considered to be treatment-related. The authors concluded that Dysport resulted in a significant reduction in muscle tone, limb pain and dependence on walking aids. The greatest benefits were in patients receiving Dysport 1,500 units, but 1,000 units also had significant effects. Dysport 500 units resulted in some improvements. Since few adverse events were reported, this therapy is considered safe and may be a useful treatment in post-stroke rehabilitation of the leg.
- In a phase IV, prospective, one-arm, non-comparative open trial, Tsai et al (2005) investigated the safety and effectiveness of Dysport in patients with idiopathic blepharospasm or hemifacial spasm. During the treatment period, patients were evaluated at baseline (week 0), week 6, and week 8, 10, or 12. A total of 32 women and 16 men completed the whole course of the study. The therapeutic efficacy of Dysport became evident from 1.5 to 15 days (mean +/- SD, 6.1 +/- 2.9 days). The maximal effect appeared 12.2 +/- 5.0 days later. Injection of Dysport resulted in amelioration of spasm symptom. Dysport significantly improved the functions (e.g., reading, watching TV, house work, working, driving and outing alone).
- Injection of Dysport resulted in amelioration of spasm symptom. Dysport significantly improved the functions (e.g., reading, watching TV, house work, working, driving and outing alone). Improvements remained at 12th week following Dysport injection. The most frequent adverse event was ptosis, which was noted in 9 cases and represented 18.7 % of total patients. Other adverse events were very mild, although lagophthalmos and dry eyes occurred in some patients, but none manifested any corneal complications. The authors concluded that Dysport injection appears to be a safe and effective procedure with only by minor, and transit adverse events
- In a large-scale, multi-center, randomized clinical trial, Truong et al (2008) examined the safety and effectiveness of Dysport (40, 80, and 120 units/eye) versus placebo in the treatment of bilateral benign essential blepharospasm (BEB). The findings of this study supported the high efficacy and good safety profile of Dysport, with improvement in functional impairment, reduction in frequency and intensity of facial spasms, and fewer withdrawals through lack of efficacy in the active treatment group compared with controls. The best balance of sustained efficacy and favorable safety profile was provided by 80 units of Dysport/eye.
- In a prospective, multi-center, randomized, double-blind, placebo-controlled study, Straube et al (2008) examined the effects of peri-cranial injection of Dysport for the treatment of tension-type headache. Patients received injections of Dysport (total dose of 420 or 210 units) or saline placebo in 18 sites on the head and neck. Of 125 patients treated, 118 were included in the intention-to-treat dataset. No significant differences between each verum group and placebo were seen for the primary efficacy parameter -- change in the number of headache-free days at 4 to 8 weeks after injection compared with 4 weeks before injection. The groups receiving 420 or 210 units of Dysport experienced 2.60 and 2.87 more

headache-free days, respectively, compared with 1.93 more headache-free days for the placebo group (p = 0.66 versus 420 units; p = 0.52 versus 210 units).

- Treatment with 420 units of Dysport was associated with significant improvements compared with placebo for two secondary efficacy parameters: mean change in headache duration from baseline to weeks 8 to 12 ($p < 0.05$) and improved global physician and patient assessment scores ($p < 0.05$). The authors concluded that further studies should address the possible value of multiple injections with extended observation periods, dose optimization, and whether duration of headache history and number of previous treatments are predictors of patient response.
- While several botulinum toxin preparations have been used in the treatment various disorders including cervical dystonia, there is much controversy regarding their respective potencies. In a Cochrane review on botulinum toxin type A therapy for cervical dystonia, Costa et al (2005) noted that indirect comparisons between trials that used Dysport against placebo and trials that used Botox against placebo showed no significant differences between Dysport and Botox in terms of benefits or adverse events. On the other hand, Chapman et al (2007) reported differences in adverse event rates between botulinum neurotoxin preparations (Botox, Dysport, and Myobloc), suggesting that use of these products should be based on their individual dosing, efficacy, and safety profiles. Moreover, Karsai and Raulin (2009) performed a systematic review of published evidence about the unit equivalence of United Kingdom and United States botulinum neurotoxin A formulations.
- The review was based on a detailed literature research in all relevant databases (MEDLINE, PubMed, Cochrane Library, specialist textbooks). The present review supports the recent assumption that dose ratios of less than 3:1 (e.g., 2.5:1 or even 2:1) between Dysport and Botox are probably more suitable. The authors stated that the current evidence is still insufficient, and further investigation of lower dose ratios is recommended. On April 29, 2009, the FDA approved Dysport (abobotulinumtoxin A) for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naive and previously treated patients, and the temporary improvement in the appearance of moderate-to-severe glabellar lines associated with procerus and corrugator muscle activity in adult patients less than 65 years of age.
- Testing for Neutralizing Antibodies to Botulinum Toxin:Patients who respond to botulinum toxin injections initially but lose the response on subsequent injections may have developed neutralizing antibodies. According to the prescribing information for Botox, the potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections. In uncontrolled studies, there are individuals who continue to respond to treatment despite the presence of neutralizing antibodies. Not all patients who became non-responsive to botulinum toxin after an initial period of clinical responsiveness had neutralizing antibodies.
- According to Hauser and Wahba (2205), an estimated 5 to 15 % of patients injected serially with 79-11 Botox developed secondary non-responsiveness from the production of neutralizing antibodies. Risk factors associated with the development of neutralizing antibodies include injection of more than 200 units per session and repeat or booster injections given within 1 month of treatment. The new BCB 2024 Botox may have a lower potential for neutralizing antibody production because of its decreased protein load, but this is not known. Some patients injected for cosmetic purposes develop neutralizing antibodies. When a patient loses his or her response, serum can be tested for neutralizing antibodies, although this rarely is performed outside research settings. Alternatively, a patient's physiological response can be evaluated with a single injection of 15 units into the frontalis on one side.

- Limited information is available as to whether neutralizing antibodies resolve over time and, consequently, whether attempts at re-injection should be made after a prolonged period. An investigation is underway to determine whether injections of rimabotulinumtoxinB are useful in patients with neutralizing antibodies to botulinum toxin A. Using the lowest dose of toxin necessary to achieve the desired clinical effect and avoiding re-injection within 1 month appear prudent in an effort to keep antibody formation as low and unlikely as possible.
- Dressler and Hallett (2006) stated that in some patients treated with botulinum toxin, antibodies are produced in association with certain treatment parameters, patient characteristics and immunological properties of the botulinum toxin preparation used. Therapeutic botulinum toxin preparations are comprised of botulinum neurotoxin, non-toxic proteins and excipients. Antibodies formed against botulinum neurotoxin can block botulinum toxin's biological activity. The antigenicity of a botulinum toxin preparation depends on the amount of botulinum neurotoxin presented to the immune system. This amount is determined by the specific biological activity, the relationship between the biological activity and the amount of botulinum neurotoxin contained in the preparation. For Botox the specific biological activity is 60 MU-EV/ng neurotoxin, for Dysport 100 MU-EV/ng neurotoxin and for Myobloc/NeuroBloc 5 MU-EV/ng neurotoxin.
- For Myobloc/NeuroBloc this translates into an antibody-induced therapy failure rate of 44 % in patients treated for cervical dystonia, whereas for botulinum toxin type A preparations this figure is approximately 5 %. No obvious differences in antigenicity of botulinum toxin type A preparations have been detected thus far. For the current formulation of Botox, the rate of antibody-induced therapy failure is reportedly less than 1 %. The authors concluded that to determine the antigenicity of different botulinum toxin preparations in more detail, prospective studies on large series of unbiased patients with sensitive and specific botulinum toxin antibody tests are needed.
- Frey's syndrome is a frequent sequela of parotidectomy, resulting in facial sweating and flushing because of gustatory stimuli. Laing et al (2008) noted that the use of botulinum toxin to treat disorders of the salivary glands is increasing in popularity in recent years. Recent reports of the use of botulinum toxin in glandular hyper-secretion suggest overall favorable results with minimal side-effects. However, few RCTs mean that data are limited with respect to candidate suitability, treatment dosages, frequency and duration of treatment. These researchers reported a selection of such cases from their own department managed with botulinum toxin and review the current data on use of the toxin to treat salivary gland disorders such as Frey's syndrome, excessive salivation (sialorrhea), focal and general hyperhidrosis, excessive lacrimation and chronic rhinitis.
- The AAN's report on botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann et al, 2008) stated that botulinum neurotoxin (BoNT) may be considered for gustatory sweating.
- Cantarella et al (2010) noted that although botulinum toxin type A has become 1st-line therapy for Frey's syndrome, some patients become resistant. In a case-series study, these researchers examined if another serotype, botulinum toxin type B, might be an effective alternative. A total of 7 patients aged 30 to 68 years, with severe Frey's syndrome, underwent the Minor test and had 80 U of botulinum toxin type B per cm(2) (mean total dose, 2,354 U) injected intra-cutaneously in the mapped area of gustatory sweating. All patients were followed-up for 12 months. One month after treatment, 6 of the 7 patients reported that gustatory sweating and flushing had resolved, and, in the remaining patient, these symptoms had decreased. The Minor test confirmed a significant improvement.
- The subjective benefits remained stable for 6 months in 4 patients and for 9 months in the remaining 3 patients; 12 months after treatment, all patients still reported some

improvement. The authors concluded that botulinum toxin type B afforded symptomatic relief in a small sample of patients with Frey's syndrome and might be considered a potential alternative to botulinum toxin type A. Moreover, they stated that no study had yet determined the ideal dose of botulinum toxin type B for Frey's syndrome. They stated that a larger series of patients is needed to confirm these preliminary results.

- On August 24, 2011, the FDA approved botulinum toxin type A (Botox) for treating bladder over-activity (neurogenic bladder) resulting from MS or spinal cord injury. The drug must be injected into the bladder using cystoscopy, which may require general anesthesia. It relaxes the bladder muscle, increasing its storage capacity and reducing incontinence. According to the FDA, treatment benefits last about 9 months. The approval was based on 2 placebo-controlled clinical studies involving a total of 691 patients. Both studies showed statistically significant decreases in the weekly frequency of incontinence episodes in the Botox group compared with placebo. Urinary tract infections and urinary retention were the most common adverse effects in this population. The latter condition may require self-catheterization to empty the bladder.
- In a 6-month follow-up study, Giannantoni et al (2011) examined the effect of intra-detrusor injection of 100 U botulinum toxin type A in patients with Parkinson's disease (PD) and refractory detrusor overactivity. A total of 8 patients (1 man and 7 women) with PD and detrusor overactivity refractory to anti-cholinergics were injected with 100 U botulinum toxin type A. Daytime and nighttime urinary frequency, and urinary incontinence episodes were recorded. Patients also completed a standardized quality of life questionnaire on incontinence and a VAS on the impact of bladder problems on daily life activities, and underwent urodynamic assessment, including pressure flow studies. Clinical and urodynamic assessment was performed before, and 1, 3 and 6 months after injection.
- In all patients 100 U botulinum toxin type A induced decreased daytime and nighttime urinary frequency, a decreased number of urinary incontinence episodes, increased quality of life scores and, as shown by increased maximum cystometric capacity, improved urodynamic findings. In 2 patients with PD post-void residual urine volume developed. The authors concluded that intra-detrusor injection of 100 U botulinum toxin type A induced clinical and urodynamic improvement in overactive bladder symptoms that lasted at least 6 months in patients with PD. Moreover, the authors stated that further studies are needed before botulinum toxin type A can be proposed as treatment for men with PD.
- Ihde and Konstantinovic (2007) performed a systematic search of the literature to identify RCTs evaluating patients treated with botulinum toxin as an adjunct to dental implant therapy, maxillofacial conditions including temporo-mandibular disorders (TMD), and cervical dystonia. Four RCTs met the authors' search criteria in the area of cervical dystonia and chronic facial pain. No RCTs were identified evaluating dental implant therapy. Patients with cervical dystonia exhibited significant improvements in baseline functional, pain, and global assessments compared to placebo. Adverse events were mild and transient with numbers needed to harm (NNH) ranging from 12 to 17. Patients with chronic facial pain improved significantly from baseline in terms of pain compared to placebo. Rates of adverse events were less than 1 %.
- The authors concluded that botulinum toxin appears relatively safe and effective in treating cervical dystonia and chronic facial pain associated with masticatory hyperactivity. No literature exists evaluating its use in dental implantology; RCTs are needed to determine its safety and efficacy in dental implantology and other maxillofacial conditions such as bruxism (i.e., teeth clenching or teeth grinding).
- In a pilot study, Guarda-Nardini et al (2008) assessed the efficacy of type A botulinum toxin (Botox) to treat myofascial pain symptoms and to reduce muscle hyperactivity in bruxers. A

total of 20 patients (10 males, 10 females; age range of 25 to 45 years) with a clinical diagnosis of bruxism and myofascial pain of the masticatory muscles were enrolled in a double-blind RCT with a treatment group (10 subjects treated with Botox) and a control group (10 subjects treated with saline placebo injections). A number of objective and subjective clinical parameters (pain at rest and during chewing; mastication efficiency; maximum non-assisted and assisted mouth opening, protrusive and laterotrusive movements; functional limitation during usual jaw movements; subjective efficacy of the treatment; tolerance of the treatment) were assessed at baseline time and at 1 week, 1 month, and 6 months follow-up appointments.

- Descriptive analysis showed that improvements in both objective (range of mandibular movements) and subjective (pain at rest; pain during chewing) clinical outcome variables were higher in the Botox-treated group than in the placebo-treated subjects. Patients treated with BTX-A had a higher subjective improvement in their perception of treatment efficacy than the placebo subjects. Differences were not significant in some cases due to the small sample size. The authors concluded that results from the present study supported the efficacy of BTX-A to reduce myofascial pain symptoms in bruxers, and provided pilot data which need to be confirmed by further research using larger samples.
- Lang et al (2009) reviewed studies involving the treatment of bruxism in individuals with developmental disabilities. Systematic searches of electronic databases, journals, and reference lists identified 11 studies meeting the inclusion criteria. These studies were evaluated in terms of: (a) participants, (b) procedures used to assess bruxism, (c) intervention procedures, (d) results of the intervention, and (e) certainty of evidence. Across the 11 studies, intervention was provided to a total of 19 participants aged 4 to 43 years. Assessment procedures included dental screening under sedation and interviews with caregivers. Intervention approaches included prosthodontics, dental surgery, injection of botulinum toxin-a, behavior modification, music therapy, and contingent massage. Positive outcomes were reported in 82 % of the reviewed studies.
- Overall, the evidence base is extremely limited and no definitive statements regarding treatment efficacy can be made. However, behavior modification and dental or medical treatment options (e.g., prosthodontics) seem to be promising treatment approaches. At present, a 2-step assessment process, consisting of dental screening followed by behavioral assessment, can be recommended. In a pilot study, Terre et al (2008) evaluated the efficacy of botulinum toxin injection in the cricopharyngeus muscle in patients with neurological dysphagia caused by alteration in the upper esophageal sphincter (UES) opening and with preserved pharyngeal contraction. A study was undertaken in 10 patients (7 brain lesions and 3 cervical spinal cord injuries), with a minimum time-lapse of 6 months from neurological lesion to botulinum toxin injection. Dysfunction of the UES
- opening and the presence of pharyngeal contraction were diagnosed by videofluoroscopy (VDF) and esophageal manometry (EM). Botulinum toxin (100 U) injection was guided by endoscopy. Clinical, VDF, and EM follow-ups were carried out at 3 weeks, 3 and 6 months, and at 1 year post-injection. Prior to treatment, 6 patients were fed by nasogastric tube. Videofluoroscopy showed impairment of the UES opening, residue in piriform sinuses, and aspiration in all cases. During follow-up, there was a decrease in the number of patients that had aspiration: 3 patients at 1 year. During swallowing, EM showed a mean UES relaxation of 90 % (range of 74.5 to 100 %), residual pressure 3.2 mmHg (range of 0 to 13 mmHg) and pharyngeal amplitude 52 mmHg (range of 25 to 80 mmHg). At follow-up, a significant improvement in UES relaxation (98 % (89 to 100 %)) and pharyngeal contraction (97 mmHg (35 to 165 mmHg)) was observed.

- At 3 months, 6 patients were eating exclusively by mouth. The authors concluded that 1 single injection of botulinum toxin in the UES has long-lasting effectiveness in patients with neurological dysphagia caused by alteration in the UES opening and with pharyngeal contraction. Nevertheless, a RCT should be done to confirm these results and rule out the effect of potential spontaneous improvement of neurological injury. Bashashati et al (2010) stated that diffuse esophageal spasm is a primary esophageal motility disorder. The prevalence is 3 to 10 % in patients with dysphagia and treatment options are limited. The author summarized the treatment of diffuse esophageal spasm, including pharmacotherapy, endoscopic treatment, and surgical treatment with a special focus on botulinum toxin injection. A PubMed search was performed to identify the literature using the search items diffuse esophageal spasm and treatment.
- Pharmacotherapy with smooth muscle relaxants, proton pump inhibitors, and antidepressants was suggested from small case series and uncontrolled clinical trials. Endoscopic injection of botulinum toxin is a well-studied treatment option and results in good symptomatic benefit in patients with diffuse esophageal spasm. Surgical treatment was reported in patients with very severe symptoms refractory to pharmacologic treatment. This article summarized the present knowledge on the treatment of diffuse esophageal spasm with a special emphasis on botulinum toxin injection. Endoscopic injection of botulinum toxin is presently the best studied treatment option but many questions remain unanswered.
- Pelvic floor tension myalgia is a diagnosis of exclusion. It is also known as coccygodynia, diaphragma pelvis spastica, levator ani syndrome, levator spasm syndrome, spastic and pelvic floor syndrome. There is insufficient evidence to support the use of botulinum toxin for pelvic floor tension myalgia. A small RCT (n = 12) concluded that botulinum toxin is safe but ineffective (Rao et al, 2009). A European Consensus Report (Apostolidis et al, 2009) found that evidence for use of botulinum toxin in pelvic floor disorders is inconclusive.
- In a Cochrane review, Waseem et al (2011) examined the effects of botulinum toxin injections in adults with LBP. These investigators searched CENTRAL (The Cochrane Library 2009, issue 3) and MEDLINE, EMBASE, and CINAHL to August 2009; screened references from included studies; consulted with content experts and Allergan. They included published and unpublished randomized controlled trials without language restrictions. They included randomized trials that evaluated botulinum neurotoxin (BoNT) serotypes versus other treatments in patients with non-specific LBP of any duration. Two review authors selected the studies, assessed the risk of bias using the Cochrane Back Review Group criteria, and extracted the data using standardized forms. They performed a qualitative analysis due to lack of data.
- These researchers excluded evidence from 19 studies due to non-randomization, incomplete or unpublished data. They included 3 randomized trials (n = 123 patients). Only 1 study included patients with chronic non-specific LBP; the other 2 examined unique subpopulations. Only 1 of the 3 trials had a low risk of bias and demonstrated that BoNT injections reduced pain at 3 and 8 weeks and improved function at 8 weeks better than saline injections. The 2nd trial showed that BoNT injections were better than injections of corticosteroid plus lidocaine or placebo in patients with sciatica attributed to piriformis syndrome. The 3rd trial concluded that BoNT injections were better than traditional acupuncture in patients with third lumbar transverse process syndrome. Both studies with high risk of bias had several key limitations. Heterogeneity of the studies prevented meta-analysis.
- There is low quality evidence that BoNT injections improved pain, function, or both better than saline injections and very low quality evidence that they were better than acupuncture

or steroid injections. The authors concluded that they identified 3 studies that investigated the merits of BoNT for LBP, but only 1 had a low risk of bias and evaluated patients with non-specific LBP (n = 31). They stated that further research is very likely to have an important impact on the estimate of effect and the confidence in it. Future trials should standardize patient populations, treatment protocols and comparison groups, enlist more participants and include long-term outcomes, cost-benefit analysis and clinical relevance of findings.

- Nuzzo et al (1997) used botulinum toxin to treat paralytic scoliosis. A total of 12 children with paralytic scoliosis and severe, complicating additional diseases required surgical delay were included in this study. Although this use of botulinum toxin is experimental, alternative treatments posed greater risks. An institutional review board protocol for non-established dosage and indication for treatment was initiated to monitor safety and effect. Treatment was intended to supplement, not replace, other desirable treatment modalities. The effect was to be measured by the return of efficacy of conservative treatment in halting curve progression. Short-term results showed that none of the children had worsened scoliosis; all had some reduction in curve measurement (up to greater than 50 degrees).
- Also, an UpToDate review on "Treatment and prognosis of adolescent idiopathic scoliosis" (Scherl, 2011) does not mention the use of botulinum toxin as a therapeutic option.
- Cordivari et al (2001) reported the findings of 14 patients with "dystonic clenched fist" (3 with cortico-basal ganglionic degeneration, 7 with Parkinson's disease, and 4 with dystonic-complex regional pain syndrome) who were treated with botulinum toxin A (BTXA, Dysport). The muscles involved were identified by the hand posture and EMG activity recorded at rest and during active and passive flexion/extension movements of the finger and wrist. EMG was useful in distinguishing between muscle contraction and underlying contractures and to determine the dosage of BTX. All patients had some degree of flexion at the proximal metacarpophalangeal joints and required injections into the lumbricals.
- The response in patients depended on the severity of the deformity and the degree of contracture. All patients had significant benefit to pain, with accompanying muscle relaxation, and palmar infection, when present, was eradicated. Four patients with Parkinson's disease and 1 patient with dystonia-complex regional pain syndrome obtained functional benefit. Thus, 36 % (5 out of 14) of patients had positive outcomes; not out of the realm of placebo effects.
- In a pilot study, Castiglione et al (2011) evaluated the effectiveness of intra-articular injection of BTX-A in relieving hemiplegic shoulder pain (HSP). Patients (n = 5) with HSP refractory to standard treatments and pain score at rest greater than 7 on a pain VAS of 0 to 10 cm were included in this study. Main outcome measure was variation in VAS score at rest and during 90 degree passive arm abduction 2 and 8 weeks after BTX-A intra-articular injection. Baseline VAS score was 8.7 +/- 1 at rest and 9.8 +/- 0.4 during passive arm abduction. It clearly decreased at 2 (1.5 +/- 1.1 at rest, $p = 0.001$; 3 +/- 1.2 during arm abduction, $p < 0.001$) and 8 weeks (1.5 +/- 1.2 at rest, $p = 0.001$; 2.3 +/- 1.1 during arm abduction, $p < 0.001$) after BTX-A intra-articular injection.
- The authors found a strong correlation between intra-articular BTX-A injection and pain relief in patients with HSP. The findings of this result could provide the rationale for RCTs designed to better evaluate the safety and effectiveness of intra-articular BTX-A injection in patients with refractory HSP.
- In a double-blind, randomized, parallel group study, Finlayson et al (2011) examined the effect of BTX-A injections to the scalene muscles on pain in subjects with thoracic outlet syndrome (TOS). Patients were followed-up at 6 weeks, 3 months, and 6 months. A total of 38 patients referred to physiatrists for management of TOS with BTX-A injection were

included. One subject was lost to follow-up and all other subjects completed the trial. A 75-unit dose of BTX-A reconstituted with 0.75 cc of normal saline was injected to the anterior scalene (37.5 units) and middle scalene (37.5 units) muscles using EMG guidance. The primary outcome measure was pain as measured on a horizontal VAS 6 weeks post-injection.

- Secondary outcomes were paresthesias measured on a VAS and function measured with the Disabilities of the Arm, Shoulder and Hand (DASH) and Short-form 36 (SF-36) questionnaires. For the primary outcome measure of VAS scores for pain at 6 weeks, the difference in the means adjusted for baseline VAS scores between placebo and BTX-A was 5.03 mm in favor of BTX-A (95 % CI: -15.7 to 5.7, p = 0.36). Changes in secondary outcome measures were also not statistically significant. The authors concluded that BTX-A injections to the scalene muscles did not result in clinically or statistically significant improvements in pain, paresthesias, or function in this population of subjects with TOS.
- Gerwin (2012) reviewed the literature relevant to the treatment of myofascial pain syndrome (MPS) by botulinum injections. The objective was to critically review the studies to see if they are appropriately designed, conducted, and interpreted to provide guidance in the management of MPS. The intent was to better understand the mixed results that these studies have provided. A search was made utilizing PubMed for literature relevant to the use of botulinum toxin in the treatment of MPS. All identifiable series were reviewed, including open label, single-blinded and double-blinded studies, randomized and controlled, or not. In general, small case series of only a few patients were not included unless they made a relevant point and there were no available randomized studies or larger studies. Single case reports were not included.
- The studies were evaluated according to their design and the selection of outcome measurements, and the interpretation of results. The studies were individually critiqued, and an overall assessment and commentary was made of the studies in the field as a whole. Problems that were common to the studies were robust placebo responders, incomplete treatment of a regional MPS, inappropriate or confounding control populations or treatments, and inappropriate time periods for assessment of outcomes, or mis-interpretation of the time-frame of action of botulinum toxin. The studies of the effect of botulinum toxin treatment of myofascial trigger points have had mixed results. However, few studies have been designed to avoid many of the pitfalls associated with a trial of botulinum toxin treatment of trigger points.
- Better-designed studies may give results that can be used to guide practice based on reliable evidence. The author concluded that the available evidence is insufficient to guide clinical practice.
- In a Cochrane review, Soares et al (2012) evaluated the effectiveness and safety of botulinum toxin in treating MPS, excluding MPS in neck and head muscles. The search strategy was composed of terms for myofascial pain and botulinum toxin. These investigators searched the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group's Specialized Register until December 2011, CENTRAL (Cochrane Database of Systematic Reviews 2011, Issue 4), PUBMED (from 1966 to 2011), EMBASE (from 1980 to 2011) and LILACS (from 1982 to 2011). There was no language restriction. These researchers included RCTs involving botulinum toxin for treating participants with MPS. They excluded studies with MPS of the neck and head from this review, as they have already been assessed in existing systematic reviews.
- They considered a diagnosis of MPS to be based on the identification of trigger points in the taut band through palpation of sensitive nodules, local twitch response and specific patterns of referred pain associated with each trigger point. Two review authors independently

screened identified studies, extracted data, assessed trial quality and analyzed results using the Cochrane PaPaS Review Group criteria. A total of 4 studies (n= 233) comparing botulinum toxin A (BTXA) with placebo, met the inclusion criteria. In one study with 145 participants, a significant improvement rate of pain intensity scores, as shown by the mean difference (MD) of -0.23 (95 % CI: -0.26 to -0.20; p value < 0.00001) and duration of daily pain (MD -1.11; 95 % CI -1.37 to -0.85; p value < 0.00001), was demonstrated when comparing BTXA with placebo. The 3 other studies showed that there was no statistically significant difference between BTXA and placebo in pain intensity.

- The authors concluded that there is inconclusive evidence to support the use of botulinum toxin in the treatment of MPS based on data from four studies with a total of 233 participants, which the authors considered adequate to be included in this review. Meta-analyses were not possible due to the heterogeneity between studies. They suggested that in future studies the same methodology to assess pain, a standardized dose of treatment, follow-up of at least 4 months (to observe the maximum/minimum curve of the drug effect) and appropriate data presentation should be used. They stated that more high-quality RCTs of botulinum toxin for treating MPS need to be conducted before firm conclusions on its effectiveness and safety can be drawn.
- In a Cochrane review, Rowe and Noonan (2012) evaluated the effectiveness of botulinum toxin in the treatment of strabismus compared with alternative treatment options, and investigated dose effect and complication rates. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2011, Issue 11), MEDLINE (January 1950 to December 2011), EMBASE (January 1980 to December 2011), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to December 2011), the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/), ClinicalTrials.gov (http://www.clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on December 5, 2011.
- These researchers manually searched the Australian Orthoptic Journal and British and Irish Orthoptic Journal and ESA, ISA and IOA conference proceedings. They attempted to contact researchers who are active in this field for information about further published or unpublished studies. They included RCTS of any use of botulinum toxin treatment for strabismus. Each review author independently assessed study abstracts identified from the electronic and manual searches. Author analysis was then compared and full papers for appropriate studies were obtained. These investigators found 4 RCTs that were eligible for inclusion; 2 trials found that there was no difference between the use of botulinum toxin and surgery for patients requiring re-treatment for acquired esotropia or infantile esotropia. There was no evidence for a prophylactic effect of botulinum toxin in a treatment trial of acute onset 6th nerve palsy.
- Botulinum toxin had a poorer response than surgery in a trial of patients requiring treatment for horizontal strabismus in the absence of binocular vision. Reported complications included ptosis and vertical deviation and ranged from 24 % in a trial using Dysport to 52.17 % and 55.54 % in trials using Botox. The authors concluded that the majority of published literature on the use of botulinum toxin in the treatment of strabismus consists of retrospective studies, cohort studies or case reviews. Although these provide useful descriptive information, clarification is needed to ascertain the effective use of botulinum toxin as an independent treatment modality.
- Four RCTs on the therapeutic use of botulinum toxin in strabismus have shown varying responses ranging from a lack of evidence for prophylactic effect of botulinum toxin in acute

6th nerve palsy, to poor response in patients with horizontal strabismus without binocular vision, to no difference in response in patients that required re-treatment for acquired esotropia or infantile esotropia. It was not possible to establish dose effect information. Complication rates for use of Botox or Dysport ranged from 24 % to 55.54 %.

- Lee et al (2010) evaluated the effect of botulinum toxin type A on nocturnal bruxism. A total of 12 subjects reporting nocturnal bruxism were recruited for a double-blind, RCT; 6 bruxers were injected with botulinum toxin in both masseters, and 6 with saline. Nocturnal electromyographic activity was recorded in the subject's natural sleeping environment from masseter and temporalis muscles before injection, and 4, 8, and 12 weeks after injection and then used to calculate bruxism events. Bruxism symptoms were investigated using questionnaires. Bruxism events in the masseter muscle decreased significantly in the botulinum toxin injection group ($p = 0.027$). In the temporalis muscle, bruxism events did not differ between groups or among times. Subjective bruxism symptoms decreased in both groups after injection ($p < 0.001$).
- The authors concluded that these findings suggested that botulinum toxin injection reduced the number of bruxism events, most likely mediated its effect through a decrease in muscle activity rather than the central nervous system. The authors controlled for placebo effects by randomizing the interventions between groups, obtaining subjective and objective outcome measures, using the temporalis muscle as a control, and collecting data at 3 post-injection times. They stated that the findings of this controlled study supported the use of botulinum toxin injection as an effective treatment for nocturnal bruxism.
- Redaelli (2011) assessed the benefits, outcome, and side effects of using botulinum toxin A (BTxA) in the treatment of bruxism. From Jan. 2009 to Jan. 2010, a total of 120 bruxers were treated; no special examinations were carried out, since the exact diagnoses were made beforehand. All were treated with BTxA in the masseter muscle with standardized doses and injection sites. A follow-up examination was made 15 days post-procedure, and all patients responded to a short satisfaction questionnaire; 23 patients were re-injected with additional doses of BTxA for insufficient results. Subjective results and side effects were assessed. All patients have declared a good/very good improvement in symptoms. No significant side effects were seen. At the study's conclusion, 36 patients (30 %) declared a fair result, 79 (65.8 %) good, and 5 (4.2 %) excellent. The authors concluded that botulinum toxin A is a simple method of treatment of bruxism, without side effects and appreciated by patients.
- Alonso-Navarro et al (2011) reported their long-term experience in the treatment of bruxism with botulinum toxin type A. The outcome of 19 patients with severe bruxism who underwent periodical treatment with botulinum toxin A infiltrations in both temporal and masseter muscles, using initial doses of 25 IU per muscle, during a follow-up period ranging from 0.5 to 11 years, was described. Doses were adjusted in follow-up visits according the response degree. None of the patients reported side-effects. Final doses of botulinum toxin ranged from 25 to 40 IU per muscle (mean of 29.7 +/- 4.9), and duration of the effect from 13 to 26 weeks (mean of 16.7 +/- 5.1). The authors concluded that botulinum toxin A infiltrations are a safe and useful treatment for patients with severe bruxism.
- Arzul et al (2012) stated that hypertrophy of the masticatory muscles most commonly affects the masseter. Less common cases of isolated or associated temporalis hypertrophy have also been reported. Para-functional habits, and more precisely bruxism, can favor the onset of the hypertrophy. This condition is generally idiopathic and can require both medical and/or surgical management. These investigators presented the case of a 29-year old patient who was referred to their department for an asymmetric swelling of the masticatory muscles. Physical examination revealed a bilateral hypertrophy of the masticatory muscles,

predominantly affecting the right temporalis and the left masseter. Major bruxism was assessed by premature dental wearing. The additional examinations confirmed the isolated muscle hypertrophy. Benign asymmetric hypertrophy of the masticatory muscles promoted by bruxism was diagnosed.

- Treatment with injections of type A botulinum toxin was conducted in association with a splint and relaxation. Its effectiveness has been observed at 6 months. The authors noted that few cases of unilateral or bilateral temporalis hypertrophy have been reported, added to the more common isolated masseter muscles hypertrophy. The condition is thought to be favored by para-functional habits such as bruxism. The conservative treatment consists in reducing the volume of the masticatory muscles using intra-muscular injections of type A botulinum toxin. Other potential conservative treatments are wearing splints and muscle relaxant drugs. Surgical procedures aiming to reduce the muscle volume and/or the bone volume (mandibular gonioplasty) can be proposed.
- In an evidence-based review, Long et al (2012) evaluated the effectiveness of botulinum toxins on bruxism. Electronic databases (PubMed, Embase and Science Citation Index), websites (Cochrane Central Register of Controlled Trials and ClinicalTrials.gov) and the literature database of SIGLE (System for Information on Grey Literature in Europe) were searched from January 1990 to April 2011 for RCTs or non-randomized studies assessing the effectiveness of botulinum toxins on bruxism. There was no language restriction. Through a pre-defined search strategy, these investigators retrieved 28 studies from PubMed, 94 from Embase, 60 from the Science Citation Index, 2 ongoing clinical trials and 2 from the Cochrane Central Register of Controlled Trials. Of these, only 4 studies met inclusion criteria and were finally included.
- Of the 4 included studies, 2 were RCTs and 2 were controlled before-and-after studies. These studies showed that botulinum toxin injections can reduce the frequency of bruxism events, decrease bruxism-induced pain levels and satisfy patients' self-assessment with regard to the effectiveness of botulinum toxins on bruxism. In comparison with oral splint, botulinum toxins are equally effective on bruxism. Furthermore, botulinum toxin injections at a dosage of less than 100 U are safe for otherwise healthy patients. The authors concluded that botulinum toxin injections are effective on bruxism and are safe to use. Therefore, they can be used clinically for otherwise healthy patients with bruxism.
- Persaud et al (2013) noted that botulinum toxin (Botox) works by blocking the release of acetylcholine from the cholinergic nerve end plates leading to inactivity of the muscles or glands innervated. Botox is best known for its beneficial role in facial aesthetics but recent literature has highlighted its usage in multiple non-cosmetic medical and surgical conditions. These investigators reviewed the current evidence pertaining to Botox use in the head and neck. A literature review was conducted using the Cochrane Controlled Trials Register, Medline and Embase databases limited to English Language articles published from 1980 to 2012. The findings suggested that there is level-1 evidence supporting the efficacy of Botox in the treatment of spasmodic dysphonia, essential voice tremor, headache, cervical dystonia, masticatory myalgia, sialorrhea, temporo-mandibular joint disorders, bruxism, blepharospasm, hemi-facial spasm and rhinitis.
- For chronic neck pain there is level-1 evidence to show that Botox is ineffective. Level-2 evidence exists for vocal tics, trigeminal neuralgia, dysphagia and post-laryngectomy esophageal speech. For stuttering, "first bite syndrome", facial nerve paresis, Frey's syndrome, oromandibular dystonia and palatal/stapedial myoclonus the evidence is level-4. Thus, the literature high-lighted a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level-1 evidence). With ongoing

research, the spectrum of clinical applications and number of people receiving Botox will no doubt increase. Botox appears to justify its title as "the poison that heals".

- Garcia-Ruiz (2013) stated that "At present, botulinum toxin (BT) is one of the most fundamental available drugs in Neurology, only comparable with levodopa. Botulinum toxin is currently used in those entities characterized by excessive muscle contraction, including dystonia and spasticity. In addition, BT has been used to control pain associated with increased muscle contraction in dystonia and spasticity, but also is useful to control chronic pain not associated with muscle contraction, such as chronic daily headache. Finally, BT is useful in sialorrhea and bruxism. The mechanism of action is complex, mainly acting on terminal neuromuscular junction, but also exhibiting analgesic properties, probably through inhibition of pain neurotransmitters release".
- In a Cochrane review, Fedorowicz et al (2013) evaluated the safety and effectiveness of botulinum toxin type A compared to placebo or no treatment, for the management of benign bilateral masseter hypertrophy. These investigators searched the following databases from inception to April 2013: the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (via PubMed); EMBASE (via embase.com); Web of Science; CINAHL; Academic Search Premier (via EBSCOhost); ScienceDirect; LILACS (via BIREME); PubMed Central and Google Scholar. Thee investigators searched 2 bibliographic databases of regional journals (IndMED and Iranmedex), which were expected to contain relevant trials. They also searched reference lists of relevant articles and contacted investigators to identify additional published and unpublished studies.
- Randomized controlled trials and controlled clinical trials (CCTs) comparing intra-masseteric injections of botulinum toxin versus placebo administered for cosmetic facial sculpting in individuals of any age with bilateral benign masseter hypertrophy, which had been self-evaluated and confirmed by clinical and radiological examination were considered for inclusion. They excluded participants with unilateral or compensatory contralateral masseter hypertrophy resulting from head and neck radiotherapy. Two review authors independently screened the search results. For future updates, 2 authors will independently extract data and assess trial quality using the Cochrane risk of bias tool. Risk ratios (RR) and corresponding 95 % CI will be calculated for all dichotomous outcomes and the mean difference (MD) and 95 % CI will be calculated for continuous outcomes.
- These investigators retrieved 683 unique references to studies. After screening these references, 660 were excluded for being non-applicable. They assessed 23 full text articles for eligibility and all of these studies were excluded from the review. The authors were unable to identify any RCTs or CCTs assessing the safety and effectiveness of intra-masseteric injections of botulinum toxin for people with bilateral benign masseter hypertrophy. They stated that the absence of high level evidence for the effectiveness of this intervention emphasizes the need for well-designed, adequately powered RCTs.
- In a pilot study, Climent et al (2013) examined the therapeutic potential of onabotulinumtoxinA in Morton neuroma. These researchers presented an open-label study with 17 consecutive patients with Morton neuroma and pain of more than 3 months' duration that had not responded to conservative treatment with physical measures or corticosteroid injection. Patients received 1 onabotulinumtoxinA injection in the area of the neuroma. The main outcome measure was the variation in the pain on walking evaluated using a VAS before treatment and at 1 and 3 months after treatment. The secondary outcome was the change in foot function, which was assessed using the Foot Health Status Questionnaire. In the overall group, the mean initial VAS score on walking was 7. This score had fallen to 4.8 at 1 month after treatment and to 3.7 at 3 months. Twelve patients (70.6 %) reported an

improvement in their pain and 5 patients (29.4 %) reported no change; exacerbation of the pain did not occur in any patient

- Improvements were also observed in 2 of the dimensions of the Foot Health Status Questionnaire: foot pain, which improved from a mean of 38.88 before treatment to 57 at 3 months, and foot function, which improved from a mean of 42.27 before treatment to 59.9 at 3 months. Clinical variables including age, sex, site and size of the lesion, standing activity, weekly duration of walking, footwear, foot type and footprint had no influence on the outcome. No adverse effects were reported. The authors concluded that in this pilot study, injection with onabotulinumtoxinA was shown to be of possible usefulness to relieve the pain and improve function in Morton neuroma. They stated that this finding opened the door to further clinical research.
- Hu and colleagues (2013) systematically reviewed the therapeutic efficacy and safety of BTX-A in trigeminal neuralgia. PubMed, EMBASE, Cochrane Library Clinical Trials and Web of Science from January 1966 to March 2013 were searched with the terms of "botulinum toxin" and "trigeminal neuralgia", and references of related articles were traced. Data on the safety and effectiveness of BTX-A in this disorder were extracted and analyzed by at least 2 reviewers. Data for individual studies were reported, and pooled data were analyzed if appropriate. A total of 5 prospective studies and 1 double-blind, randomized, placebo-controlled study were identified. Response was achieved in approximately 70 to 100 % of patients, and the mean pain intensity and frequency were reduced by approximately 60 to 100 % at 4 weeks after treatment in most studies. Major adverse events were not reported.
- The authors concluded that available studies showed BTX-A may be effective in treatment of trigeminal neuralgia. Moreover, they stated that well-designed randomized, controlled, double-blinded trial is still lacking. Future BTX-A treatment studies on optimal dose, duration of the therapeutic efficacy, common AEs, and the time and indications for repeat injection would be promising.

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- Reviewed by a Board Certified Internist
- Reviewed by David Evans, MD, Medical Director, Active Health Management - Feb 2014

Footnotes

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[A] Note: Strabismus repair is considered cosmetic in adults with uncorrected congenital strabismus and no binocular fusion [A in Context Link 1]

[B] Note: Refer all cases with combined symptoms of cervical dystonia or torticollis and symptoms of tension headaches and/or migraines to the medical director for further review [B in Context Link 1]

[C] If members do not respond to a course of treatment (usually lasts for 12 weeks), treatment should be discontinued [C in Context Link 1]

[D] Note: Refer all cases with combined symptoms of cervical dystonia or torticollis and symptoms of tension headaches and/or migraines to the medical director for further review [D in Context Link 1]

[E] Note: Refer all cases with combined symptoms of cervical dystonia or torticollis and symptoms of tension headaches and/or migraines to the medical director for further review [E in Context Link 1]

[F] Note: Refer all cases with combined symptoms of cervical dystonia or torticollis and symptoms of tension headaches and/or migraines to the medical director for further review [F in Context Link 1]

[G] The response interval following Botox treatment ranges from a few months to as long as one year (common range between two and six months) [G in Context Link 1]

Codes

CPT® : 31513, 31570, 31571, 43201, 43236, 46505, 52287, 64611, 64612, 64615, 64650, 64653, 67345, 95873, 95874, 96372

HCPCS: J0585, J0586, J0588