



Botulinum Toxins Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
abobotulinumtoxinA (Dysport®) ¹	Ipsen Biopharma/ Galderma	<ul style="list-style-type: none"> ▪ Treatment of adults with cervical dystonia ▪ Treatment of spasticity in adults ▪ Treatment of lower limb spasticity in pediatric patients ≥ 2 years old ▪ Treatment of upper limb spasticity in pediatric patients ≥ 2 years old, excluding spasticity caused by cerebral palsy ▪ Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults < 65 years of age
incobotulinumtoxinA (Xeomin®) ²	Merz	<ul style="list-style-type: none"> ▪ Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients ▪ Treatment of upper limb spasticity in adults in elbow, wrist, finger, and thumb flexors ▪ Treatment of blepharospasm in adults that are botulinum toxin-naïve or previously treated with onabotulinumtoxinA (Botox) ▪ Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and/or corrugator muscle activity in adults ▪ Treatment of chronic sialorrhea (excessive drooling) in adults
onabotulinumtoxinA* (Botox®) ³	Allergan	<ul style="list-style-type: none"> ▪ Treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain in patients 16 years and older ▪ Treatment of upper limb spasticity in adults to decrease the severity of increased muscle tone in elbow, wrist, finger, and thumb flexors ▪ Treatment of lower limb spasticity in adults to decrease the severity of increased muscle tone in ankle and toe flexors ▪ Treatment of upper limb spasticity in pediatric patients ≥ 2 years old ▪ Treatment of lower limb spasticity pediatric patients ≥ 2 years old, excluding spasticity caused by cerebral palsy ▪ Treatment of severe primary axillary hyperhidrosis that is inadequately managed by topical agents in adults ▪ Treatment of blepharospasm associated with dystonia in patients ≥ 12 years ▪ Treatment of strabismus in patients ≥ 12 years ▪ Prophylaxis of headaches in adults with chronic migraine (defined as ≥ 15 days/month with headache duration of ≥ 4 hours) ▪ Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication ▪ Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication

*Limitations for the use of onabotulinumtoxinA (Botox) include (1) safety and effectiveness have not been established for the prophylaxis of episodic migraine (< 15 headache days per month) in 7 placebo-controlled studies; (2) safety and effectiveness have not been established for the treatment of other upper or lower limb muscle groups; (3) the safety and effectiveness of onabotulinumtoxinA for hyperhidrosis in other body areas have not been established; (4) improvement in upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture has not been demonstrated; and (5) treatment is not intended to substitute for usual standard of care rehabilitation regimens.

FDA-Approved Indications (continued)

Drug	Manufacturer	Indications
rimabotulinumtoxinB (Myobloc®) ⁴	Solstice Neurosciences	<ul style="list-style-type: none">▪ Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain▪ Treatment of chronic sialorrhea (excessive drooling) in adults

OVERVIEW

Cervical dystonia, also known as spasmodic torticollis, is a painful, localized neurologic movement disorder. Symptoms are caused by intermittent or sustained contractions of the neck muscles that control the position of the head. Head position is altered, and the effect can spread down to the shoulders. Head or arm tremor can also be experienced. Botulinum toxins are a common treatment for this disorder. The ability to administer botulinum toxins directly to the affected area(s) makes these products a logical first option. Other therapeutic options include dopamine agonists. Pharmaceutical-grade botulinum toxins are purified and are dosed well below amounts that could cause botulism in patients.

Other conditions resulting from increased neuromuscular activity for which botulinum toxins are treatment options include muscle spasticity, eyelid twitching (blepharospasm), improper eye alignment (strabismus), axillary hyperhidrosis (excessive armpit sweating due to overactive sweat glands), chronic migraine, and chronic sialorrhea (excessive drooling).

OnabotulinumtoxinA (Botox) injection is approved to treat urinary incontinence in people with neurologic conditions, such as spinal cord injury and multiple sclerosis, who have overactivity of the bladder.⁵ Uninhibited urinary bladder contractions in people with some neurological conditions can lead to an inability to store urine. Management of this condition includes medications to relax the bladder (anticholinergics) and consistent use of a urinary catheter to empty the bladder. The treatment consists of onabotulinumtoxinA injections into the detrusor muscle of the bladder. The result is relaxation of the bladder, an increase in its storage capacity, and a decrease in urinary incontinence. Intradetrusor injections are performed via cystoscopy and may require general anesthesia. The duration of the effect of onabotulinumtoxinA on urinary incontinence in this patient population is up to 10 months.

OnabotulinumtoxinA is also approved for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency. Current treatment options are very similar for the 2 conditions.⁶ Joint treatment guidelines, reviewed and updated in 2019, from the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) recommend first-line treatment with education and behavioral therapies (e.g., bladder training and pelvic floor exercises). Clinicians are then advised to add medication management with antimuscarinics or β_3 -adrenoreceptor agonists as second-line treatment; combination therapy with both classes is now recommended as an option in patients refractory to monotherapy. Third-line treatments should be considered only for carefully selected patients (e.g., refractory OAB symptoms or those who are not a candidate for second-line treatment) and consist of intradetrusor onabotulinumtoxinA, peripheral tibial nerve stimulation (PTNS), or sacral neuromodulation (SNS).^{7,8,9} The duration of the effect of onabotulinumtoxinA on OAB is approximately 24 weeks; however, repeat doses should be administered no sooner than 12 weeks after to the last injection.¹⁰

In 2016, the American Academy of Neurology (AAN) published updated guidelines on the use of botulinum toxins to treat cervical dystonia, blepharospasm, adult spasticity, and headache. These guidelines were reaffirmed in 2019.¹¹ Overall, the updated guideline states that botulinum toxin is generally safe and effective for these 4 conditions. For blepharospasm, they state that onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin) are probably effective and should be considered. AbobotulinumtoxinA (Dysport) is possibly effective and may be considered for treatment of blepharospasm. For cervical dystonia, both abobotulinumtoxinA and rimabotulinumtoxinB (Myobloc) are established therapies and should be offered. While data are less robust, onabotulinumtoxinA and incobotulinumtoxinA are probably effective and should be considered for treatment of cervical dystonia as well. For adult spasticity, abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA have demonstrated efficacy and should be offered; rimabotulinumtoxinB should also be considered for upper limb spasticity but has less efficacy data in adult spasticity compared to the other agents within the class. For headache, onabotulinumtoxinA has demonstrated efficacy in increasing headache-free days and some improvement in quality of life in patients with chronic migraine; thus, AAN recommends onabotulinumtoxinA be offered in patients with chronic migraine. However, AAN further notes that onabotulinumtoxinA has been established as ineffective in episodic migraine and probably ineffective in chronic tension-type headache.

Earlier guidelines from the AAN published in 2008 on the use of botulinum neurotoxin for the treatment of spasticity, movement disorders, and autonomic disorders and pain are considered current for other conditions not specifically updated in the 2016 AAN guidelines.^{12,13,14,15} Notably, only onabotulinumtoxinA (Botox) and rimabotulinumtoxinB (Myobloc) were available at the time of publication of the 2008 guidelines. AAN recommends that botulinum neurotoxin be offered as a treatment option for spasticity in children. For movement disorders, they state that botulinum neurotoxin may be offered for focal arm extremity, dystonia, adductor laryngeal dystonia, and upper extremity essential tremor. Due to limited data, botulinum neurotoxin may also be considered for hemifacial spasm, focal lower limb dystonia, and motor tics. For autonomic disorders and pain, AAN recommends that botulinum neurotoxin should be offered for axillary hyperhidrosis and detrusor overactivity and should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia following spinal cord injury. In addition, it may be considered for gustatory sweating and low back pain, but is probably ineffective in episodic migraine and chronic tension-type headache. In addition, the AAN published a Practice Parameter specifically regarding the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy in 2010 (reaffirmed in 2013).¹⁶ These guidelines also recommend offering the use of botulinum toxin type A as an effective and generally safe treatment (Level A). Data were insufficient to recommend other agents, including botulinum toxin type B (Level U), but the group recommended that diazepam (short-term use; Level B) and tizanidine could be considered (Level C).

Sialorrhea is related to reduced oromotor control and autonomic dysfunction. It can be caused by impaired swallowing associated with neurologic conditions, such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), and cerebral palsy.¹⁷ Excessive drooling can also be due to increased production of saliva from the parotid, submandibular, and sublingual glands due to idiopathic or drug-induced causes, or due to decreased clearance of saliva. Afferent innervations of cranial nerves also play a role. Conservative treatments of sialorrhea include diet modification, oral-motor exercise, palatal training devices, and medication therapy (e.g., oral anticholinergics, injectable botulinum toxins). Invasive treatments include surgical and radiation therapy. The 2010 AAN guidelines for the treatment of

nonmotor symptoms of Parkinson's disease state that botulinum toxin should be considered for sialorrhea (Level B); however, these guidelines have since been retired.¹⁸

This review focuses on the non-cosmetic use of agents in this class.

PHARMACOLOGY^{19,20,21,22}

Botulinum toxins inhibit the release of acetylcholine from peripheral cholinergic nerve endings. This occurs via binding of toxins to specific surface receptors on nerve endings. The toxins enter nerve terminals and cause intracellular blockage of neurotransmitter activity. Thus, conditions characterized by excessive nervous activity are therapeutically altered. Following intramuscular (IM) administration, the muscle may atrophy; however, re-innervation of the muscle may occur, slowly reversing muscle denervation.

Intradermal axillary injections cause temporary denervation of the sweat gland leading to local sweat reduction. Intradetrusor injections inhibit acetylcholine release and alters efferent detrusor activity.

PHARMACOKINETICS^{23,24,25,26}

Botulinum toxins are not detectable in the peripheral blood following IM injection.

CONTRAINDICATIONS/WARNINGS^{27,28,29,30}

Botulinum toxins are contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or their components. Hypersensitivity reactions, including anaphylaxis, have been reported. Patients who are allergic to cow's milk protein should not be treated with abobotulinumtoxinA (Dysport). All products are contraindicated in patients with infection at the proposed injection site.

All products in this review contain a Boxed warning regarding the potential for distant spread of the toxin effect. Although effects are localized and drug is not detected in the blood, effects can be observed beyond the site of local injection. Symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysarthria, dysphoria, and urinary incontinence (symptoms reported hours to weeks after injection). In addition, treatment with botulinum toxins can result in swallowing or breathing difficulties. Patients with pre-existing conditions involving these symptoms, particularly cervical dystonia and other neuromuscular disorders, may be more susceptible to complications.

Potency units are specific to each product and the assay method utilized. Therefore, products are not interchangeable, and units cannot be converted to those of any other product.

AbobotulinumtoxinA labeling warns against its use in patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in target muscles, marked facial asymmetry, inflammation at the injection site, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin; caution should be used with these patients. Botulinum toxins can cause reduced blinking, leading to corneal exposure and ulceration when used to treat blepharospasm. In addition, retrobulbar hemorrhages have occurred during administration of onabotulinumtoxinA for strabismus.

Intradetrusor injection of onabotulinumtoxinA (Botox) is contraindicated in patients with a urinary tract infection (UTI) and post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC). OnabotulinumtoxinA increased the incidence of UTI and therapy should only be considered when the benefit outweighs the potential risk. In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment

and periodically as medically appropriate for up to 12 weeks. This is of particular concern in patients with diabetes or multiple sclerosis. Autonomic dysreflexia associated with intradetrusor injections of onabotulinumtoxinA could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. Due to the risk of urinary retention, only those patients willing and able of catheterization post-treatment should be treated for bladder dysfunction.

Patients with compromised respiratory status must be closely monitored while undergoing botulinum toxin treatment for upper limb spasticity. Event rate in change of forced vital capacity (FVC) was greater and upper respiratory tract infections and bronchitis were more common in patients treated with onabotulinumtoxinA (Botox) as compared with placebo.

Serious adverse reactions, including fatal outcomes have been reported in patients treated with onabotulinumtoxinA for unapproved uses. Adverse reactions included excessive weakness, dysphagia, and aspiration pneumonia. The safety and effectiveness of onabotulinumtoxinA for unapproved uses have not been established.

These products contain human albumin and, therefore, carry a remote risk for transmission of viral diseases.

There is a theoretical risk of Creutzfeldt-Jakob disease for agents in this class; to date no actual cases have been reported. In patients with certain pre-existing peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (myasthenia gravis or Lambert-Eaton syndrome), close monitoring is required when botulinum toxin is administered. Increased risk of clinically significant effects such as generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of onabotulinumtoxinA (Botox) or rimabotulinumtoxinB (Myobloc) may occur in patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders.

DRUG INTERACTIONS^{31,32,33,34}

No formal drug interaction studies have been conducted with botulinum toxins. However, patients undergoing treatment concomitantly with aminoglycosides or other agents that interfere with neuromuscular transmission should be closely monitored for additive effects. The use of anticholinergic drugs following botulinum toxins may potentiate anticholinergic effects like blurred vision. The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown.

Prior to being treated with intradetrusor injections of onabotulinumtoxinA (for urinary incontinence or OAB); patients should discontinue anti-platelet therapy at least 3 days before the procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding.

In addition, patients receiving muscle relaxants prior to or after treatment with botulinum toxins may present with excessive weakness.

ADVERSE EFFECTS^{35,36,37,38}

Drug	Injection site discomfort	Muscular weakness	Musculoskeletal pain	Dysphagia	Dry mouth	Dysphonia
abobotulinumtoxinA (Dysport)	3-22 (10)	2-56 (0-1)	1-7 (1-5)	29-39 (5)	18-39 (10)	18-28 (0)
incobotulinumtoxinA (Xeomin)	4-9 (7)	7-11 (1)	3-15 (0-4)	13-18 (3)	2-16 (0-3)	3 (0)
onabotulinumtoxinA (Botox)	2-10	2-3 (0)	5-9 (4)	19	2-10	2-10
rimabotulinumtoxinB (Myobloc)	12-16 (9)	3-6 (3)	6-13 (10)	10-25 (3)	3-34 (3)	nr

Adverse effects data are obtained from product package information and, therefore, should not be considered comparative or all inclusive. Adverse effect rates have been taken from different patient populations; frequency of occurrence is not representative of all patients. Placebo rates are in parentheses. nr = not reported.

The formation of neutralizing antibodies to botulinum toxins has been reported. The presence of these antibodies may reduce the effectiveness of treatment by inactivating the biological activity of the toxin. Study results suggest that frequent injections and high doses are factors which may lead to immunogenicity. Potential for antibody formation may be minimized by using the lowest effective dosing and longest interval.

The following adverse event rates with onabotulinumtoxinA (Botox) in the treatment of urinary incontinence due to neurogenic detrusor overactivity were reported at any time following initial injection and prior to re-injection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%). The following adverse event rates with onabotulinumtoxinA (Botox) in the treatment of overactive bladder were reported as occurring within 12 weeks of the first intradetrusor injection: urinary tract infection (18%), dysuria (9%), urinary retention (6%), bacteriuria (4%), and residual urine volume (3%). A higher incidence of UTI was observed in patients with diabetes mellitus.

For detailed adverse effect data, including adverse effects by indication, please see full prescribing information for each product.

SPECIAL POPULATIONS^{39,40,41,42}

Pediatrics

AbobotulinumtoxinA (Dysport) is approved for the treatment of lower limb spasticity in pediatric patients at least 2 years of age. It is also approved in pediatric patients at least 2 years of age for the treatment upper limb spasticity not caused by cerebral palsy. Safety and effectiveness of abobotulinumtoxinA has not been established in patients under 18 for other indications or for the treatment of spasticity in children under 2 years of age.

Safety and effectiveness of onabotulinumtoxinA (Botox) in the treatment of blepharospasm and strabismus have not been established in patients less than 12 years of age. Safety and effectiveness of onabotulinumtoxinA in the treatment of cervical dystonia have not been established in patients less than 16 years of age. Safety and effectiveness of onabotulinumtoxinA (Botox) in the treatment of limb

spasticity have not been established in patients under 2 years of age; treatment of lower limb spasticity caused by cerebral palsy is not included in the pediatric indication (patients ages 2 to 17 years old). Safety and effectiveness of onabotulinumtoxinA (Botox) in the treatment of axillary hyperhidrosis, chronic migraine prophylaxis or urinary incontinence due to neurogenic detrusor overactivity/overactive bladder in patients below the age of 18 years have not been established.

Safety and efficacy of incobotulinumtoxinA (Xeomin) and rimabotulinumtoxinB (Myobloc) in children have not been established.

Pregnancy

While previously considered Pregnancy Category C, the labeling for abobotulinumtoxinA (Dysport), onabotulinumtoxinA, (Botox), rimabotulinumtoxinB (Myobloc) and incobotulinumtoxinA (Xeomin) have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and instructs that there are no adequate data on drug-related developmental risks in pregnant women; therefore, the products should be used only if the potential benefit justifies the potential risks.

Geriatrics

In clinical trials, urinary retention and UTI were more common in patients 65 years and older treated with either onabotulinumtoxinA (Botox) or placebo. There were no overall differences in other safety signals between patients 65 years and older and younger populations. In addition, no overall differences between these populations were reported across other indications.

DOSAGES^{43,44,45,46}

Drug	Dose	Availability
abobotulinumtoxinA (Dysport)	<p>Cervical dystonia: 500 units IM as a divided dose among affected muscles; Doses ranging from 250 to 1,000 units may be re-administered upon return of clinical symptoms</p> <p>Spasticity in adults: number of units dependent on size, number and location of muscles affected, severity of spasticity, presence of local muscle weakness, response to prior treatment and/or adverse events; total dose/treatment session, upper and lower limb combined, is 1,500 units, and no more than 1 mL should generally be administered at any single injection site</p> <ul style="list-style-type: none"> • Upper limb: dosing ranges between 500 units and 1,000 units (divided) • Lower limb: dosing ranges between 1,000 units and 1,500 units (divided) <p>Spasticity in children patients ≥ 2 years old: number of units dependent on size, number, and location of muscles involved, severity of spasticity, presence of local muscle weakness, response to prior treatment, and/or adverse events; maximum recommended dose in a single treatment session or 3-month interval is the lower of 30 units/kg or 1,000 units; no more than 0.5 mL should be generally administered to any single injection site</p> <ul style="list-style-type: none"> • Upper limbs (weight ≥ 10 kg and excluding spasticity caused by cerebral palsy): lower of 8 to 16 units/kg or 640 units among both limbs • Lower limbs: 10 to 15 units/kg for unilateral lower limb injections, 20 to 30 units/kg for bilateral lower limb injections, or 1,000 units, whichever is lower 	300 unit, 500 unit vials

Doses may be repeated when clinical effects from the previous dose diminish. In general, repeat doses should not be administered more frequently than every 3 months.

Dosages (continued)

Drug	Dose	Availability
incobotulinumtoxinA (Xeomin)	<p>Do not exceed 400 units in a treatment session for any indication</p> <p>Cervical dystonia: initial total dose of 120 units IM per treatment session; frequency of repeat treatment depends on clinical response, but should typically be no more frequent than every 12 weeks</p> <p>Blepharospasm: 1.25 to 2.5 units per injection site; if known, dose depends on previous dose of onabotulinumtoxinA (Botox); Initial total dose should not exceed 70 units for both eyes (35 units per eye)</p> <p>Upper limb spasticity: dosage, frequency, and number of injections sites is dependent on patient size, number and location of muscles to be treated, severity of spasticity, presence of local muscle weakness, response to previous treatment and adverse events</p> <p>Chronic sialorrhea: 100 units per treatment session, consisting of 30 units per parotid gland and 20 units per submandibular gland; repeat no sooner than every 16 weeks.</p>	50 unit, 100 unit, 200 unit vials
onabotulinumtoxinA (Botox)	<p>Cervical dystonia: Number of units given IM dependent on head and neck position, divided among affected muscles (maximum 50 units/site)</p> <p>Spasticity in adults: number of units dependent on affected muscles; for upper limbs the range is 75 to 400 units; for lower limbs the range is 300 to 400 units</p> <p>Spasticity in children \geq 2 years old: number of units dependent on affected muscles; do not exceed 10 units/kg or 340 units in a 3-month interval when treating both upper and lower limb spasticity</p> <ul style="list-style-type: none"> • Upper limbs: lower of 3 to 6 units/kg or 200 units • Lower limbs (excluding spasticity caused by cerebral palsy): lower of 4 to 8 units/kg or 300 units <p>Axillary hyperhidrosis: 50 units intradermally per axilla</p> <p>Blepharospasm: 1.25 to 2.5 units into each of 3 sites per affected eye</p> <p>Strabismus: 1.25 to 2.5 units in any 1 muscle</p> <p>Neurogenic detrusor overactivity: 200 units IM (divided into 1 mL injections over 30 sites) per treatment into the detrusor muscle</p> <p>Overactive Bladder (OAB): 100 units (divided into 0.5 mL injections over 20 sites, approximately 1 cm apart) into the detrusor muscle (avoiding the trigone)</p> <p>Chronic migraine prophylaxis: 155 units IM (divided) across 7 head and neck muscle areas</p> <p>In treating one or more indications, the maximum cumulative dose should not exceed 400 units</p>	100 unit, 200 unit vials
rimabotulinumtoxinB (Myobloc)	<p>Cervical dystonia: 2,500 to 5,000 units IM divided among affected muscles (for patients with a prior history of tolerating botulinum toxin injections) Patients without prior history should receive a lower initial dose</p> <p>Chronic sialorrhea: 1,500 units to 3,500 units, divided among the parotid and submandibular glands; frequency is based on clinical response, not to exceed every 12 weeks</p>	2,500 unit, 5,000 unit, 10,000 unit vials

Doses may be repeated when clinical effects from the previous dose diminish. In general, repeat doses should not be administered more frequently than every 3 months.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class for approved indications. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

While there are some comparative studies in this class for select indications, there is a paucity of data for other FDA-approved indications. IncobotulinumtoxinA (Xeomin) has demonstrated efficacy in double-blind, placebo-controlled clinical trials for use in upper limb spasticity and for chronic sialorrhea (resulting from Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury).^{47,48} AbobotulinumtoxinA (Dysport) also has demonstrated efficacy against placebo in double-blind clinical trials for use in both upper and lower limb spasticity in adults as well as lower limb spasticity and **non-cerebral palsy-related upper limb spasticity** in pediatric patients ages ≥ 2 years, as described above.⁴⁹ IncobotulinumtoxinA (Xeomin) and **rimabotulinumtoxinB (Myobloc)** have each demonstrated efficacy for the treatment of chronic sialorrhea in a double-blind, placebo-controlled trial.^{50,51} OnabotulinumtoxinA (Botox), which carries the most FDA-approved indications, has demonstrated superiority over placebo in the treatment of upper limb spasticity (**including pediatric patients ages ≥ 2 years**), lower limb spasticity (**including pediatric patients ages ≥ 2 years when not caused by cerebral palsy**), chronic migraine prophylaxis, primary axillary hyperhidrosis, urinary incontinence due to detrusor overactivity, and overactive bladder in double-blind clinical trials.^{52,53,54,55}

Blepharospasm

abobotulinumtoxinA (Dysport) and onabotulinumtoxinA (Botox)

A double-blind study was performed on 212 patients with essential blepharospasm who received 1 injection of abobotulinumtoxinA and 1 injection of onabotulinumtoxinA in 2 separate treatment sessions.⁵⁶ Patients were randomized at the first session to 1 product, and then given the other product at the second session. The average dose of onabotulinumtoxinA per treatment was 45.4 units \pm 13.3 and of abobotulinumtoxinA 182.1 units \pm 55.1. An empirical ratio for onabotulinumtoxinA: abobotulinumtoxinA of 1:4 was used. All patients had received botulinum toxin injections prior to the present study. The effect of onabotulinumtoxinA lasted 7.98 weeks \pm 3.8, while the effect of abobotulinumtoxinA lasted 8.03 weeks \pm 4.6. There was no statistically significant difference in the duration of the treatment effect between the 2 preparations ($p=0.42$). The rate of occurrence of ptosis was significantly lower with onabotulinumtoxinA ($p<0.01$). Adverse effects (ptosis, tearing, blurred vision, double vision, hematoma, foreign body sensation) were observed with onabotulinumtoxinA in

17% of the treatment sessions and with abobotulinumtoxinA in 24.1% ($p < 0.05$). AbobotulinumtoxinA is not indicated for the treatment of blepharospasm.

Cervical Dystonia

abobotulinumtoxinA (Dysport) and onabotulinumtoxinA (Botox)

Patients with cervical dystonia were randomized to receive either the clinically indicated dose of onabotulinumtoxinA or 3 times that dose in abobotulinumtoxinA units.⁵⁷ Drug was administered in a double-blind fashion at 1 or more sites per muscle. Patients ($n = 73$) returned for assessment 2, 4, 8, and 12 weeks after treatment. The Tsui scale was used for evaluation of patient outcomes. The Tsui scale is a clinician-assessed scale (range, 0 [no dystonia] to 25 [severe dystonia]) of impairment that grades the severity of postural deviance, as well as notes the presence or absence of head tremor. It also incorporates whether movements are continuous or intermittent. The mean post-treatment Tsui scores for the abobotulinumtoxinA group (4.8) and the onabotulinumtoxinA group (5.0) were not statistically different ($p = 0.66$). Both groups showed substantial improvement in Tsui score by week 2 (abobotulinumtoxinA 46%; onabotulinumtoxinA, 37%), with a peak effect at week 4 (abobotulinumtoxinA 49%; onabotulinumtoxinA 44%). The duration of effect, assessed by time to retreatment, was also similar (abobotulinumtoxinA 83.9 days; onabotulinumtoxinA 80.7 days; $p = 0.85$). During the study, 58% of abobotulinumtoxinA patients and 69% of onabotulinumtoxinA patients reported adverse events ($p = 0.35$). A global assessment of efficacy and safety considered that 76% of abobotulinumtoxinA patients and 66% of onabotulinumtoxinA patients were treatment successes ($p = 0.32$).

A double-blind, randomized, 3-period crossover study involving 54 patients with cervical dystonia was performed.⁵⁸ The patients received the following treatments in a randomized order: onabotulinumtoxinA at the usually effective dose, abobotulinumtoxinA at a dose of 1:3 to onabotulinumtoxinA, and abobotulinumtoxinA at a dose of 1:4 to onabotulinumtoxinA. The improvement of the Tsui and in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) pain scales between baseline and a control visit 1 month after each of the 3 injections, as well as the incidence of adverse events, was assessed. The TWSTRS scale is comprised of 3 subscales (Severity, Disability, and Pain) that are scored independently and then combined (range, 0 [best] to 87 [worst]) to assess the measure of impact of cervical dystonia on patients. Comparison of the Tsui scores and of the TWSTRS pain scores showed a better effect on impairment and pain with abobotulinumtoxinA 1:3 ($p = 0.02$ and 0.04, respectively) and 1:4 ($p = 0.01$ and 0.02, respectively) than with onabotulinumtoxinA. The number of adverse events was higher with both abobotulinumtoxinA treatments. The most frequent adverse event was dysphagia, found in 3%, 15.6%, and 17.3% (onabotulinumtoxinA, abobotulinumtoxinA 1:3, and abobotulinumtoxinA 1:4, respectively) of the patients.

onabotulinumtoxinA (Botox) and rimabotulinumtoxinB (Myobloc)

A randomized, double-blind, parallel-arm study compared onabotulinumtoxinA with rimabotulinumtoxinB in 139 subjects with cervical dystonia who had a previous response from onabotulinumtoxinA.⁵⁹ Patients were evaluated at baseline, 4 weeks, 8 weeks, and 2 week intervals thereafter until loss of 80% of clinical effect or completion of 20 weeks of observation. Improvement in TWSTRS score was found at 4 weeks after injection and did not differ between serotypes. Dysphagia and dry mouth were more frequent with rimabotulinumtoxinB (dysphagia: 19 versus 48%, $p = 0.0005$; dry

mouth 41 versus 80%, $p < 0.0001$). In clinical responders, onabotulinumtoxinA had a modestly longer duration of benefit (14 weeks versus 12.1 weeks, $p = 0.033$).

Botulinum toxin-naïve cervical dystonia subjects ($n = 111$) were randomized in a double-blind manner to onabotulinumtoxinA or rimabotulinumtoxinB and evaluated at baseline and every 4 weeks following 1 treatment.⁶⁰ The primary measure was the change in TWSTRS from baseline to week 4 post-injection. Improvement in TWSTRS-total scores 4 weeks after rimabotulinumtoxinB was noninferior to onabotulinumtoxinA (adjusted means 11 and 8.8, respectively). The median duration of effect of onabotulinumtoxinA and rimabotulinumtoxinB was not different (13.1 versus 13.7 weeks, respectively; $p = 0.833$). There were no significant differences in the occurrence of injection site pain and dysphagia. Mild dry mouth was more frequent with rimabotulinumtoxinB, but there were no differences for moderate/severe dry mouth. This study was performed by the manufacturer of rimabotulinumtoxinB.

SUMMARY

All botulinum toxin products are safe and effective treatments for neuromuscular disorders. The American Academy of Neurology (AAN) 2016 guideline on the use of botulinum toxins includes recommendation for each formulation and indication in blepharospasm, cervical dystonia (CD), adult spasticity, and headache. Overall the updated guideline states that botulinum toxin is generally safe and effective for these 4 conditions, although level of recommendations do vary based on the extent of published data. Earlier guidelines (2008) from AAN are considered to be current and address the use of botulinum toxins in other disorders as well and remain unchanged; these guidelines include spasticity (including pediatrics), movement disorders, autonomic disorders and pain and updates to these documents are in progress. All 4 agents in this review are indicated to treat cervical dystonia in adults; onabotulinumtoxinA (Botox) is indicated in patients as young as 16 years. AbobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and onabotulinumtoxinA (Botox) are indicated to treat upper and lower limb spasticity in adults. AbobotulinumtoxinA (Dysport) and onabotulinumtoxinA (Botox) are approved for limb spasticity in patients 2 years and older; of note, the abobotulinumtoxinA upper limb indication excludes spasticity due to cerebral palsy while the onabotulinumtoxinA lower limb indication excludes spasticity due to cerebral palsy. IncobotulinumtoxinA (Xeomin) and rimabotulinumtoxinB (Myobloc) are also indicated for chronic sialorrhea.

Based on clinical data, onabotulinumtoxinA (Botox) is at least as tolerable as the other available products. The increased incidences of adverse events with other botulinum toxins in clinical trials may be due to the uncertain methods of achieving equipotent doses between different products. While not considered interchangeable, some published head-to-head clinical trials support the interchangeability of these products at various ratios (not based on a 1:1 unit conversion).

A variety of treatments are available for prevention of chronic and episodic migraines. The 2016 AAN guideline notes that onabotulinumtoxinA has demonstrated efficacy in increasing headache-free days and some improvement in quality of life in chronic migraine; thus, AAN recommends onabotulinumtoxinA be offered in patients with chronic migraine, though it is only approved for adult use in this indication. OnabotulinumtoxinA has been established as ineffective in episodic migraine; AAN recommends against its use in this type of headache.

Different treatment modalities are available for management of OAB. OnabotulinumtoxinA during cystoscopy is modestly effective in reducing OAB symptoms and is considered a third-line agent in select patients in clinical guidelines. Urinary tract infections and urinary retention have been associated with

onabotulinumtoxinA. Upper respiratory infections in patients with compromised respiratory status and neuromuscular adverse effects in patients with pre-existing neurodegenerative disorders have been reported.

OnabotulinumtoxinA is also FDA-approved to treat blepharospasm and strabismus in patients 12 years and older. IncobotulinumtoxinA is indicated to treat blepharospasm in **botulinum toxin-naïve** or experienced adults.

REFERENCES

- 1 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 2 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 3 Botox [package insert]. Madison, NJ; Allergan; October 2019.
- 4 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 5 Food and Drug Administration. News Release August 25, 2011. Available at: <https://wayback.archive-it.org/7993/20170112032339/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269509.htm>. Accessed March 3, 2020.
- 6 Botox [package insert]. Madison, NJ; Allergan; October 2019.
- 7 Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFA guideline. *J Urol.* 2012; 188(6): 2455-2463. DOI: 10.1016/j.juro.2012.09.079.
- 8 Gormley EA, Lightner DJ, Faraday M, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFA guideline amendment. *J Urol.* 2015; 193(5): 1572-1580. DOI: 10.1016/j.juro.2015.01.087.
- 9 Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. *J Urol.* 2019; 202(3):558-563. DOI: 10.1097/JU.0000000000000309. Available at: <https://www.auanet.org/guidelines>. Accessed March 3, 2020.
- 10 Botox [package insert]. Madison, NJ; Allergan; October 2019.
- 11 Simpson DN, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. *Neurology.* 2016; 86(19): 1818-1826. DOI: 10.1212/WNL.0000000000002560. Available at: <https://www.aan.com/Guidelines/Home/Search>. Accessed March 3, 2020.
- 12 Simpson M, Gracies JM, Graham HK, et al. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2008; 70: 1691-1698. Available at: <https://www.aan.com/Guidelines/Home/Search>. Accessed March 3, 2020.
- 13 Simpson M, Blitzer A, Brashear A, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2008; 70: 1699-1706. Available at: <https://www.aan.com/Guidelines/Home/Search>. Accessed March 3, 2020.
- 14 Naumann M, So Y, Argoff CE, et al. Assessment: botulinum toxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2008; 70: 1707-1714. Available at: <https://www.aan.com/Guidelines/Home/Search>. Accessed March 3, 2020.
- 15 Simpson DN, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult, spasticity, and headache. *Neurology.* 2016; 86(19): 1818-1826. DOI: 10.1212/WNL.0000000000002560. Available at: <https://www.aan.com/Guidelines/Home/Search>. Accessed March 3, 2020.
- 16 Delgado MR, Hirtz D, Aisen M, et al for the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2010 Jan 26;74(4):336-43. DOI: 10.1212/WNL.0b013e3181cbcd2f. Available at: <https://www.aan.com/Guidelines/home/ByTopic?topicid=14>. Accessed March 3, 2020.
- 17 Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: Anatomy, Pathophysiology and Treatment with Emphasis on the Role of Botulinum Toxins. *Toxins.* 2013. 5(5):1010-1031.
- 18 Zesiewicz TA, Sullivan L, Arnulf I, et al. Practice Parameter: Treatment of nonmotor symptoms of Parkinson disease Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* Mar 2010, 74 (11) 924-931. DOI: 10.1212/WNL.0b013e3181d55f24. Available at: <https://www.aan.com/Guidelines/Home/Search>. Accessed March 3, 2020.
- 19 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 20 Botox [package insert]. Madison, NJ; Allergan; October 2019.
- 21 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 22 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 23 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 24 Botox [package insert]. Madison, NJ; Allergan; October 2019.
- 25 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 26 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 27 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 28 Botox [package insert]. Madison, NJ; Allergan; October 2019.
- 29 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 30 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 31 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 32 Botox [package insert]. Madison, NJ; Allergan; October 2019..
- 33 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.

-
- 34 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 35 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 36 Botox [package insert]. Madison, NJ; Allergan; October 2019..
- 37 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 38 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 39 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 40 Botox [package insert]. Madison, NJ; Allergan; October 2019..
- 41 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 42 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 43 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 44 Botox [package insert]. Madison, NJ; Allergan; October 2019..
- 45 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 46 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 47 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 48 Elovic EP, Munin MC, Kanovsky P, et al. Randomized, placebo-controlled trial of incobotulinumtoxinA for upper-limb post-stroke spasticity. *Muscle Nerve* 2016; 53: 415–421.
- 49 Dysport [package insert]. Basking Ridge, NJ; Ipsen; September 2019.
- 50 Xeomin [package insert]. Rahleigh, NC; Merz; May 2019.
- 51 Myobloc [package insert]. Louisville, KY; Solstice Neurosciences; August 2019.
- 52 Botox [package insert]. Madison, NJ; Allergan; October 2019..
- 53 Owen RK, Abras KR, Mayne C, et al. Comparison of the effectiveness of repeated injections of onabotulinum toxin A for refractory idiopathic detrusor overactivity: analysis of an open label extension of a randomized trial (the RELAX study). *NeuroUrol Urodyn*. 2017 Apr;36(4):1201-1207. DOI: 10.1002/nau.23095.
- 54 Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010; 30(7):804-814.
- 55 Nitti VW, Dmochowski R, Herschorn, et al. EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol*. 2013; 189(6): 2186-93. DOI: 10.1016/j.juro.2012.12.022.
- 56 Nüssgens Z, Roggenkämper P. Comparison of two botulinum-toxin preparations in the treatment of essential blepharospasm. *Graefes Arch Clin Exp Ophthalmol*. 1997; 235(4):197-199.
- 57 Odergren T, Hjaltason H, Kaakkola S, et al. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry*. 1998; 64(1):6-12.
- 58 Ranoux D, Gury C, Fondarai J, et al. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. *J Neurol Neurosurg Psychiatry*. 2002; 72(4):459-462.
- 59 Comella CL, Jankovic J, Shannon KM, et al. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology*. 2005; 65(9):1423-1429.
- 60 Pappert EJ, Germanson T; Myobloc/Neurobloc European Cervical Dystonia Study Group. Botulinum toxin type B vs. type A in toxin-naïve patients with cervical dystonia: Randomized, double-blind, noninferiority trial. *Mov Disord*. 2008; 23(4):510-517.