Therapeutic Class Overview
Botulinum Toxins

Therapeutic Class

- **Overview/Summary:** Botulinum toxin is a neuromodulator derived from neurotoxins produced by the bacteria *Clostridium botulinum*, a gram positive bacillus.[1,2] Botulinum toxin inhibits the release of acetylcholine at presynaptic cholinergic nerve terminals of the peripheral nervous system and at ganglionic nerve terminals of the autonomic nervous system, thereby preventing neurotransmission and inducing flaccid paralysis.[1-6] Botulinum toxins are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, in which the goal of therapy is to reduce contraction of striated or smooth muscle.[1-6] Three botulinum toxin A products are approved by the Food and Drug Administration (FDA) including abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®) and onabotulinumtoxinA (Botox®). RimabotulinumtoxinB (Myobloc®) is the only botulinum toxin B product approved by the FDA.[3-6] None of the botulinum toxin products are available generically.[7] Botulinum toxin types A and B primarily differ in the specific mechanism by which they prevent acetylcholine from being released into the neuromuscular junction and in their risk for antibody development.[8] The development of antibodies against botulinum toxin may confer resistance or a diminished therapeutic response with subsequent treatments. RimabotulinumtoxinB appears to carry a higher risk of antibody development compared to the botulinum toxin A products.[3-6] IncobotulinumtoxinA is the only botulinum toxin product that is free of complexing proteins (hemagglutinins and nonhemagglutinins); however, whether this results in a lower rate of antibody development or greater therapeutic benefit compared to the other botulinum toxin products has not been established.[9] The botulinum toxin products are not interchangeable with one another. The potency (in units) of one botulinum toxin product is specific to the preparation and assay method utilized by the manufacturer and units of biological activity of one product cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.[3-6] Following injection, the onset of action occurs within two to six days and the therapeutic effect generally last at least 12 weeks. All botulinum toxin products include a black box warning in their labeling regarding the risk of botulinum toxin spreading beyond the site of injection, resulting in adverse events and death in some cases.[3-6]

Table 1. Current Medications Available in Therapeutic Class[3-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
AbobotulinumtoxinA (Dysport®)	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults younger than 65 years, treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia†	Powder for solution for injection: 300 Units 500 Units	-
IncobotulinumtoxinA (Xeomin®)	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults younger than 65 years, treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia† and treatment of adults with blepharospasm	Powder for solution for injection: 50 Units 100 Units	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	who were previously treated with onabotulinumtoxinA		
OnabotulinumtoxinA (Botox®)	Prophylaxis of headaches in adult patients with chronic migraine*, temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults younger than 65 years, treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia†, treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency‡, treatment of severe primary axillary hyperhidrosis§, treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders‖, treatment of upper limb spasticity in adults¶ and treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis)‡	Powder for solution for injection: 100 Units 200 Units	-
RimabotulinumtoxinB (Myobloc®)	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia	Solution for injection: 2,500 Units (0.5 mL) 5,000 Units (1 mL) 10,000 Units (2 mL)	-

*At least 15 days per month with headache lasting four hours a day or longer.
†In toxin-naive and previously treated patients.
‡ In adults who have an inadequate response to or are intolerant of an antimuscarinic medication.
§ Following an inadequate response to topical agents.
‖ In patients 12 years of age and older.
¶To decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Evidence-based Medicine

- In adults with cervical dystonia, results of head-to-head studies have not demonstrated a statistically significant difference between botulinum toxin products with regard to improvements in Toronto Western Spasmodic Torticollis Rating Scale total or subscale scores for symptomatic improvement.[10-12]
- In studies comparing incobotulinumtoxinA and onabotulinumtoxinA in patients with blepharospasm, similar improvements in Jankovic Rating Scale scores and other clinical outcomes have been reported, with no statistically significant differences between treatments.[13-16]
- OnabotulinumtoxinA may have a longer duration of action compared to abobotulinumtoxinA, with a similar duration of action as incobotulinumtoxinA and rimabotulinumtoxinB.[14,15,17,18]
- OnabotulinumtoxinA has consistently demonstrated statistically significant improvements in symptoms and quality of life in patients with severe primary axillary hyperhidrosis compared to

placebo.[19-21] Compared to aluminum chloride 20%, significantly more patients treated with onabotulinumtoxinA were achieved a treatment response at 12 weeks (92 vs 33%; *P*<0.001).[22]
- In patients experiencing symptoms of overactive bladder with urge urinary incontinence (UUI), urgency and frequency, onabotulinumtoxinA treatment significantly reduced the number of daily urgency episodes, voids and UUI episodes compared to placebo.[23-25]

Key Points within the Medication Class
- According to Current Clinical Guidelines:
    - The American Academy of Neurology and European Federation of Neurological Societies consider botulinum toxin A (or type B if there is resistance to type A) to be initial treatment for primary cranial or cervical dystonias due to their increased efficacy relative to standard therapies. In addition, botulinum toxin should also be considered for the treatment of blepharospasm, despite suboptimal evidence supporting use its use.[26,27]
    - In adults with spasticity of the upper and lower limb, botulinum toxin reduces muscle tone, improves passive function and may improve active function.[28]
    - In the management of nonneurogenic urinary incontinence, intravesical injections of botulinum toxin A are recommended as a third-line treatment in patients with UUI that is refractory to behavioral modification and antimuscarinic therapy, or when antimuscarinics are poorly tolerated. [29,30]
    - Botulinum toxin injections in the detrusor are considered the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity.[31,32]
    - In patients with esotropia or exotropia, injections of botulinum toxin may be an alternative to conventional extraocular muscle surgery in selected patients; however, the value in managing infantile esotropia has not been established.[33]
    - Based on inconsistent results from clinical trials, there is insufficient evidence to support or refute a benefit of botulinum toxin for the treatment of chronic daily headache.[34]
- Other Key Facts:
    - None of the botulinum toxin products are available generically.[7]
    - It is unknown if patients who developed neutralizing antibodies to onabotulinumtoxinA are at increased risk of developing tolerance to rimabotulinumtoxinB.[8]
    - All botulinum toxin A products are available as powders and must be reconstituted prior to use.[3-5]

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Therapeutic Class Review
Botulinum Toxins

Overview/Summary

Botulinum toxin is a neuromodulator derived from neurotoxins produced by the bacteria *Clostridium botulinum*, a gram positive bacillus. To date, several serotypes of botulinum toxin (A, B, C1, D, E, F and G) have been identified. Each serotype differs in their pharmacologic activity and only types A and B are approved for use in the United States.[1,2] Botulinum toxin inhibits the release of acetylcholine at presynaptic cholinergic nerve terminals of the peripheral nervous system and at ganglionic nerve terminals of the autonomic nervous system, thereby preventing neurotransmission and inducing flaccid paralysis.[1-6] Depending on the tissue injected, botulinum toxin blocks acetylcholine neuromuscular transmission as well as the cholinergic autonomic innervation of sweat, tear and salivary glands and smooth muscles.[7] Botulinum toxins are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, in which the goal of therapy is to reduce contraction of striated or smooth muscle.[1-6] All of the botulinum toxin A products are approved for cosmetic use to improve the appearance of moderate to severe glabellar lines (wrinkles) in adults younger than 65 years; however, this review will focus on the medical indications for which botulinum toxin A and B are approved.

Three botulinum toxin A products are approved by the Food and Drug Administration (FDA) including abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®) and onabotulinumtoxinA (Botox®). RimabotulinumtoxinB (Myobloc®) is the only botulinum toxin B product approved by the FDA.[3-6] The specific indications for each botulinum toxin product are listed in Table 2. None of the botulinum toxin products are available generically.[8] Botulinum toxin types A and B primarily differ in the specific mechanism by which they prevent acetylcholine from being released into the neuromuscular junction and in their risk for antibody development.[1-7] There is the potential for antibody development against botulinum toxin, which may confer resistance or a diminished therapeutic response to the product with subsequent treatments. RimabotulinumtoxinB appears to carry a higher risk of antibody development compared to the botulinum toxin A products.[3-6] IncobotulinumtoxinA is the only botulinum toxin product that is free of complexing proteins (hemagglutinins and non hemagglutinins); however, whether this results in a lower rate of antibody development or greater therapeutic benefit compared to the other botulinum toxin products has not been established.[9] It is unknown if patients who developed neutralizing antibodies to onabotulinumtoxinA are at increased risk of developing tolerance to rimabotulinumtoxinB. All botulinum toxin A products are available as powders and must be reconstituted prior to use. IncobotulinumtoxinA is the only product that may be stored at room temperature prior to reconstitution.[3-6]

The botulinum toxin products are not interchangeable with one another. The potency (in units) of one botulinum toxin product is specific to the preparation and assay method utilized by the manufacturer and units of biological activity of one product cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.[3-6] Following injection, the onset of action occurs within two to six days and the therapeutic effect generally last at least 12 weeks. Adverse events associated with botulinum toxins are injection-site specific, but generally include injection site discomfort, dry mouth, fatigue, flu-like symptoms and excessive muscle weakness in adjacent muscles. All botulinum toxin products include a black box warning in their labeling regarding the risk of botulinum toxin spreading beyond the site of injection, resulting in adverse events and death in some cases.[3-6,10]

Current consensus guidelines by the American Academy of Neurology and European Federation of Neurological Societies consider botulinum toxin A (or type B if there is resistance to type A) to be initial treatment for primary cranial or cervical dystonias due to their increased efficacy relative to standard therapies. In addition, botulinum toxin should also be considered for the treatment of blepharospasm, despite suboptimal evidence supporting use its use.[11,12] In adults with spasticity of the upper and lower limb, botulinum toxin reduces muscle tone, improves passive function and may improve active function.[13] In the management of nonneurogenic urinary incontinence, intravesical injections of botulinum toxin A are recommended as a third-line treatment in patients with urgency urinary incontinence that is refractory to behavioral modification and antimuscarinic therapy, or when antimuscarinics are poorly tolerated.

Botulinum toxin injections in the detrusor are considered the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity.[14-18] In patients with esotropia or exotropia, injections of botulinum toxin may be an alternative to conventional extraocular muscle surgery in selected patients; however, the value in managing infantile esotropia has not been established.[19]

Medications

Table 1. Medications Included Within Class Review[3-6]

Generic Name (Trade name)	Medication Class	Generic Availability
AbobotulinumtoxinA (Dysport®)	Botulinum toxin type A	-
IncobotulinumtoxinA (Xeomin®)	Botulinum toxin type A	-
OnabotulinumtoxinA (Botox®)	Botulinum toxin type A	-
RimabotulinumtoxinB (Myobloc®)	Botulinum toxin type B	-

Indications

Table 2. Food and Drug Administration-Approved Indications[3-6]

Generic Name	AbobotulinumtoxinA	IncobotulinumtoxinA	OnabotulinumtoxinA	RimabotulinumtoxinB
Prophylaxis of headaches in adult patients with chronic migraine			✔ *	
Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults younger than 65 years	✔	✔	✔	
Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia	✔ †	✔ †	✔ †	✔
Treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA		✔		
Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency			✔ ‡	
Treatment of severe primary axillary hyperhidrosis			✔ §	
Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders			✔ ‖	
Treatment of upper limb spasticity in adults			✔ ¶	
Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis)			✔ ‡	

*At least 15 days per month with headache lasting four hours a day or longer.
†In toxin-naive and previously treated patients.
‡ In adults who have an inadequate response to or are intolerant of an antimuscarinic medication.
§ Following an inadequate response to topical agents.
‖ In patients 12 years of age and older.
¶To decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

The botulinum toxin products have been used extensively for a variety of off-label indications. Currently available evidence demonstrates the effectiveness of botulinum toxin products in the management of achalasia, acquired nystagmus, gustatory sweating, hand dystonias, sialorrhea in children and adults as well as spasticity of cerebral palsy.

Pharmacokinetics

Using available analytic technology, it is not possible to detect botulinum toxins in the peripheral blood following intramuscular injections at recommended doses.

Clinical Trials

Clinical studies evaluating the safety and efficacy of the botulinum toxin products are described in Table 3.[20-70] In August 2009, the Food and Drug Administration (FDA) revised the labeling of each botulinum toxin product, giving each product a unique generic name, since the units used to measure the products are different and to emphasize that the different botulinum toxin products are not interchangeable. Studies completed prior to 2009 or in some cases after 2009 do not distinguish between specific botulinum toxin products, and may be referred to as botulinum toxin A or botulinum toxin B, respectively.[71]

OnabotulinumtoxinA was evaluated for prophylaxis of headaches in adults with chronic migraines in two multicenter, double-blind, randomized controlled trials known as PREEMPT I and II (Phase 3 Research Evaluating Migraine Prophylaxis Therapy). In each trial patients received onabotulinumtoxinA 155 to 195 units or placebo every 12 weeks for 24 weeks. In a pooled analysis of these studies by Dodick et al, the number of headache days, the primary endpoint, was significantly reduced at 24 weeks with onabotulinumtoxinA compared to placebo (-8.4 vs -6.6 days; $P<0.001$). The onabotulinumtoxinA treatment group also experienced significantly greater improvements compared to the placebo group in days with moderate or severe headache ($P<0.001$), cumulative hours of headache on headache days ($P<0.001$), headache episodes ($P=0.009$) and migraine episodes ($P=0.004$).[21] Several studies have evaluated the efficacy of onabotulinumtoxinA compared to standard migraine prophylaxis medications. In a three month study by Magalhães et al, the proportion of patients who experienced a ≥50% reduction in the number of days with pain was similar between the botulinum toxin A and amitriptyline groups (67.8 vs 73%; $P=0.78$). Furthermore, there were no significant differences with regard to improvements in visual analog scale pain scores ($P=0.79$) or the reduction in pain medication utilization between treatments ($P=0.76$). In two studies treatment response rates on the physician's global assessment (PGA) were not significantly different between the onabotulinumtoxinA and topiramate treatment groups.[24,25] In a study by Blumenfeld et al, the reduction from baseline in headache days per month was significant for both the onabotulinumtoxinA (-5.13 ±1.19; $P=0.0002$) and divalproex sodium (-4.94±1.26; $P=0.0001$) groups; however, the difference between the groups was not statistically significant. The treatment response rates were similar between the onabotulinumtoxinA and divalproex sodium treatment groups at nine months (68.2 vs 52.4%, respectively; *P* value not reported) for patients with episodic migraines or for patients experiencing chronic migraines (42.9 vs 50.0%, respectively; *P* value not reported).[23]

IncobotulinumtoxinA is approved for the treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA. In a study by Jankovic et al (N=109), the primary endpoint, Jankovic Rating Scale (JRS) severity subscale score at week six, was significantly reduced with incobotulinumtoxinA compared to placebo (-0.83 vs 0.21 points; $P<0.001$). Furthermore, treatment response rates were significantly higher with incobotulinumtoxinA compared to placebo at six weeks (54.7 vs 14.7%; odds ratio [OR], 11.29; 95% confidence interval [CI], 3.23 to 39.42; $P<0.001$).[27] IncobotulinumtoxinA was compared to onabotulinumtoxinA in three double-blind, randomized controlled trials. In 304 patients with blepharospasm and a therapeutic response to onabotulinumtoxinA, there was no statistically significant difference with regard to the improvements in JRS score between the treatment groups at three weeks ($P=0.031$). Furthermore, investigator-assessed efficacy demonstrated a similar response to treatment among patients receiving incobotulinumtoxinA or onabotulinumtoxinA, respectively ($P=0.14$).[28] In another 16-week study, treatment with incobotulinumtoxinA or onabotulinumtoxinA significantly improved the JRS score at three weeks compared to baseline (-2.90 and -2.67, respectively; $P<0.0001$ for both); however, there was no significant difference between treatment groups (*P* value not reported).[30] In a smaller study by Wabbels et al (N=65), there was no statistically significant difference in the reduction from baseline in Blepharospasm Disability Index total score at four weeks between patients treated with incobotulinumtoxinA or onabotulinumtoxinA (-1.3 vs -2.8; $P=0.93$). The PGA score at four weeks was similar between the treatment groups ($P=0.176$).[29] In a study by Nüssgens et al, the duration of treatment effect was similar between the groups ($P=0.42$).[43] Significantly greater improvements in JRS and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores were reported with

onabotulinumtoxinA compared to abobotulinumtoxinA in patients with blepharospasm (*P*<0.006) and cervical dystonia (*P*<0.011). A longer duration of effect was reported with onabotulinumtoxinA compared to abobotulinumtoxinA for treatment of blepharospasm (62.2 vs 47.4 days; *P*=0.001), cervical dystonia (64.3 vs 44.6 days; *P*=0.014) and hemifacial spasm (65.1 vs 41.8 days; *P*<0.014).[44]

All four botulinum toxin products are approved for the treatment of adults with cervical dystonia. Each botulinum toxin product has demonstrated a statistically significant improvement from baseline in TWSTRS total score over the course of treatment.[31,32,34-36] In a 16-week study of patients with cervical dystonia who were previously treated with onabotulinumtoxinA, patients were randomized to receive incobotulinumtoxinA or onabotulinumtoxinA at the same dose of the previous onabotulinumtoxinA treatment. At four weeks, the mean reduction from baseline in TWSTRS total score was 11 points in both treatment groups (*P* value not reported). At the final visit there was no statistically significant difference between the treatment groups with regard to TWSTRS severity (*P*=0.7378) or pain scores (*P*=0.0983).[37] OnabotulinumtoxinA and rimabotulinumtoxinB were compared in two double-blind, multicenter studies of patients with primary cervical dystonia. In a study by Comella et al, treatment with onabotulinumtoxinA and rimabotulinumtoxinB significantly improved TWSTRS total score from baseline at four weeks; however, no significant difference between the treatment groups was reported (-9.3 vs -10.2, respectively; *P*=0.75). Furthermore, there were no statistically significant differences in TWSTRS subscale scores for severity (*P*=0.90), disability (*P*=0.71) or pain (*P*=0.24) between patients in either treatment group.[38] In a second study, patients receiving onabotulinumtoxinA or rimabotulinumtoxinB experienced statistically significant reductions from baseline in TWSTRS total scores at four weeks (-8.9 and -10.9, respectively; *P*<0.0001 for both). The mean treatment difference between the onabotulinumtoxinA and rimabotulinumtoxinB treatment groups was -2.2 points (90% CI, -4.9 to 0.6), demonstrating non inferiority as the upper limit of the CI (0.6) was below the prespecified non inferiority margin (less than a four point difference between treatments).[39] Costa and colleagues conducted two Systematic Reviews evaluating botulinum toxin A and B in the treatment of idiopathic cervical dystonia. The results demonstrated that patients treated with botulinum toxin A were more likely to experience an improvement on the Tsui scale of at least one point (Peto OR, 8.16; 95% CI, 4.0 to 16.5) or at least three points (Peto OR, 4.25; 95% CI, 2.0 to 9.1) compared to patients treated with placebo.[40] Treatment with 10,000 units of botulinum toxin B significantly improved TWSTRS total score compared to treatment with placebo (weighted mean difference [WMD], -5.92; 95% CI, -9.61 to -2.23); however, the reduction in TWSTRS total score with 500 units of botulinum toxin B was not significantly more effective compared to placebo (WMD, -2.20; 95% CI, -8.44 to 4.04).[41]

OnabotulinumtoxinA has consistently demonstrated statistically significant improvements in symptoms and quality of life for patients with severe primary axillary hyperhidrosis.[47-49] Compared to treatment with aluminum chloride 20%, significantly more patients treated with onabotulinumtoxinA were considered to be treatment responders at 12 weeks (92 vs 33%; *P*<0.001).[51] In a small study comparing botulinum toxin A to botulinum toxin B, patients treated with botulinum toxin B experienced a significantly lower sweat weight and smaller area of sweating compared to botulinum toxin A at all time points (*P*<0.05 for all); however, botulinum toxin B is not approved for this indication.[46]

In patients experiencing symptoms of overactive bladder with urge urinary incontinence (UUI), urgency and frequency, onabotulinumtoxinA treatment significantly reduced the number of urgency episodes, voids and UUI episodes compared to treatment with placebo.[54-56] In a study by Visco et al, women with five or more UUI episodes daily were randomized to receive onabotulinumtoxinA 100 units injected into the detrusor muscle or solifenacin 5 mg daily for up to 12 months. The mean number of daily UUI episodes was reduced by 3.3 episodes in the onabotulinumtoxinA group and by 3.4 episodes in the antimuscarinic group (*P*=0.81). Significantly more patients treated with onabotulinumtoxinA experienced complete resolution of UUI compared to patients treated with solifenacin (27 vs 13%; *P*=0.003). No difference in quality of life was reported between the treatment groups.[58]

OnabotulinumtoxinA is also indicated to treat urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis). In a meta-analysis by Mehta et al, botulinum toxin A significantly improved post void residuals (PVR) compared to control at one month

(standardized mean difference [SMD], 1.119±0.140; 95% CI, 0.844 to 1.394; *P*<0.001), three months (SMD, 0.772±0.135; 95% CI, 0.507 to 1.037; *P*<0.001) and six months (SMD, 0.379±0.169; 95% CI, 0.048 to 0.711; *P*<0.025). One month following injection, the treatment effect represented an actual, average decrease in PVR from 252 to 153mL (99 mL). One month following injection, there was a moderate treatment effect on detrusor pressure with botulinum toxin A injection compared to the control group (SMD, 0.570±0.217; 95% CI, 0.145 to 0.995; *P*=0.009), while a large effect size was seen on urethral pressure (SMD, 0.896±0.291; 95% CI, 0.327 to 1.466; *P*=0.002). The average detrusor pressure decreased from 88.7 to 20.46 cmH_2O, and the urethral pressure improved from 119.7 to 102.3 cmH_2O.[64] In a 36-week study, onabotulinumtoxinA treatment was associated with significantly fewer daily urinary incontinence episodes compared to treatment with placebo (1.3±1.3 vs 4.8±2.9; *P*<0.0001).[62] In a similar study, the mean numbers of weekly urinary incontinence episodes were significantly reduced in patients treated with onabotulinumtoxinA 200 or 300 units compared to placebo (-21.8 and -19.4 vs -13.2 episodes weekly, respectively; *P*<0.01 for both comparisons).[63]

Several systematic reviews and meta-analyses have evaluated the use of botulinum toxin A in the management of adults with upper limb spasticity. Rosales et al reported that the mean change from baseline in Modified Ashworth Scale (MAS) score favored treatment with botulinum toxin A compared to treatment with placebo at four to six weeks following treatment (WMD, 0.87; 95% CI, 0.52 to 1.22). Similarly, patients treated with botulinum toxin A were more likely to achieve a change in MAS score of at least one point following botulinum toxin A treatment compared to treatment with placebo (OR, 4.5; 95% CI, 2.79 to 7.25).[68] Compared to placebo or non-pharmacologic measures, botulinum toxin A significantly improves Disability Assessment Scale (DAS) score (SMD, 0.688; 95% CI, 0.454 to 1.012; *P*<0.0001) and motor function (Action Research Arm Test) scores (SMD, 0.406; 95% CI, 0.85 to 0.73; *P*=0.013) in patients with spasticity. Authors reported that there were no statistically significant improvements in Barthel index scores, a measurement of generalized disability, in patients treated with botulinum toxin A compared to patients treated with placebo (SMD, 0.372; 95% CI, -0.002 to 0.0746; *P*=0.051).[70] In a small study (N=60) comparing onabotulinumtoxinA to tizanidine in patients with spasticity resulting from a prior stroke, onabotulinumtoxinA significantly improved wrist MAS scores from baseline compared to patients treated with tizanidine or placebo (-1.32±0.89 vs -0.22±0.88 and -0.68±1.00, respectively; *P*≤0.08 compared to both). No statistically significant differences in any secondary outcomes were reported with onabotulinumtoxinA compared to tizanidine or placebo with the exception of the cosmetic component of the DAS scale (*P*<0.003).[67]

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Prophylaxis of Headaches in Adult Patients with Chronic Migraine				
Magalhães et al[20] Botulinum toxin A 250 units injected into head and neck muscles vs amitriptyline 25 to 50 mg daily The total number of units to be administered was divided among 15 pre-established points around the head. The choice of the injection points was made based on the location of the sensitive innervations around the head and included areas over the trigeminal, C2 and C3 nerves.	AC, RCT, SC Patients 18 to 60 years of age with chronic daily migraines according to the International Classification of Headache Disorders-II	N=72 3 months	Primary: Reduction of the number of days in pain, reduction in the intensity of pain, reduction in the number of pain drug doses used for migraines, self-assessment of improvement, (patient reported), impression of improvement (physician reported) and adverse events Secondary: Not reported	Primary: There was no statistically significant difference between the botulinum toxin A and amitriptyline groups in the proportion of patients who experienced a reduction ≥50% in the number of days pain was recorded (67.8 vs 73.0%; *P*=0.78). A similar proportion of patients in the botulinum toxin A and amitriptyline groups experienced a ≥50% reduction in VAS pain score (50.0 vs 55.6%, respectively; *P*=0.79). No significant difference was reported between the botulinum toxin A and amitriptyline treatment groups with regard to the reduction in doses of pain drugs administered (77 vs 71%, respectively; *P*=0.76). Physician assessment at the first visit demonstrated an improvement in 88% of patients treated with botulinum toxin A compared to 87% of patients treated with amitriptyline (*P*=1.00). There was no difference between the treatments with regard to the proportions of patients who experienced symptomatic improvements at visits two or three (*P*=0.65 and *P*=0.70, respectively). Weight gain occurred in significantly fewer patients treated with botulinum toxin A compared to patients treated with amitriptyline (11.8 vs 58.3%; *P*=0.0001). Somnolence was less frequent in the botulinum toxin A group compared to the amitriptyline group (4.0 vs 52.7%; *P*=0.0001). Fourteen percent of the botulinum toxin A group and 44% of the amitriptyline group complained of dry mouth (*P*=0.0045). Constipation occurred in 0% of the toxin group and in 38.8% of the amitriptyline group (*P*=0.0001). Secondary: Not reported
Dodick et al[21] OnabotulinumtoxinA 155	2 DB, MC, PC, RCT	N=1,384 24 weeks	Primary: Change in frequency of	Primary: There was a significantly greater reduction in headache days at 24 weeks with onabotulinumtoxinA compared to placebo (-8.4 vs -6.6 days; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
units injected into the head and neck muscles vs placebo The total number of units to be administered was divided among 31 sites across seven specific head/neck muscle areas. At the investigator's discretion, an additional dose <40 units of onabotulinumtoxinA could be administered among three muscle groups (occipitalis, temporalis, or trapezius).	Patients 18 to 65 years of age with migraine headaches occurring ≥15 days per month, headache occurring on ≥15 days over four weeks, each day consisting of at least four hours of continuous headache		headache days at 24 weeks Secondary: Proportion of patients with severe HIT-6 score (≥60), mean changes in frequency of migraine days, frequency of moderate or severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted at least four continuous hours), frequency of migraine episodes (defined as patient-reported migraine headache with a start and stop time indicating that the pain lasted at least four continuous hours), frequency	Secondary: Significantly greater improvements with onabotulinumtoxinA were observed at all time points compared to placebo, starting at the first post treatment study visit (week four) and including week 24, for the following: change from baseline in frequencies of migraine days (P<0.001), moderate or severe headache days (P<0.001), cumulative hours of headache on headache days (P<0.001), headache episodes (P=0.009), migraine episodes (P=0.004) and the proportion of patients with severe (≥60) HIT-6 score (P<0.001). Both treatments were associated with an overall mean reduction in acute pain medication intake; however, there was no statistically significant difference between the treatments (P=0.247). In a post-hoc analysis, there was significantly less use of triptans as acute pain medication at week 24 in the onabotulinumtoxinA group than in the placebo group (P<0.001). Significantly more patients treated with onabotulinumtoxinA had a ≥50% decrease from baseline in the frequency of headache days compared to placebo at 24 weeks (47.1 vs 35.1%; P<0.001). The proportion of onabotulinumtoxinA-treated patients with a ≥50% decrease from baseline in the frequency of headache episodes was only significantly greater compared to placebo at eight weeks (P=0.001). There was a significantly greater improvement in HIT-6 score associated with onabotulinumtoxinA compared to placebo at 24 weeks (P<0.001). OnabotulinumtoxinA treatment also significantly improved QOL (P<0.001) as measured by changes from baseline in MSQ role function domains (restrictive, preventive and emotional).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			of acute headache medication use, proportion of patients who experienced decreases ≥50% in frequency of headache days, migraine days, moderate or severe headache days, headache episodes, and migraine episodes, total cumulative hours of headache on headache days, disease impact on disability in functioning, vitality, psychological distress and QOL parameters	
Aurora et al[22] OnabotulinumtoxinA 155 units injected into the head and neck muscles vs placebo The total number of units to be administered was divided among 31 sites across	2 DB, MC, PC, RCT Patients 18 to 65 years of age with migraine headaches occurring ≥15 days per month, headache occurring on ≥15 days over	N=1,384 56 weeks (24 weeks DB, 32 week OL)	Primary: Change in frequency of headache days at 24 weeks Secondary: Proportion of patients with severe HIT-6 score (≥60), mean changes in frequency of	Primary: There was a statistically significant reduction in the frequency of headache days at week 24 weeks for patients treated with onabotulinumtoxinA compared to placebo (*P*<0.001). At 56 weeks there was a statistically significant reduction in the frequency of headache days for patients treated with onabotulinumtoxinA in both the DB and OL periods compared to patients receiving placebo in the DB period before switching to onabotulinumtoxinA at 24 weeks (*P*=0.019). Secondary: The mean reductions from baseline for all secondary outcomes were significantly greater in patients who received onabotulinumtoxinA in both the DB and OL period compared to patients who received placebo in the DB

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
seven specific head/neck muscle areas. At the investigator's discretion, an additional dose <40 units of onabotulinumtoxinA could be administered among three muscle groups (occipitalis, temporalis, or trapezius).	four weeks, each day consisting of at least four hours of continuous headache		migraine days, frequency of moderate-to-severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted at least four continuous hours), frequency of migraine episodes (defined as patient-reported migraine headache with a start and stop time indicating that the pain lasted at least four continuous hours), frequency of acute headache medication use, proportion of patients who experienced decreases ≥50% in frequency of headache days, migraine days, moderate-to-severe	period before using OL onabotulinumtoxinA with the exception of acute headache medication intake. Statistically significant reductions in triptan use were observed at 24 weeks for patients treated with onabotulinumtoxinA compared to placebo (*P*<0.001). OnabotulinumtoxinA treatment significantly reduced the days of acute headache medication use compared to placebo at 24 weeks (*P*=0.016). During the OL phase, there were significant differences in frequencies of migraine days, moderate to severe headache days and total cumulative hours of headache on headache days at 56 weeks favoring patients treated with 56 weeks of onabotulinumtoxinA treatment compared to patients who received placebo for the first 24 weeks (*P*<0.05 for all). The proportion of patients with a ≥50% decrease from baseline in frequencies of headache days, migraine days, moderate or severe headache day, and total cumulative hours of headache on headache days was significantly higher in patients treated with onabotulinumtoxinA compared to placebo at 24 weeks (*P*<0.001). After all patients were treated with onabotulinumtoxinA, clinically significant improvements were observed in both treatment groups for headache frequency and migraine days, with almost 70% of patients treated with onabotulinumtoxinA throughout the entire study exhibiting ≥50% decrease from baseline in migraine and headache days at the week 56 visit. Treatment with onabotulinumtoxinA significantly reduced mean total HIT-6 score compared to placebo at 24 weeks. There continued to be between-group differences throughout the OL phase; however, the difference was not significant at week 56 (*P*=0.069). A clinically meaningful between-group difference for onabotulinumtoxinA compared to placebo was observed at 24 weeks in the mean change from baseline in total HIT-6 score (*P*<0.001). OnabotulinumtoxinA treatment significantly improved scores for all MSQ role function domains compared to placebo (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			headache days, headache episodes, migraine episodes, total cumulative hours of headache on headache days disease impact on disability in functioning, vitality, psychological distress and QOL parameters	
Blumenfeld et al[23] OnabotulinumtoxinA 100 units injected into the head and neck muscles vs divalproex sodium 250 mg daily Injection sites and dosages were individualized based on patient symptoms and locations of pain and tenderness. Muscle areas were injected using the "follow-the pain" approach.	AC, DB, PRO, RCT, SC Patients 18 to 65 years of age with episodic migraine (at least three migraine headaches but ≤15 days per month) or chronic migraine (migraine headaches on ≥15 days per month) and had stable headache severity and pattern	N=59 10.5 months	Primary: Reduction in headache days per month, responder rate (patients with a ≥50% reduction in attack frequency per month) and overall Headache Index Score Secondary: MIDAS, HIT-6, 24-migraine QOL questionnaire scores and adverse events	Primary: OnabotulinumtoxinA treatment was associated with a significant reduction from baseline in the number of headache days at one (-2.52±0.78; *P*=0.0031), three (-4.22±0.96; *P*=0.0001), three (-6.19±1.14; *P*=0.0001) and nine months (-5.13 ±1.19; *P*=0.0002). Divalproex sodium treatment significantly reduced the number of headache days at one (-2.61±1.19; *P*=0.001), three (-4.87±1.28; *P*=0.0001), six (-5.15±1.25; *P*<0.0001) and nine months (-4.94±1.26; *P*=0.0001 compared to baseline. Patients with chronic migraine who were treated with divalproex sodium experienced significant reductions in the number of days with headache at three (-6.85±1.72; *P*=0.0105), six (-7.49 ±1.60; *P*=0.0055) and nine months (-7.40±1.75; *P*=0.0082). No differences were observed between treatment groups at any time point. The responder rates for patients with episodic migraines were not significantly different between the onabotulinumtoxinA and divalproex sodium treatments at one (18.2 vs 23.8%), three (50.0 vs 52.4%), six (72.7 vs 47.6%) and nine months (68.2 vs 52.4%), respectively (*P* values not reported). For patients with chronic migraines, no significant difference in responder rates was reported at one (0.0 vs 33.3%), three (28.6 vs 50.0%), six (57.1 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				50.0%) or nine months (42.9 vs 50.0%). There were no significant reductions from baseline in headache severity scores for the onabotulinumtoxinA or divalproex sodium groups (*P* value not reported). The composite Headache Index scores decreased significantly from baseline in the onabotulinumtoxinA and divalproex sodium groups at one (-23.0±44.8%; *P*=0.01 for onabotulinumtoxinA and -3.0±152.8%; *P*=0.003 for divalproex sodium), three (-36.5±48.0%; *P*=0.0003 for onabotulinumtoxinA and -21.7±156.1%; *P*=0.0003 for divalproex sodium), six (-35.4±86.7%; *P*=0.0122 for onabotulinumtoxinA and -16.2±156.3%; *P*=0.0016 for divalproex sodium) and nine months (-31.1±82.6%; *P*=0.0197 for onabotulinumtoxinA and -12.5±155.8%; *P*=0.0018 for divalproex sodium). No significant between-group differences were reported. Secondary: Treatment with onabotulinumtoxinA or divalproex sodium significantly improved MIDAS scores from baseline at all time points evaluated with the exception of divalproex sodium at nine months (*P*≤0.0197 for all except divalproex sodium at nine months). There were no significant differences between the treatment groups at any time point. The HIT-6 scores were significantly improved in both treatment groups at six and nine months; however, only the onabotulinumtoxinA group was associated with improvements at one and three months (*P*≤0.03 for all). No significant differences between treatment groups were reported. There were no statistically significant improvements in QOL for patients treated with divalproex sodium at any point evaluated, and onabotulinumtoxinA improved QOL only at month three on the social and energy/vitality domains (*P*=0.027). Significantly fewer adverse events were considered possibly related to treatment in the onabotulinumtoxinA group compared to the divalproex sodium group (50.0 vs 75.8%; *P*=0.04). The most common adverse events in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients treated with onabotulinumtoxinA were eyelid and/or eyebrow drooping (26.7 and 16.7%, respectively), while the most frequently observed adverse events with divalproex sodium treatment were nausea/gastrointestinal discomfort (41.2%), hair loss (17.2%) and fatigue/sleepiness (31.0%).
Mathew et al[24] OnabotulinumtoxinA up to 200 units injected into the head and neck muscles vs topiramate 100 mg daily Patients received 100 units injected into fixed locations and up to an additional 100 units in a "follow the pain" scheme determined at the investigators discretion. Topiramate could be escalated to 200 mg daily after one month at the discretion of the investigator.	AC, DB, RCT, SC Patients 18 to 65 years of age with chronic migraines not attributable to another cause (migraine with/ without aura occurring on ≥15 days per month for more than three months in the absence of medication overuse) and at least two of the following: unilateral location, pulsating quality, moderate or severe pain intensity, and/or aggravation by or causing avoidance of	N=60 9 months	Primary: Treatment responder rate based on PGA Secondary: Change from baseline in number of headache/ migraine days per month, headache/ migraine-free days per month, days on headache medication, and average severity of headache/ migraine episodes per months, HIT-6, MIDAS and MIQ scores	Primary: Most patients in both groups reported "moderate" or "marked" improvements at all time points. No significant differences between the onabotulinumtoxinA and topiramate groups were noted, except for the percentage of patients reporting "marked" improvement at nine months (27.3 vs 60.9% for the onabotulinumtoxinA and topiramate groups, respectively; *P*=0.0234). Secondary: The number of headache/migraine days was significantly decreased from baseline for patients in both the onabotulinumtoxinA and topiramate groups (*P*≤0.01 for both). No differences between groups were noted. The proportion of patients with a ≥50% reduction in the number of headache/migraine days with onabotulinumtoxinA and topiramate, respectively were 38.5 and 22.7% at month three, 58.3 and 31.8% at month six and 40.9 and 42.9% at month nine. The number of headache/migraine-free days per month was significantly increased from baseline in both treatment groups (*P*<0.001 for all). The average severity of headache/migraine, measured on a five-point scale decreased from baseline at three (0.20; *P*=0.0466) six (0.09; *P*=0.4023) and nine months (0.23; *P*=0.0513) in the onabotulinumtoxinA group (In the topiramate group, severity scores decreased by 0.37, 0.50 and 0.44 points from a baseline three, six and nine months, respectively (*P*=0.0506 at three months, *P*=0.0128 at six months and *P*=0.03 at nine months). A significant improvement in MIDAS score from baseline was reported with topiramate (*P*<0.0001) but not onabotulinumtoxinA at three months (*P*=0.0541). At six months, MIDAS scores were improved in both the onabotulinumtoxinA and topiramate groups (*P*=0.0046 and *P*<0.0001,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	routine physical activity			respectively); however, significantly lower MIDAS scores were reported with topiramate compared to onabotulinumtoxinA (*P*=0.0086). No differences in MIDAS scores were reported at nine months. At three months, HIT-6 scores decreased from baseline in both groups (*P*≤0.0114). Improvements in mean HIT-6 scores were also maintained in the onabotulinumtoxinA and topiramate groups at month six (*P*=0.0004 and *P*=0.0097, respectively) and at nine months respectively (*P*<0.0001 and *P*=0.0002). Patient reported QOL measures after treatment with onabotulinumtoxinA paralleled those seen after treatment with topiramate in most respects.
Cady et al[25] OnabotulinumtoxinA up to 200 units injected into the head and neck muscles vs topiramate 100 mg daily Patients received 100 units injected into fixed locations and up to an additional 100 units in a "follow the pain" scheme determined at the investigators discretion. Topiramate could be escalated to 200 mg daily after one month at the discretion of the investigator.	AC, DB, MC, RCT Patients with documented histories of chronic migraines who fulfilled criteria of International Classification of Headache Disorders-II	N=59 12 weeks	Primary: Treatment responder rate based on PGA Secondary: Headache days, headache-free days, MIDAS total score, HIT-6 score and money spent on migraine medications	Primary: There were no statistically significant differences in PGA response rates between patients treated with onabotulinumtoxinA and topiramate at four weeks (60.7 vs 74.0%, respectively; *P*=0.3221). At 12 weeks, 79.2% of the onabotulinumtoxinA group and 70.8% of the topiramate group were considered PGA responders to treatment (*P*=0.9914). Secondary: The mean number of days per month with headache was reduced by three days (from 21.8 18.8) for the onabotulinumtoxinA group compared to 4.4 days (from 20.5 to 16.1) for the topiramate group at week four (*P*<0.05 for both); however, there was no significant difference between groups (*P*>0.05). At 12 weeks, the mean number headache days was reduced by eight days in the onabotulinumtoxinA group and by 8.1 days in the topiramate group (*P*<0.05 for both); however, there was no difference between the groups (*P*>0.05). The increase in the number of headache-free days at four weeks was not significantly different between patients treated with onabotulinumtoxinA and topiramate (3.0 vs 4.4 days; *P*>0.05); however, the increase from baseline was significant in all treatment groups (*P*≤0.05 for all). At 12 weeks, the number of headache-free days increased to eight and 8.1 days with onabotulinumtoxinA and topiramate, respectively (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At 12 weeks, there were statistically significant reductions from baseline in MIDAS scores for both the onabotulinumtoxinA and topiramate treatment groups (*P*<0.05 for both); however, the difference between treatments was not statistically significant. At four weeks, HIT-6 scores were reduced by 4.84 points in the onabotulinumtoxinA group and 5.87 points in the topiramate group (*P*≤0.05); however, the difference between groups was not statistically significant (*P*>0.05). Similar results were reported at 12 weeks. The amount of money spent on prescription drugs over the previous 12 weeks was reduced by $497.60 with onabotulinumtoxinA treatment and by $121.05 with topiramate treatment; however, the difference was not statistically significant (*P* value not reported).
Jackson et al[26] Botulinum toxin A injected into the head and neck muscles (dose not reported) vs prophylactic migraine medications (amitriptyline, methylprednisolone, topiramate and valproate [dose not reported]) vs placebo	MA (31 RCTs) Trials that lasted at least four weeks and evaluated botulinum toxin A treatment for the reduction in frequency or severity of headaches Treatment could be combined with other prophylactic and analgesic medications.	N>5300 At least four weeks	Primary: Headache frequency Secondary: Likelihood of achieving a >50% improvement in chronic migraine headaches and adverse events	Primary: Treatment with botulinum toxin A was associated with a significant reduction in monthly headaches for patients with chronic daily headaches (-2.06 headaches per month; 95% CI, -3.56 to -0.56) and chronic migraines (-2.30 headaches per month; 95% CI, -3.66 to -0.94). Botulinum toxin A treatment did not reduce the number of episodic migraine headaches (0.05 headaches per month; 95% CI, -0.26 to 0.36) or chronic tension type headaches (-1.43 headaches per month; 95% CI, -3.13 to 0.27). In one trial of patients with episodic and chronic tension-type headaches, botulinum toxin A did not significantly reduce headache frequency (3.70 headaches per month; 95% CI, -2.85 to 10.26). Two studies reported outcomes as headache indices rather than headache frequency. In both trials botulinum toxin A treatment was not associated with improvement in the headache indices compared to placebo for chronic tension type headache (SMD, -0.22; 95% CI, -0.51 to 0.07) or episodic migraine (SMD, -0.13; 95% CI, -0.33 to 0.07). Treatment with botulinum toxin A did not reduce headache frequency compared to topiramate (1.4 headaches per month; 95% CI, -2.5 to 1.3) or amitriptyline (2.1 headaches per month; 95% CI, -1.2 to 5.4) for prophylaxis against chronic migraine headaches. Botulinum toxin A did not reduce

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				headache frequency compared to valproate in patients with chronic and episodic migraines (0.84 headaches per month; 95% CI, 1.40 to 3.10) or patients with episodic migraines (0.3 headaches per month; 95% CI, -1.1 to 0.50). Botulinum toxin A significantly reduced average headache severity compared to methylprednisolone in a single trial of patients experiencing chronic tension-type headaches (-2.5 headaches per month; 95% CI, -3.5 to -1.5). Secondary: Botulinum toxin A was associated with a greater likelihood of experiencing a ≥50% reduction in monthly chronic migraines in two studies (RR, 2.21; 95% CI, 1.30 to 3.78). Treatment with botulinum toxin A did not significantly increase the risk of experiencing a ≥50% reduction in monthly headaches in one study of patients with chronic daily headaches (RR, 1.15; 95% CI, 0.91 to 1.45), episodic migraine headaches (two studies: RR, 1.00; 95% CI, 0.85 to 1.18), or chronic tension-type headaches (three studies: RR, 1.00; 95% CI, 0.57 to 1.76). Patients treated with botulinum toxin A were more likely to experience any adverse event compared to those treated with placebo (25 studies: RR, 1.25; 95% CI, 1.14 to 1.36), although they were not more likely to withdraw from the study (23 studies: RR, 1.04; 95% CI, 0.85 to 1.27). Adverse effects more common among patients treated with botulinum toxin A, including blepharoptosis (RR, 9.5; 95% CI, 4.7 to 18.9), muscle weakness (RR, 8.9; 95% CI, 2.5 to 30.9), neck pain (RR, 4.7; 95% CI, 3.2 to 6.9), neck stiffness (RR, 3.2; 95% CI, 1.9 to 5.6), paresthesia (RR, 3.3; 95% CI, 1.3 to 7.9) and skin tightness (RR, 3.6; 95% CI, 1.6 to 8.3).
Treatment of Adults with Blepharospasm Who Were Previously Treated with OnabotulinumtoxinA				
Jankovic et al[27] IncobotulinumtoxinA up to 50 units injected per eye vs	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with bilateral blepharospasm	N=109 Up to 20 weeks	Primary: Change from baseline to six weeks in JRS severity subscore Secondary:	Primary: The mean JRS severity subscore was significantly reduced at six weeks with incobotulinumtoxinA treatment compared to treatment with placebo (-0.83 vs 0.21 points; *P*<0.001). Treatment response rates at six weeks were significantly higher with incobotulinumtoxinA treatment compared to placebo (54.7 vs 14.7%; OR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Dosing was based on previous two doses of onabotulinumtoxinA administered. A new injection was permitted six weeks following the initial injection based on JRS severity subscore of at least two at week six. Concomitant medication for focal dystonia (e.g., antimuscarinics or benzodiazepines) and TCAs or SSRIs were permitted, assuming doses had been stable for ≥12 weeks prior to trial entry.	and a JRS severity subscore of at least two and a documented stable therapeutic response to the last two consecutive injections with onabotulinum-toxinA (<50 units per eye) administered >10 weeks prior to trial entry		Change from baseline to each subsequent visit in JRS severity subscores, change from baseline to six weeks in BSDI and PEGR at the final visit	11.29; 95% CI, 3.23 to 39.42; *P*<0.001). Secondary: There were statistically significant improvements in JRS frequency subscore and total score with incobotulinumtoxinA compared to placebo throughout the study. There was a significant treatment difference in favor of incobotulinumtoxinA for the mean change from baseline in BSDI at six weeks compared to placebo (*P*=0.002). Fifty-one patients (68%) in the incobotulinumtoxinA group and six patients (17.6%) in the placebo group reported an improvement in symptoms by the final visit as assessed by the PEGR scale. Of patients who received treatment with placebo, 35.3% evaluated their symptoms as unchanged and 38.2% reported their symptoms had worsened. The mean therapeutic effect was rated as 1.3 (slight to moderate improvement) for incobotulinumtoxinA compared to -0.6 (unchanged to slightly worsened) for the placebo group (*P*<0.001). Efficacy was rated as "good" or "very good" in 65.3% of patients treated with incobotulinumtoxinA and 23.5% of patients treated with placebo. Twenty-four percent of patients treated with incobotulinumtoxinA were rated as having a "poor" response compared to 67.6% of placebo patients (*P*<0.001).
Roggenkämper et al[28] IncobotulinumtoxinA up to 35 units injected per eye vs onabotulinumtoxinA up to 35 units injected per eye	AC, DB, MC, RCT Patients with a diagnosis of blepharospasm requiring treatment by injection and who had	N=304 16 weeks	Primary: Change from baseline to three weeks in JRS score Secondary: Change from baseline in JRS score at the final	Primary: At three weeks, there was a statistically significant reduction from baseline in JRS score with either incobotulinumtoxinA or onabotulinumtoxinA (-2.83 and -2.65, respectively; *P*<0.0001 for both); however, the difference between the treatment groups was not statistically significant (*P*=0.31). Secondary: At the final visit, the JRS scores remained significantly reduced in both the incobotulinumtoxinA and onabotulinumtoxinA treatment groups (-0.84 and -0.66, respectively; *P*<0.0001 for both); however, the difference between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dosing was based on previous two doses of onabotulinumtoxinA administered. Injection sites were determined based on the pattern received in previous onabotulinumtoxinA injection cycle.	previous exposure to at least two onabotulinum-toxinA injections resulting in a stable therapeutic response		visit, BSDI score at three weeks and final visit and global response to treatment	treatment groups was not statistically significant (*P*=0.27). The BSDI scores were significantly improved from baseline in both treatment groups (*P*<0.0001 for both) with no statistically significant differences between groups (*P*=0.91). Similar BSDI scores were reported between the treatment groups at the final visit (*P*=0.06). Patient evaluation of global response to treatment was significantly improved from baseline in both treatment groups at three weeks (*P*<0.0001 for both); however, there were no statistically significant differences between treatment groups (*P*=0.21). Investigator-assessed efficacy demonstrated a similar response to treatment among patients treated with either incobotulinumtoxinA or onabotulinumtoxinA (*P*=0.14).
Wabbels et al[29] IncobotulinumtoxinA 20 to 45 units injected per eye vs onabotulinumtoxinA 20 to 45 units injected per eye Dosing was based on previous dose of onabotulinumtoxinA administered. Treatment was administered bilaterally in six to 16 injections based on the pattern of injections received in previous onabotulinumtoxinA injection cycle.	AC, DB, PG, RCT Adults with benign essential blepharospasm who received ≥20 units per eye of onabotulinum-toxinA for at least one dose prior to study entry and who required another treatment; patients had a baseline JRS score of more than two	N=65 14 weeks	Primary: Change from baseline to four weeks in total BSDI score Secondary: Change from baseline to eight weeks in total BSDI score, change from baseline to four and eight weeks in the JRS total score and PGA score at four weeks	Primary: There was no statistically significant difference in the reduction from baseline in BSDI total score at four weeks between patients treated with incobotulinumtoxinA or onabotulinumtoxinA (-1.3 vs -2.8; *P*=0.93). Secondary: At eight weeks, there was no statistically significant difference in the reduction from baseline in BSDI total score between patients treated with incobotulinumtoxinA or onabotulinumtoxinA (-0.8 vs -1.3; *P*=0.384). No statistically significant difference in JRS total score was reported in either eye at four or eight weeks between patients who were injected with incobotulinumtoxinA or onabotulinumtoxinA (*P*<0.05 for each eye at both time points). The mean scores on the PGA at four weeks were 2.1 in the incobotulinumtoxinA group compared to 2.6 in the onabotulinumtoxinA group (*P*=0.176). The duration of treatment effect did not differ between groups, with mean and median durations of 13 weeks recorded for both treatment groups (*P*=0.877).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jankovic et al[30] IncobotulinumtoxinA up to 35 units injected per eye vs onabotulinumtoxinA up to 35 units injected per eye Dosing was based on previous two doses of onabotulinumtoxinA administered. Investigators decided the appropriate number of injection sites and the distribution of the dose between these sites; however, most used eight to 10 injection sites.	AC, DB, MC, PC, PG, RCT Patients with blepharospasm	N=304 Up to 16 weeks	Primary: Change from baseline to three weeks in JRS total score Secondary: Change from baseline in the JRS total score at the final visit, change in BSDI score, patient evaluation of global response, assessment of efficacy by the investigator, duration of treatment effect, time to onset of treatment effect and time to waning of treatment effect	Primary: Treatment with incobotulinumtoxinA and onabotulinumtoxinA significantly improved JRS total score at three weeks compared to baseline (-2.90 and -2.67, respectively; *P*<0.0001); however, there was no statistically significant difference between treatment groups (*P* value not reported). Secondary: The mean JRS total scored was reduced with incobotulinumtoxinA and onabotulinumtoxinA at the final visit (-0.84 vs -0.66, respectively); however, the difference between treatments was not significant (*P* value not reported). There was no statistically significant difference between the incobotulinumtoxinA and onabotulinumtoxinA treatment groups with regard to changes in BSDI scores (-0.83 and -0.82, respectively; *P* value not reported). The median onset of treatment effect was four days in both treatment groups (*P*=0.73). The duration of treatment effect was nearly 10 weeks in both treatment groups (*P*=0.58). No differences were reported between the treatment groups with regard to any other outcomes evaluated.
Treatment of Adults with Cervical Dystonia to Reduce the Severity of Abnormal Head Position and Neck Pain Associated with Cervical Dystonia				
Factor et al[31] RimabotulinumtoxinB 10,000 to 25,000 units injected intramuscularly Patients were started with 10,000 units in the first session then increased by up to 5,000 units per session as needed to an optimal dose or a maximum dose of	PRO, OL Patients ≥18 years of age with cervical dystonia for at least one year, a TWSTRS total score ≥20, prior response to botulinum toxin A with	N=34 2.5 years	Primary: Change from baseline to four weeks in TWSTRS total score Secondary: Change from baseline in TWSTRS severity score, ADL score, pain score and	Primary: Treatment with rimabotulinumtoxinB significantly reduced TWSTRS total score compared to baseline at four weeks (*P*<0.001). There was a significant decrease in treatment effectiveness with subsequent treatment sessions (*P*=0.001) The response to treatment was not significantly different among patients who were considered resistant and non-resistant to previous botulinum toxin A treatment (*P*=0.36), nor was the duration of the treatment effect difference between these groups (*P*=0.42). Secondary: RimabotulinumtoxinB treatment significantly improved TWSTRS severity score from baseline (*P*<0.001). There was no significant decrease in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
25,000 units. The decision to increase the dose was based on patient satisfaction, adverse events, concerns for secondary nonresponse, and whether the patient's response had reached a plateau.	either continued response or secondary non-responsiveness; the last injection was at least 16 weeks prior to enrollment		global assessment	treatment effect over time or the number of treatment sessions required with rimabotulinumtoxinB. Previous response to botulinum toxin A did not significantly affect changes in TWSTRS score (*P*=0.57), the effectiveness of treatment in reducing the score from baseline to four weeks (*P*=0.99), or response to treatment with subsequent injections (*P*=0.90). The TWSTRS ADL score was significantly improved from baseline following rimabotulinumtoxinB treatment (*P*<0.001). Despite higher baseline scores in the patients resistant to botulinum toxin A, this had no influence on the effectiveness of the treatment (*P*=0.19) or reduced effectiveness with subsequent injection (*P*=0.38). RimabotulinumtoxinB was associated with a significant reduction from baseline to four weeks in TWSTRS pain subscale scores (*P*<0.001). Patients resistant to botulinum toxin A had significantly higher scores, reflecting more pain compared to patients who were not resistant to treatment (*P*=0.001). Despite the higher TWSTRS pain subscale scores, previous botulinum toxin A response status did not affect the effectiveness of the treatment (*P*=0.58) or the response to subsequent injections (*P*=0.72). Global assessment scores were significantly improved from baseline with rimabotulinumtoxinB treatment (*P*<0.001). The botulinum toxin A resistant group has a significantly lower overall global score compared to patients who were not resistant (*P*=0.026). The rate at which the treatment effect diminished was not statistically significant when stratified by prior botulinum toxin A response status (*P*=0.857).
Chinnapongse et al[32] RimabotulinumtoxinB 10,000 units injected intramuscularly The total number of units to be administered was divided among five sites in each of two to four affected neck	MC, OL, PRO Patients ≥18 years of age with cervical dystonia for at least one year, a baseline TWSTRS total score of ≥20	N=145 12 weeks	Primary: Treatment-emergent adverse events and laboratory evaluations Secondary: Change from baseline in	Primary: No clinically significant changes were noted in laboratory evaluations, vital signs or physical examinations following the injection of each dose compared to baseline. Mild to moderate dry mouth and dysphagia were the most commonly reported adverse event throughout the trial and the incidence of each decreased with subsequent treatments. Dysphagia reported as "severe" occurred in 6% of patients in the study (two patients treated with the 10,000 dose, two patients treated with the 12,500 unit dose and four patients who received the 15,000

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and/or shoulder muscles that were the most affected. Dose escalation for each subject was based on the investigator's assessment of the patient and was to occur when the patient had returned to their baseline. In the second phase, 12,500 units were injected under the same protocol as above, and then subsequently 15,000 units were injected similarly in the third and final phase.	(severity ≥10, disability score of at least three and pain score of at least one) and previously treated with botulinum toxin A		TWSTRS total score at two and four weeks (maximal efficacy) and every four weeks thereafter and VAS pain scale scores	unit dose). Ten serious adverse events were reported; however, none were considered to be related to the study drug. Three serious adverse events occurred following the 10,000 unit dose (psychotic depression, kidney calculus and cellulitis), four patients following the 12,500 unit dose (cholelithiasis, non-Hodgkin's lymphoma, sarcoidosis and gastroenteritis) and three following the 15,000 unit dose (gastrointestinal carcinoma, varicose vein and peptic ulcer). Secondary: Following treatment with all three rimabotulinumtoxinB doses, the mean improvement from baseline in TWSTRS total score after four weeks ranged from -9.6 to -10.6 points. There was a statistically significant improvement from baseline to two, four, eight and 12 weeks (with the exception of disability and pain at week 12 with the rimabotulinumtoxinB 10,000 unit dose) in the TWSTRS total and subscale scores following the administration of each rimabotulinumtoxinB dose ($P \leq 0.0013$ for all time points and scales). Each of the three rimabotulinumtoxinB doses significantly improved VAS pain scale scores at four weeks compared to their baseline values ($P < 0.0001$ for all doses).
Brans et al[33] Botulinum toxin A injected intramuscularly (Dysport®; dose not reported) vs trihexyphenidyl 2 to 24 mg daily	AC, DB, RCT Patients ≥18 years of age with signs and symptoms of idiopathic, mainly focal, cervical dystonia	N=66 12 weeks	Primary: Change in TWSTRS disability score Secondary: Patients experiencing an improvement of at least three points in TWSTRS disability score, change in Tsui scale score, patients experiencing an improvement of at	Primary: There was a significantly greater improvement in TWSTRS disability score for patients treated with botulinum toxin A compared to trihexyphenidyl (-2 vs 0; $P=0.0097$). Secondary: An improvement of at least three points in TWSTRS disability score was observed in significantly more patients treated with botulinum toxin A compared to patients treated with trihexyphenidyl (18.8 vs 42.8%; $P=0.059$). There was a significantly greater improvement in Tsui scale score for patients treated with botulinum toxin A compared to trihexyphenidyl (-5 vs 0; $P=0.0009$). Twelve patients (37.5%) in the trihexyphenidyl group and 23 patients (71.9%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			least three points in Tsui scale score, TWSTRS pain score and MOS-QOL	in the botulinum toxin A group experienced an improvement on the Tsui Scale of at least three points (*P*=0.012). Patients treated with botulinum toxin A experienced greater reductions in TWSTRS pain scores compared to patients treated with trihexyphenidyl; however, the difference was not statistically significant (-3 vs -1; *P*=NS). Botulinum toxin A treatment was associated with a statistically significant improvement on the MOS-QOL scale compared to trihexyphenidyl, which was associated with worsening scores for this outcome (*P*=0.0023). There were significantly fewer adverse events reported in the botulinum toxin A treatment group compared to the trihexyphenidyl treatment group (31 vs 76; *P*<0.0001).
Truong et al (abstract)[34] AbobotulinumtoxinA 500 units injected intramuscularly vs placebo	DB, PC, RCT Patients with cervical dystonia for ≥18 months regardless of previous botulinum toxin treatment status	N=116 12 weeks (Patients completing 12 weeks of DB treatment could enroll in an OL extension study)	Primary: Change from baseline to four weeks in TWSTRS total score Secondary: TWSTRS subscale scores, pain scale scores and subject/ investigator assessments	Primary: Treatment with abobotulinumtoxinA was associated with a significant decrease from baseline (±SE) in TWSTRS total score compared to placebo at four weeks (-15.6±-2.0 vs -6.7±-2.0; *P*<0.001). Significant improvements were sustained through 12 weeks (*P*=0.019). Secondary: Patients treated with abobotulinumtoxinA experienced significant improvements in TWSTRS subscale scores, VAS pain scores and subject/investigator's VAS symptom assessments compared to patients treated with placebo (*P* values not reported).
Truong et al[35] AbobotulinumtoxinA 500 units injected intramuscularly vs placebo	DB, MC, PC, PG, RCT Patients with cervical dystonia who reported symptoms for ≥18 months Patients	N=80 Up to 20 weeks	Primary: Change from baseline to four weeks in TWSTRS total score Secondary: Pain scale scores and patient assessment of	Primary: There was a significantly greater reduction from baseline in TWSTRS total score at four weeks with abobotulinumtoxinA treatment compared to placebo (-9.9 vs -3.9; *P*≤0.013). Statistically significant improvements with abobotulinumtoxinA compared to placebo were sustained through 12 weeks (-5.8 vs -1.6; *P*≤0.02). Secondary: The ratings for pain on the VAS scale decreased by 13.4 mm at four weeks in the abobotulinumtoxinA group compared to a decrease of 1.9 mm in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Muscle relaxants and benzodiazepines were permitted if the dose had been stable for six weeks prior to study entry and was expected to remain stable. A short course of such medication was allowed if required for patient care during the study.	previously treated with botulinum toxin A or botulinum toxin B were excluded unless it had been ≥16 weeks since their previous injection.		signs and symptoms at four weeks	placebo group (*P*≤0.02). Significant improvements in pain associated with abobotulinumtoxinA were sustained through eight weeks (*P*=0.025). Patient assessments of signs and symptoms of cervical dystonia were significantly improved at four (*P*<0.001), eight (*P*=0.002) and 12 weeks (*P*=0.022) with abobotulinumtoxinA treatment compared to placebo. Similar results were reported for the investigator's assessment of improvement (*P* values not reported).
Comella et al[36] IncobotulinumtoxinA 120 units injected intramuscularly vs incobotulinumtoxinA 240 units injected intramuscularly vs placebo The number of injection sites per muscle was at the discretion of the investigator. Subjects taking medications for focal dystonia (e.g., antimuscarinics and benzodiazepines) were required to be on a stable dose for at least three	DB, MC, PC, PRO, RCT Patients 18 to 75 years of age with primary cervical dystonia with predominantly rotational form, baseline TWSTRS total score ≥20 and TWSTRS subscale scores as follows: severity ≥10, disability at least three, and pain at least one; treatment naïve and experienced patients to botulinum toxin were included if they had	N=233 Up to 20 weeks	Primary: Change from baseline to four weeks in TWSTRS total score Secondary; Change from baseline to four and eight weeks and final visit for the TWSTRS subscales of severity, disability, and pain, change from baseline eight weeks and final visit for TWSTRS total score, PEGR and IGAE	Primary: Treatment with 120 or 240 units of incobotulinumtoxinA was associated with a statistically significant reduction from baseline in TWSTRS total score at four weeks compared to treatment with placebo (-9.9±10.4 and -10.9±11.7 vs -2.2±7.3, respectively; *P*<0.001 for both). Secondary: The reduction in TWSTRS motor severity subscale score from baseline was significantly greater with either dose of incobotulinumtoxinA compared to placebo at four and eight weeks as well as the final visit (*P*<0.05 for all). Statistically significant improvements in TWSTRS disability subscale scores occurred with either dose of incobotulinumtoxinA compared to placebo at four and eight weeks as well as the final visit (*P*≤0.001 for all). Both doses of incobotulinumtoxinA significantly reduced TWSTRS pain subscale scores from baseline compared to placebo at all time points evaluated (*P*<0.001 for all). There continued to be a significantly greater reduction from baseline in TWSTRS total score with 120 or 240 units of incobotulinumtoxinA compared to placebo at eight weeks (-6.9±11.2 and -8.2±10.5 vs 0.4±7.2, respectively; *P*<0.001 for both) and at the final visit (-3.6±8.1 and -4.6±7.5 vs 1.7±6.2, respectively; *P*<0.001). There were significant improvements in PEGR for patients treated with 120 or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
months prior to and throughout the trial.	received no more than 300 units of botulinum toxin A or 12,000 units botulinum toxin B and the previous injection was at least 10 weeks prior to entry			240 units of incobotulinumtoxinA compared to placebo (*P*<0.001 for both). The most frequent treatment response category selected in the 120 and 240 unit groups was "marked improvement", while the most frequently used category in the placebo group was "unchanged". No difference was observed between the 120 and 240 unit groups (*P*=0.930). The mean IGAE score was 2.5 in the 120 incobotulinumtoxinA group and 2.3 in the 240 unit incobotulinumtoxinA group, which corresponds with a "good" overall response. In the placebo group, the mean score was 3.6, corresponding to a "poor to moderate" response. Investigators classified the therapeutic efficacy of the 120 and 240 unit incobotulinumtoxinA doses as "very good" (26.9 and 35.8%, respectively) or "good" (24.4 and 21%, respectively). In the placebo group, the investigator classified the global assessment of efficacy as "poor" in 70% of subjects.
Benecke et al[37] IncobotulinumtoxinA 70 to 300 units injected intramuscularly vs onabotulinumtoxinA 70 to 300 units injected intramuscularly Dosing was based on previous doses of onabotulinumtoxinA administered.	AC, DB, MC, PG, RCT Patients with cervical dystonia predominantly of rotational form with a stable previous therapeutic response to onabotulinum-toxinA and a TWSTRS severity score of ≥10, a rotation score of at least two, and a rotation score higher than the score for laterocollis and	N=463 16 weeks	Primary: Change from baseline to four weeks in TWSTRS total score Secondary: TWSTRS severity score at final visit, TWSTRS pain subscore, VAS pain score, treatment responder rate (improvement of ≥20% in the TWSTRS severity score) and the investigator's global assessment of efficacy at the	Primary: The mean reduction from baseline to four weeks in TWSTRS total score was -11 points in both treatment groups (*P* value not reported). Secondary: At the final visit, both incobotulinumtoxinA and onabotulinumtoxinA treatments improved TWSTRS severity score from baseline (-1.8 for each; *P*<0.0001 for both); however, there was no significant difference between the treatments (*P*=0.7378). At four weeks, the TWSTRS pain subscale scores were significantly reduced from baseline for patients receiving incobotulinumtoxinA or onabotulinumtoxinA (-0.4 and -0.6, respectively; *P*<0.001 for both). The difference between groups was not significant (*P*=0.4082). At the final visit, only the onabotulinumtoxinA group experienced a significant reduction from baseline in TWSTRS pain subscale score (*P*=0.0032); however, there was no significant difference between treatment groups (*P*=0.0983). Patients treated with incobotulinumtoxinA and onabotulinumtoxinA experienced statistically significant improvements from baseline in VAS pain

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	retrocollis		final visit	scores at four weeks (-8.8 and -11.7, respectively, *P*<0.0001 for both); however, there was no statistically significant differences between the treatment groups (*P*=0.2892). At the final study visit, only the onabotulinumtoxinA treatment group continued to have significant improvements from baseline in VAS pain scores (*P*=0.0019); however, no significant difference between the treatment groups was reported (*P*=0.0648). There were no statistically significant differences between the incobotulinumtoxinA and onabotulinumtoxinA treatment groups with regard to any other outcomes.
Comella et al[38] OnabotulinumtoxinA 250 units injected intramuscularly vs rimabotulinumtoxinB 10,000 units injected intramuscularly Muscle selection, dosing into each muscle, number of injection sites and use of EMG were at the discretion of the injecting physician.	AC, DB, MC, RCT Patients ≥18 years of age with primary cervical dystonia for at least one year with moderate severity (baseline TWSTRS total score ≥20 and TWSTRS motor severity subscale score ≥15) with previous successful onabotulinum-toxinA treatment (≥30% benefit)	N=139 Up to 20 weeks	Primary: Change from baseline to four weeks in TWSTRS total score, duration of clinical effect (time in days until the target TWSTRS was reached) and adverse events Secondary: Change in TWSTRS subscale scores (motor severity, pain and ADL) PGA and SGA at four weeks	Primary: Treatment with onabotulinumtoxinA or rimabotulinumtoxinB was associated with a significant reduction from baseline in TWSTRS total score at four weeks (-9.7; *P*<0.0001). There was no significant difference between treatment groups (-9.3 vs -10.2, respectively; *P*=0.75). When all treated subjects were included, the median duration of effect of onabotulinumtoxinA and rimabotulinumtoxinB did not differ (13 vs 11.7 weeks, respectively; *P*=0.095). When patients who experienced improvements by four weeks were separately analyzed, the median duration of effect was 14 weeks for patients treated with onabotulinumtoxinA and 12.1 weeks for patients treated with rimabotulinumtoxinB (*P*=0.033). Patients in the rimabotulinumtoxinB group had an increase in frequency and severity of dysphagia and dry mouth following treatment. The incidence of dry mouth and dysphagia were correlated (*P*=0.40 and *P*<0.0001). Adverse events reported included muscle weakness (N=14), back pain (N=14), upper respiratory tract infection (n=14), headache (N=12), hypertonia (N=9) and dyspepsia (N=9). No deaths were reported. Secondary: At four weeks, there were no statistically significant differences between the onabotulinumtoxinA and rimabotulinumtoxinB treatment groups with regard to TWSTRS subscale scores for severity (*P*=0.90), disability (*P*=0.71) or pain (*P*=0.24).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significant improvements on the PGA and SGA scales were reported for patients in the onabotulinumtoxinA and rimabotulinumtoxinB treatment groups at four weeks (*P*<0.05 for both).
Pappert et al[39] OnabotulinumtoxinA 150 units injected intramuscularly vs rimabotulinumtoxinB 10,000 units injected intramuscularly The total number of units to be administered was divided and injected into two to four affected neck and/or shoulder muscles in up to five sites.	AC, DB, MC, NI, RCT Patients ≥18 years of age with cervical dystonia for at least six months, a TWSTRS total score of ≥20 (severity ≥10, disability at least three and pain at least one)	N=111 Mean of 13 weeks	Primary: Change from baseline to four weeks in TWSTRS total score Secondary: Change from baseline to four weeks in TWSTRS subscale scores, VAS pain score, investigator and patient global VAS assessments	Primary: Patients treated with onabotulinumtoxinA or rimabotulinumtoxinB experienced statistically significant reductions from baseline in TWSTRS total score at four weeks (-8.9 and -10.9, respectively; *P*<0.0001 for both). The mean treatment difference between onabotulinumtoxinA and rimabotulinumtoxinB was -2.2 points (90% CI, -4.9 to 0.6). The upper limit of the CI (0.6) was below the non inferiority margin (less than a four point difference between treatments), thus demonstrating non inferiority for onabotulinumtoxinA compared to rimabotulinumtoxinB. Secondary: There were similar improvements in TWSTRS subscale scores at four weeks with onabotulinumtoxinA and rimabotulinumtoxinB with regard to severity score (LS mean difference, -0.7; 90% CI, -2.0 to 0.6), disability score (LS mean difference, -0.5; 90% CI, -1.7 to 0.8) and pain score (LS mean difference, -1.0; 90% CI, -2.0 to 0.1). Four weeks after treatment 85% of patients treated with onabotulinumtoxinA demonstrated improvement in TWSTRS total score compared to 93% of rimabotulinumtoxinB-treated patients (*P*=0.316). The median duration of effect was 13.1 and 13.7 weeks for the onabotulinumtoxinA and rimabotulinumtoxinB groups, respectively (HR, 0.95; 95% CI, 0.56 to 1.59).
Costa et al[40] Botulinum toxin A injected intramuscularly (Botox® or Dysport®; dose not reported) vs placebo	SR (13 RCTs) Patients with idiopathic cervical dystonia who were receiving treatment with botulinum toxin	N=361 Up to 16 weeks	Primary: Improvement in symptomatic rating scales Secondary: Changes in subjective evaluation of	Primary: Patients treated with botulinum toxin A were more likely to experience an improvement on the Tsui scale of at least one point (Peto OR, 8.16; 95% CI, 4.0 to 16.5; NNT, 3) or at least three points (Peto OR, 4.25; 95% CI, 2.0 to 9.1; NNT, 4) compared to placebo treatment. Moreover, botulinum toxin A treatment was associated with significantly greater odds of experiencing any improvement on the Tsui scale compared to placebo (Peto OR, 5.47; 95% CI, 3.5 to 8.5; NNT, 3).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Intramuscular injections of all administration schedules and injection techniques were allowed.	A or placebo		clinical status both by patients and clinicians, pain scores, QOL, deterioration and adverse events	Secondary: There was a greater improvement in clinical status as evaluated by both the physician (Peto OR, 4.2; 95% CI, 2.7 to 6.4; NNT, 3) and patient (Peto OR, 6.6; 95% CI, 4.6 to 9.5; NNT, 3) associated with botulinum toxin A treatment compared to placebo. Treatment with botulinum toxin A significantly improved pain scores in patients with idiopathic cervical dystonia compared to patients receiving placebo (Peto OR, 11.9; 95% CI, 6.2 to 22.5; NNT, 2). The odds of experiencing no improvement or deterioration were significantly lower with botulinum toxin A compared to placebo with regard to physician rating (Peto OR, 0.25; 95% CI, 0.16 to 0.41) and patient ratings (Peto OR, 0.17; 95% CI, 0.11 to 0.25). Botulinum toxin A treatment significantly increased the odds of experiencing an adverse event compared to placebo treatment (Peto OR, 2.1; 95% CI, 1.5 to 3.4; NNH, 6). Neck weakness (Peto OR, 4.9; 95% CI, 2.6 to 9.3), dysphagia (Peto OR, 3.9; 95% CI, 2.2 to 7.2), dry mouth/sore throat (Peto OR, 2.5; 95% CI, 1.4 to 4.6) were more likely to occur with botulinum toxin A compared to placebo. Indirect comparisons between trials that used Botox® against placebo and trials that used Dysport® against placebo showed no significant differences between treatments in terms of clinical benefits or adverse events.
Costa et al[41] Botulinum toxin B injected intramuscularly (dose not reported) vs placebo	SR (3 RCT) Patients with idiopathic cervical dystonia who were receiving treatment with botulinum toxin B or placebo	N=308 Up to 16 weeks	Primary: Improvement in symptomatic rating scales Secondary: Changes in subjective evaluation of clinical status both by patients and	Primary: Treatment with 10,000 units of botulinum toxin B significantly improved TWSTRS total score compared to treatment with placebo (WMD, -5.92; 95% CI, -9.61 to -2.23); however, the reduction in TWSTRS total score with 5,000 units of botulinum toxin B was not significantly more effective compared to placebo (WMD, -2.20; 95% CI, -8.44 to 4.04). Botulinum toxin B significantly reduced TWSTRS pain score compared to placebo (WMD, -3.70; 95% CI, -5.64 to -1.76); however there was no significant improvement in scores with regard to symptom severity (WMD, -2.10; 95% CI, -4.39 to 0.19) or disability (WMD, -1.60; 95% CI, -3.77 to 0.57).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			clinicians, pain scores, QOL, deterioration and adverse events	Compared to placebo, botulinum toxin B significantly increased the likelihood of achieving a ≥20% improvement in TWSTRS total score (Peto OR, 4.69; 95% CI, 2.06 to 10.69), symptom severity score (Peto OR, 3.18; 95% CI 1.39 to 7.24), disability score (Peto OR, 4.10; 95%CI, 1.80 to 9.34) and pain score (Peto OR, 3.48; 95% CI, 1.49 to 8.13). Secondary: Patients treated with botulinum toxin B experienced statistically significant improvements in PGA scores regardless of whether they received a dose of 5,000 units (WMD, 17.00; 95% CI, 6.93 to 27.07) or 10,000 units (WMD, 20.84; 95% CI, 14.22 to 27.45). Patients treated with botulinum toxin B experienced statistically significant improvements in IGA scores compared to placebo regardless of whether dose received (WMD, 13.30; 95% CI, 5.10 to 21.50) or 10,000 units (WMD, 12.52; 95% CI, 7.97 to 17.08). There were significant improvements in pain assessment scores for patients receiving 5,000 units (WMD, 18.00; 95% CI, 5.69 to 30.31) or 10,000 units (WMD, 19.63; 95% CI, 11.69 to 27.56) of botulinum toxin B compared to placebo. Adverse events were generally transient and either mild or moderate. Dry mouth and dysphagia were significantly more common with botulinum toxin B compared to placebo. Patients considered to be resistant or a nonresponder to botulinum toxin A were significantly more likely to experienced an improvement in TWSTRS total score with botulinum toxin B treatment compared to placebo (Peto OR, 7.35; 95% CI, 1.60 to 33.78). Similarly, previous responders to botulinum toxin A were more likely to experience improvement in TWSTRS total score with botulinum toxin B compared to placebo (Peto OR, 3.90; 95% CI, 1.46 to 10.37).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Strabismus and Blepharospasm Associated with Dystonia, Including Benign Essential Blepharospasm or VII Nerve Disorders				
Rowe et al[42] Botulinum toxin A injected intramuscularly (Botox® or Dysport®; dose not reported) vs strabismus surgery vs conservative treatment	SR (4 RCTs) Patients of all ages who were to receive botulinum toxin for the treatment of strabismus to align the angle of deviation	N=186 Not reported	Primary: Improved ocular alignment (reduction in the angle of deviation measured by prisms or the synoptophore) Secondary: Achievement of binocular single vision (assessed by cover test, motor fusional vergences and stereoacuity) and adverse events	Primary: Results were not comparable across the trials due to different conditions being targeted by each trial plus the different types and doses of botulinum toxin A used in each trial. A reduction in angle of deviation using botulinum toxin A to within 10 PD was achieved in all trials, ranging from 29.4 to 95.5%. The lowest percentage was achieved in a strabismus condition that did not have binocular potential and this was significantly different from the reduction in angle of deviation achieved by surgery in this trial. The highest percentage was achieved in an ocular motility condition in which all patients had binocular potential. The reduction in angle of deviation achieved using botulinum toxin A in three trials where patients had binocular potential showed no significant difference to the reduction in angle of deviation achieved by strabismus surgery (OR, 0.48; 95% CI, 0.23 to 1.00) or by observation or conservative treatment (OR, 5.25; 95% CI, 0.56 to 48.95). Secondary: The achievement of binocular single vision was not comparable among studies due to differences in the condition being treated and use of botulinum toxin A (Botox® or Dysport®). Full control of the ocular deviation (measurement within 10 PD and with normal binocular single vision) was evaluated in one trial and was achieved in 86% of patients treated with botulinum toxin A compared to 80% of patients with sixth nerve palsy who received conservative treatment (OR, 5.25; 95% CI, 0.56 to 48.95). In two studies there was no difference in the occurrence of full control of the ocular deviation between patients treated with botulinum toxin A and those who received strabismus surgery (OR, 0.73; 95% CI, 0.33 to 1.61). Transient ptosis was reported in 9.00 to 37.03% of patients and transient vertical deviation occurred in 17.39 to 18.51% of patients. The overall

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				complication rate ranged from 27.00 to 55.54%. The overall complication rate was 24% per injection. No other adverse outcomes were reported. The duration of transient ptosis or vertical deviation was not stated. There were no adverse outcomes stated in any of the three trials relating to the strabismus surgery.
Nüssgens et al[43] AbobotulinumtoxinA injected intramuscularly (mean dose 182.1 units) vs onabotulinumtoxinA injected intramuscularly (mean dose of 45.4 units)	AC, DB, RCT, XO Patients with essential blepharospasm who had previously received treatment with botulinum toxin	N=212 Duration not reported	Primary: Duration of treatment and adverse events Secondary: Not reported	Primary: The effect of onabotulinumtoxinA lasted 7.98±3.8 weeks compared to 8.03±4.6 weeks with abobotulinumtoxinA (*P*=0.42). Adverse events (ptosis, tearing, blurred vision, double vision, hematoma and foreign body sensation) were observed in 36/212 patients (17.0%) receiving onabotulinumtoxinA and in 51/212 patients (24.1%) receiving abobotulinumtoxinA. Ptosis was observed with onabotulinumtoxinA in three cases (1.4%) and with abobotulinumtoxinA in 14 cases (6.6%). The total number of adverse events was significantly lower with onabotulinumtoxinA compared to abobotulinumtoxinA (*P*<0.05). The rate ptosis occurrence was significantly lower with onabotulinumtoxinA (*P*<0.01). Secondary: Not reported
Bihari et al[44] AbobotulinumtoxinA injected intramuscularly (mean dose 120 to 654 units depending on condition) vs onabotulinumtoxinA injected intramuscularly (mean dose 30 to 131 units depending on condition) Patients were converted from abobotulinumtoxinA to	AC, DB, RCT, XO Patients with a diagnosis of blepharospasm, cervical dystonia or hemifacial spasm stabilized on Dysport® with no known hypersensitivity to any component of the formulation	N=48 24 weeks	Primary: Change from baseline in TWSTRS score, JRS score, patient self-assessment and duration of treatment effect Secondary: Not reported	Primary: There were significantly greater improvements in JRS and TWSTRS scores with onabotulinumtoxinA compared to abobotulinumtoxinA for blepharospasm (*P*<0.006) and cervical dystonia (*P*<0.011). Patients using a self-assessment scale for hemifacial spasm reported significantly greater improvements with onabotulinumtoxinA treatment compared to abobotulinumtoxinA treatment (*P*<0.009). A significantly longer duration of effect was reported with onabotulinumtoxinA compared to abobotulinumtoxinA for treatment of blepharospasm (62.2 vs 47.4 days; *P*=0.001), cervical dystonia (64.3 vs 44.6 days; *P*=0.014), and hemifacial spasm (65.1 vs 41.8 days; *P*<0.014). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
onabotulinumtoxinA based on a conversion ratio of 4:1 or 5:1 depending on the condition being treated.				
Costa et al[45] Botulinum toxin A injected intramuscularly (dose not reported) vs placebo	SR (13 trials) Trials evaluating botulinum toxin A for the treatment of blepharospasm	N=Not reported Duration not reported	Primary: Improvements in symptomatic rating scales, changes in subjective evaluation of clinical status both by patients and clinicians, QOL and adverse events Secondary: Not reported	Primary: All studies reviewed were excluded from analysis because their methods did not match the criteria for inclusion. The results of the individual studies evaluated are described below. One double-blind study enrolled eight patients with blepharospasm to receive botulinum toxin A in one eye and placebo in the contralateral eye. The primary outcome was an electrophysiological measurement of impairment and not clinical benefit. In another study of 12 patients with blepharospasm, patients received botulinum toxin A or placebo. Of the 12 patients, four received placebo without improvement and 11 received botulinum toxin A with 72% improvement over baseline on the severity rating score, 61% on the self-assessment score, and 29% on the videotape score. Compared to baseline disability scores, these patients had a mean peak effect at 3.7 days and a mean duration of improvement of 12.5 weeks. Six of eleven patients had blurred vision, five had tearing, three had bruising, two had ptosis and one had diplopia following botulinum toxin A injection. One of four patients had bruising after placebo injections. Twenty six patients with essential blepharospasm patients were randomized to receive botulinum toxin A or placebo. Five patients were botulinum toxin A naïve. All patients received botulinum toxin A in the upper eyelids and only the lower eyelids were randomized to botulinum toxin A or placebo. The primary outcome was unclear, but likely the patient's subjective opinion about spasm relief. Thirteen of 15 patients who received placebo in their lower eyelids experienced relief of spasm, with the same spasm-free interval as those who received botulinum toxin A. In a prospective case series of 101 patients with hemifacial spasm, it was not clear if any patients had previously received botulinum toxin A. The report gave no clear data comparing the botulinum toxin A to placebo and the mean doses were not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In another study, patients received botulinum toxin A in one eye and placebo in the other eye. The primary outcome was neurophysiological changes and this was not an efficacy study. Two trials compared different botulinum toxin A formulations (Botox® and Dysport®) in patients with blepharospasm and hemifacial spasm. No placebo group was included and similar clinical efficacy between the two treatment groups was reported when given in a 4:1 conversion ratio (Dysport®: Botox®). Various studies compared the treatment with botulinum toxin A to botulinum toxin F in patients with blepharospasm; however, no botulinum toxin F products are currently approved in the United States. Secondary: Not reported
Treatment of Severe Primary Axillary Hyperhidrosis				
Frasson et al[46] Botulinum toxin A 50 units injected into one axilla vs botulinum toxin B 2,500 units injected in contralateral axilla The total number of units to be administered was divided among 20 injections into each axilla.	AC, RCT, SB Patients with idiopathic focal axillary hyperhidrosis since childhood unresponsive to other nonsurgical treatments	N=10 6 months	Primary: Sweat production rates, area of sweating and patient satisfaction with treatment Secondary: Not reported	Primary: Patients treated with botulinum toxin B experienced a significantly lower sweat weight compared to treatment with botulinum toxin A at one (*P*=0.01) and two weeks (*P*=0.04) and one (*P*=0.049), three (*P*=0.03) and six months (*P*=0.02) following injection. Treatment with botulinum toxin B was associated with a significantly smaller area of sweating compared to treatment with botulinum toxin A at one (*P*=0.049) and two weeks (*P*=0.04) and one (*P*=0.047), three (*P*=0.02) and six months (*P*=0.002) following injection. Patients who received an injection of botulinum toxin B reported significantly higher treatment satisfaction scores compared to patients receiving botulinum toxin A at all time points (*P*<0.05 for all) with the exception of six months (*P*=0.78). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Naumann et al[47] OnabotulinumtoxinA 50 units injected into each axilla vs placebo The total number of units to be administered was divided among 10 to 15 injections into each axilla.	DB, MC, PC, RCT Patients 18 to 75 years of age with idiopathic persistent bilateral primary axillary hyperhidrosis that interfered with daily activities and who had spontaneous sweat production in each axilla of ≥50 mg, measured over five minutes at room temperature and at rest	N=320 16 weeks	Primary: Proportion of treatment responders at four weeks (a ≥50% reduction in axillary sweating from baseline) Secondary: Proportion of treatment responders at 16 weeks, change in the size of the sweat-producing area and subject global assessment of treatment satisfaction	Primary: There was a significantly greater proportion of treatment responders in the onabotulinumtoxinA group compared to the placebo group at four weeks (94 vs 36%; *P*<0.001). Secondary: Significantly more patients continued to be treatment responders at 16 weeks following treatment with onabotulinumtoxinA compared to placebo (82 vs 21%; *P*<0.001). There was a significantly greater reduction in sweat production with onabotulinumtoxinA at four (-83.5 vs -20.8%; *P*<0.001) and 16 weeks (-69.3 vs -3.8; *P*<0.001) compared to placebo. The absolute sweat production was significantly lower following onabotulinumtoxinA treatment compared to placebo treatment at four (28.1 vs 153.0 mg; *P*<0.001) and 16 weeks (53.7 vs 190.5 mg; *P*<0.001). OnabotulinumtoxinA was associated with a significantly smaller area of sweat production at four (0.2 vs 4.5 cm; *P*<0.001) and 16 weeks (0.2 vs 2.3 cm; *P*<0.001) compared to the placebo group. Treatment satisfaction scores were significantly higher at four (3.3 vs 0.8; *P*<0.001) and 16 weeks (2.6 vs 0.3; *P*<0.001) for patients treated with onabotulinumtoxinA compared to placebo (*P*<0.001).
Naumann et al[48] OnabotulinumtoxinA 50 units injected into each axilla vs placebo The total number of units to be administered was divided	DB, MC, PC, RCT Patients 18 to 75 years of age with idiopathic persistent bilateral primary axillary hyperhidrosis that interfered	N=207 16 months	Primary: Proportion of treatment responders at four weeks (a ≥50% reduction in axillary sweating from baseline) Secondary: Percentage change	Primary: At four weeks, the treatment response rate was 96.1% for patients receiving onabotulinumtoxinA compared to 34.7% of patients who received placebo (*P* value not reported). Secondary: The change from baseline in sweat production was significant for both the onabotulinumtoxinA and placebo groups at four weeks (-84.6±18.2 and -19.1±54.0; *P*≤0.01 for each). At 16 weeks, only the onabotulinumtoxinA group sustained significant reductions in sweat production compared to baseline (-69.7±37.5; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
among 10 to 15 injections into each axilla.	with daily activities and who had spontaneous sweat production in each axilla of ≥50 mg, measured over five minutes at room temperature and at rest		from baseline in sweat production, mean duration of effect (time between treatments), change in the size of the sweat-producing area, subject global assessment of treatment satisfaction, antibody development and QOL	A prolonged treatment effect was observed following each onabotulinumtoxinA treatment, with an overall duration of 30.6 weeks between onabotulinumtoxinA treatments. Treatment with onabotulinumtoxinA was associated with a statistically significant reduction from baseline in the area of sweating at both four and 12 weeks (*P*<0.001 for both). Moreover, the overall area of sweating continued to be significantly reduced from baseline following all subsequent treatment cycles (*P*<0.001 for all). The placebo group experienced a reduction in the sweating area from baseline at 16 weeks (*P*<0.001) but not four weeks (*P*=0.28). Patients treated with onabotulinumtoxinA had mean satisfaction scores of 3.5 at four weeks demonstrating marked improvement, while the satisfaction score in the placebo group was 1.4 (*P* values not reported). Of the patients enrolled in the study, only one had possible seroconversion from negative to positive for neutralizing antibodies after 16 months of treatment, despite experiencing a treatment response with onabotulinumtoxinA. OnabotulinumtoxinA treatment was associated with higher QOL scores and satisfaction with current treatment compared to the placebo treatment group at all time points (*P* values not reported).
Lowe et al[49] OnabotulinumtoxinA 50 units injected into each axilla vs onabotulinumtoxinA 75 units injected into each axilla vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with persistent bilateral primary axillary hyperhidrosis, a HDSS score of three or four	N=322 52 weeks	Primary: Proportion of treatment responders, (at least a two point improvement from baseline HDSS score at four weeks or who had a sustained response after their first	Primary: The proportion of treatment responders was significantly greater with onabotulinumtoxinA compared to placebo (*P*<0.001), with no significant difference between the two onabotulinumtoxinA groups. Forty-nine (54/110), 55 (57/104) and 6% (6/108) of subjects in the 50 and 75 unit and placebo groups, respectively, were treatment responders. Secondary: A significantly greater proportion of onabotulinumtoxinA-treated patients had at least a two point improvement in HDSS score from baseline four weeks after their first treatment (75% in both groups) compared to 25% of patients in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo The total number of units to be administered was divided among 10 to 15 injections into each axilla.	and a baseline gravimetric measurement of spontaneous resting sweat production in each axilla of at least 50 mg, measured over five minutes at room temperature		treatment session and did not receive re-treatment during the 52-week study) Secondary: Proportion of subjects with an improvement of at least two points on the HDSS score four weeks after each treatment session, proportion of patients reporting an HDSS score of one, percent reduction from baseline in gravimetric measurement, duration of effect and DLQI score	the placebo group (*P*<0.001). A significantly greater proportion of onabotulinumtoxinA-treated patients reported complete resolution of symptoms (HDSS score of zero) compared to patients treated with placebo (42 and 48 vs 9% of patients treated with 50 or 75 units of onabotulinumtoxinA and placebo, respectively; *P*<0.01). The administration of onabotulinumtoxinA resulted in a significantly greater decrease in axillary sweat production compared to placebo after four weeks (82 and 87 vs 33% in the onabotulinumtoxinA 50 and 75 unit groups compared to the placebo group, respectively; *P*<0.001). Similar results were reported among the treatment groups for sweat measurements following the second dose. The improvements in DLQI score were significantly greater in patients treated with 50 or 75 units of onabotulinumtoxinA compared to patients treated with placebo at all time points (*P*<0.001 for all).
Talarico-Filho et al[50] AbobotulinumtoxinA 150 units injected into one axilla vs onabotulinumtoxinA 50 units injected into contralateral axilla The total number of units to	AC, DB, RCT Patients 19 to 56 years of age presenting with sweating ≥50 mg/minute by gravimetric measurements who also had some degree of social and	N=10 1 year	Primary: Change from baseline in sweat quantity at one month, duration of treatment effect and treatment response rate Secondary: Not reported	Primary: The sweat quantity was significantly reduced from baseline for patients treated with either abobotulinumtoxinA or onabotulinumtoxinA at one month (97.7 vs 99.4%, respectively; *P*=NS). Three months after the beginning of treatment, two patients experienced a sweat production that remained higher than 50% of baseline values. The duration of injection benefits observed was similar between the treatment groups, with a mean of 290 days for patients treated with abobotulinumtoxinA (range 90 to 360 days) and 260 days for onabotulinumtoxinA (range, 90 to 360 days), with no significant difference between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
be administered was divided among 20 injections into each axilla.	psychological restriction due to the increased sweating			The longest symptom-free interval recorded up to the present was 12 months (five patients, 55.6%) and seven months (one patient). Three patients reported recurrence of sweating in both axilla between three and five months. At four months the treatment success rate was 88.9% in the abobotulinumtoxinA group and 77.8% in the onabotulinumtoxinA. There was no significant difference in treatment response between the treatment groups. Secondary: Not reported
Flanagan et al[51] OnabotulinumtoxinA 50 units injected into each axilla vs aluminum chloride 20% applied to each axilla	AC, OL, RCT, SC Patients ≥18 year of age with bilateral primary axillary hyperhidrosis with an HDSS score of three or four	N=50 12 weeks	Primary: Treatment response (at least two point change in HDSS) Secondary: Change in HDSS score and adverse events	Primary: Significantly more patients treated with onabotulinumtoxinA were considered to be treatment responders compared to patients treated with aluminum chloride (92 vs 33%; *P*<0.001). Secondary: The change in HDSS score was significantly greater in the onabotulinumtoxinA group compared to the aluminum chloride group after four weeks of treatment (-2.45 vs -1.33; *P*<0.0001). At eight weeks, 90.9% of the onabotulinumtoxinA group were considered to be treatment responders with a reduction from baseline in HDSS score of -2.32 (*P*<0.001) while 83% of patients treated with aluminum chloride were treatment responders with a change in HDSS score of -2.83 (*P* value not reported). At 12 weeks, 77.3% of onabotulinumtoxinA-treated patients continued to be treatment responders and had a mean reduction in HDSS of -2.23. By week 12, of the seven aluminum chloride treatment responders, the HDSS score was reduced by -2.86. There was no significant difference between the treatment groups. At four weeks, significantly more patients treated with onabotulinumtoxinA were “very satisfied” with treatment compared to 33.3% of these patients in the aluminum chloride treatment group (*P*<0.003). By week 12, there was no significant difference between the treatment groups with regard to the proportion of patients who were satisfied with treatment (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). Overall, there were very few reports of irritation in the onabotulinumtoxinA group. Patients receiving aluminum chloride complained of more irritation across all categories. Overall, there were 60 adverse events reported in 30 patients. Significantly more events occurred in patients treated with aluminum chloride compared to onabotulinumtoxinA (*P*<0.0001). The most commonly reported adverse events included skin related irritation (burning, itching and redness).
Treatment of Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency and Frequency				
Kanagarajah et al[52] Botulinum toxin A 100 units injected into the detrusor muscle vs botulinum toxin A 150 units injected into the detrusor muscle The total number of units to be administered was divided among 10 to 15 injections into the detrusor muscle.	DB, PRO, RCT, SC Patients 18 to 80 years of age, with OAB for at least one year and at least one episode of UUI and/or at least nine voids per day; patients either failed or had been unable to tolerate treatment with at least two antimuscarinic agents	N=32 12 weeks	Primary: Improvement in outcomes (≥50% reduction in UUI episodes per day if incontinence at baseline [OAB-wet] or ≥50% reduction in urinary frequency per day if no incontinence present at baseline [OAB-dry]), urodynamic outcomes, VAS scores and UDI-6 questionnaire scores Secondary: Not reported	Primary: Of OAB-dry patients, 84% (16/19) experienced a ≥50% improvement in urinary frequency by 12 weeks following treatment and 85% (11/13) of the OAB-wet patient achieved a ≥50% reduction in UUI episodes at 12 weeks following injection (*P*<0.02). Of the OAB-dry patients, the mean baseline±SD urinary frequency was reduced from 24±11 to 10±4 episodes per day 12 weeks following treatment (*P*<0.02). In OAB-wet patients, the mean baseline±SD UUI episodes were reduced from 7.9±5 to 0±2.6 by week 12 weeks following treatment (*P* value not reported). There was no statistically significant difference in response rate between OAB-dry and OAB-wet patients with regard to UDI-6 and VAS scores (*P*<0.75). Moreover, the reported UDI-6 and VAS scores did not differ significantly between patients randomized to receive 100 or 150 units of botulinum toxin A. The OAB-wet patients experienced a significant decrease in maximum detrusor pressure during the voiding phase at 12 weeks following treatment compared to baseline (*P*=0.02). No other differences in urodynamic parameters were reported. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Anger et al[53] Botulinum toxin A injected into the detrusor muscle (dose not reported) vs placebo	SR (23 studies) Botulinum toxin A in adult men and women with refractory idiopathic OAB	N=951 Duration not reported	Primary: Improvement in incontinent episodes, QOL and adverse events Secondary: Not reported	Primary: Treatment with botulinum toxin A was associated with a significant reduction in the number of incontinence episodes per day compared to placebo (-3.88 episodes per day; 95% CI, -6.15 to -1.62). There was a significant improvement in QOL (as evaluated by UDI-6 and UDI scores) following treatment with botulinum toxin A compared to placebo (SMD, -0.62; 95% CI, -1.04 to -0.21). Patients treated with botulinum toxin A were significantly more likely to have a PVR complication compared to the placebo group (OR, 8.55; 95% CI, 3.22 to 22.71). Rates of post-procedure CIC varied among patients from 0 to 41% and lasted up to six months. Other adverse events reported included UTIs, hematuria and dysuria. The UTIs were associated with an elevation in PVR and the need for CIC. Secondary: Not reported
Tincello et al[54] OnabotulinumtoxinA 200 units injected into the detrusor muscle vs placebo The total number of units to be administered was divided among 20 injections into the detrusor muscle.	DB, MC, PC, RCT Women with OAB and detrusor overactivity on urodynamics within previous two years that was deemed to be refractory to treatment (eight weeks of treatment with antimuscarinic drugs	N=240 6 months	Primary: Urinary voiding frequency per day Secondary: Incontinence episodes per day, urgency episodes per day, IUSS score, ICIQ score and I-QOL score	Primary: The mean urinary voiding frequency per day was significantly reduced following treatment with onabotulinumtoxinA compared to placebo (8.33 vs 9.67; *P*=0.0001). Secondary: Patients treated with onabotulinumtoxinA experienced significantly greater reductions in incontinence episodes per day compared to patients receiving placebo (6.00 vs 1.67; *P*<0.0001). Greater reductions in urgency episodes per day were also reported with onabotulinumtoxinA compared to placebo (6.33 vs 3.83; *P*<0.0001). There were significantly greater improvements in IUSS scores (*P*=0.0006), ICIQ scores (*P*<0.0001) and I-QOL scores (*P*<0.0001) for patients who received treatment with onabotulinumtoxinA compared to patients treated with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Denys et al[55] OnabotulinumtoxinA 50 units injected into the detrusor muscle vs onabotulinumtoxinA 100 units injected into the detrusor muscle vs onabotulinumtoxinA 150 units injected into the detrusor muscle vs placebo The total number of units to be administered was divided among 15 injections into the detrusor muscle, avoiding the trigone.	DB, MC, PC, RCT Patients ≥18 years of age with idiopathic OAB for at least six months and at least three episodes of urgency with or without UUI daily, at least eight voids per day, and detrusor overactivity that was refractory to antimuscarinics, or the patient could not tolerate antimuscarinics	N=99 6 months	Primary: Proportion of patients showing ≥50% improvement in both urgency and UUI episodes at three months Secondary: Change in micturitions per day, UUI per day, urgency episodes per day pads per day, urodynamic measures and QOL	Primary: In patients who completed the study, the proportion of patients who achieved a ≥50% improvement in urgency and UUI episodes at three months was not significantly greater in patients treated with onabotulinumtoxinA 50 (37%; *P*=0.46), 100 (68%; *P*=0.06) or 150 units (58%; *P*=0.49) compared to patients treated with placebo (30%). Similarly, in the LOCF analysis, the proportion of patients who achieved a ≥50% improvement in urgency and UUI episodes at three months was not significantly greater in patients treated with onabotulinumtoxinA 50 (37%; *P*=0.39), 100 (65%; *P*=0.09) or 150 units (56%; *P*=0.27) compared to patients treated with placebo (29%). Secondary: In patients who completed the study, the proportion of patients who achieved a ≥75% improvement in urgency and UUI episodes at three months was significantly greater with onabotulinumtoxinA treatment overall compared to placebo (*P*=0.03); however, this was not a prespecified study endpoint. Similarly, in the LOCF analysis, the proportion of patients who achieved a ≥75% improvement in urgency and UUI episodes at three months was significantly greater with onabotulinumtoxinA treatment overall compared to placebo (*P*=0.01); however, this was not a prespecified study endpoint. Most patients experienced an improvement in urgency or UUI episodes by the first evaluation (day eight) and was significantly different from placebo after one month with the onabotulinumtoxinA 150 unit dose. Although the improvements were similar between the onabotulinumtoxinA 100 and 150 units treatment groups, only the 150 unit dose was more effective compared to placebo. The reduction in micturitions per day remained significantly greater for patients treated with onabotulinumtoxinA 150 units for up to six months compared to placebo. At month three, 15.8, 55.0, 50.0 and 10.7% (*P*<0.001 for all) and at month five, 15.8, 45.0, 45.8 and 7.1% (*P*<0.009) of patients achieved complete continence, respectively, with onabotulinumtoxinA 50,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				100, 150 units and placebo. Urodynamic measures were significantly improved with onabotulinumtoxinA 150 units compared to placebo for all parameters with the exception on detrusor pressure (*P*<0.05 for all). Patients treated with onabotulinumtoxinA 100 units experienced significant improvements in voided volumes, and volume of first contraction compared to placebo (*P*<0.05 for both). No other significant improvements were reported. Patients receiving treatment with onabotulinumtoxinA 100 or 150 units experienced a significant improvement in QOL after one month; however, results were not significant at any time point thereafter (*P*>0.05 for all time points except at six months). The EQ-5D was also significantly improved with both of these doses after one month compared to the placebo group.
Dmochowski et al[56] OnabotulinumtoxinA 50 units injected into the detrusor muscle vs onabotulinumtoxinA 100 units injected into the detrusor muscle vs onabotulinumtoxinA 150 units injected into the detrusor muscle vs onabotulinumtoxinA 200 units injected into the	DB, MC, PC, RCT Patients 18 to 85 years of age with idiopathic OAB and UUI for at least six months who were no longer taking antimuscarinic medication due to an inadequate response or intolerable adverse events; patients were required to have eight or more UUI	N=313 36 weeks	Primary: Change from baseline in number of weekly UUI episodes Secondary: Weekly frequency of micturition, urgency and nocturia, MVV and adverse events	Primary: At week 12, the mean change from baseline in weekly UUI episodes was -20.7, -18.4, -23.0, -19.6, -19.4 and -17.4 for the onabotulinumtoxinA 50, 100, 150, 200 and 300 unit groups and placebo, respectively. Although a significant difference from placebo was observed at many points, no clear dose response was observed with this analysis of the data (*P* values not reported). Secondary: Significant decreases in weekly episodes of micturition, urgency and nocturia, and increases in MVV were observed with onabotulinumtoxinA compared to placebo at week 12 (*P* values not reported). The magnitude the reduction was consistently lower without a sustained response in the onabotulinumtoxinA unit 50 unit group compared to groups receiving a dose of 100 units or more. The proportion of incontinence-free patients was consistently lower for patients treated with onabotulinumtoxinA 50 units compared to the other onabotulinumtoxinA treatment groups. A dose-response was observed at week 12 (29.8, 37.0, 40.8, 50.9, 57.1 and 15.9% in the onabotulinumtoxinA 50, 100, 150, 200 and 300 unit and placebo groups, respectively; *P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
detrusor muscle vs onabotulinumtoxinA 300 units injected into the detrusor muscle vs placebo The total number of units to be administered was divided among 20 injections into the detrusor muscle, avoiding the trigone and dome.	episodes per week and an average of at least eight micturitions per day			The only adverse events that occurred significantly more frequently in the onabotulinumtoxinA groups compared to the placebo group were urinary retention and urinary tract infection (*P*<0.05 for both). All patients who reported urinary retention maintained the ability to void spontaneously regardless of whether CIC was implemented. A total of 45 serious adverse events were reported by 34 patients during the study and of these, 43 were not treatment related. The only serious adverse events related to treatment were urinary retention and a gastroparesis flare (reported in the 100 and 50 unit onabotulinumtoxinA groups, respectively).
Fowler et al[57] OnabotulinumtoxinA 50 units injected into the detrusor muscle vs onabotulinumtoxinA 100 units injected into the detrusor muscle vs onabotulinumtoxinA 150 units injected into the detrusor muscle vs	Subanalysis of Dmochowski et al[56] Patients 18 to 85 years of age with idiopathic OAB and UUI for at least six months who were no longer taking antimuscarinic medication due to an inadequate response or intolerable adverse events;	N=313 36 weeks	Primary: I-QOL, KHQ and SF-36 scores Secondary: Not reported	Primary: Improvements from baseline in I-QOL total score were significantly greater in all groups receiving ≥100 units of onabotulinumtoxinA compared to placebo at week two and were maintained through 36 weeks (*P*<0.05 for all groups). There was a dose-response relationship in patients who received onabotulinumtoxinA, with mean improvements in I-QOL total scores of 29.8, 32.9, 35.2, 37.1 and 39.7 at 12 weeks for the onabotulinumtoxinA 50, 100, 150, 200 and 300 unit groups, respectively, compared to 17.9 for placebo. Similar improvements were observed for the avoidance and limiting behavior, psychosocial impact and social embarrassment domains of the I-QOL scores, with diminishing incremental gains observed for doses above 150 units. The proportion of patients who achieved the minimally important difference of at least five points on the I-QOL instrument was greater for all onabotulinumtoxinA groups compared to placebo (59.6, 68.5, 69.4, 69.8 and 75.0% for onabotulinumtoxinA 50, 100, 150, 200 and 300 units, respectively, compared to 43.2% with placebo). A similar improvement was reported for the proportion of patients with a minimally important difference of ≥10 points

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
onabotulinumtoxinA 200 units injected into the detrusor muscle vs onabotulinumtoxinA 300 units injected into the detrusor muscle vs placebo The total number of units to be administered was divided among 20 injections into the detrusor muscle, avoiding the trigone and dome.	patients were required to have eight or more UUI episodes per week and an average of at least eight micturitions per day			(54.4, 64.8, 63.3, 69.8 and 69.6% compared to 36.4%, respectively). The placebo-adjusted differences KHQ scores at 12 weeks ranged from -2.7 to -10.8 favoring all onabotulinumtoxinA groups receiving ≥100 units (*P*<0.05 for all). The differences in the KHQ score improvements was minimal between onabotulinumtoxinA groups receiving ≥100 units, and most showed significant improvements from weeks 12 to 30 compared to placebo. Compared to placebo, statistically significant improvements on the SF-36 were observed in the onabotulinumtoxinA 300 unit group (physical functioning, role-physical, bodily pain and vitality subscales; *P*≤0.045) and the 200 unit group (role-physical domain; *P*=0.048). Secondary: Not reported
Visco et al[58] OnabotulinumtoxinA 100 units injected in detrusor muscle vs solifenacin 5 mg daily Dose escalation was allowed at two and four months if the score on the PGSC was one to three, indicating inadequate symptom control, and if the	AC, DB, MC, RCT Women with at least five UUI episodes per day and urgency-predominant urinary incontinence who were treatment naïve to antimuscarinic drugs or had	N=249 Up to 12 months	Primary: Change in the mean number of UUI episodes per day Secondary: Proportion of patients with complete resolution of UUI, proportion of patients with a ≥75% reduction in UUI and scores on OABq-SF, PFIQ-SF and PFDI-SF	Primary: The mean reduction from baseline in UUI episodes per day was 3.3 in the onabotulinumtoxinA group and 3.4 in the antimuscarinic group (*P*=0.81). Secondary: Significantly more patients treated with onabotulinumtoxinA experienced complete resolution of UUI compared to patients treated with solifenacin (27 vs 13%; *P*=0.003); however, there was no difference in the proportion of patients with a ≥75% reduction in UUI episodes (54 vs 40%, respectively; *P*=0.06). There were no statistically significant differences between onabotulinumtoxinA and solifenacin treatments with regard to OABq-SF symptom severity scores (-44.08 vs -44.55, respectively; *P*=0.87) and QOL scores (37.13 vs 37.05, respectively; *P*=0.98).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
participant reported that the drug were tolerable.	previously received up to two antimuscarinic agents other than solifenacin, darifenacin or trospium chloride			Similarly, improvements in PFDI-SF (*P*=0.47), PFIQ-SF (*P*=0.88) and PGI at three (*P*=0.37) and six months (*P*=0.71) were not significantly different between patients receiving onabotulinumtoxinA or solifenacin. Dry mouth occurred in significantly fewer participants in the onabotulinumtoxinA group compared to the solifenacin group (31 vs 46%; *P*=0.02). More women in the onabotulinumtoxinA group had a UTI compared to women in the solifenacin group (33 vs 13%; *P*<0.001). Serious adverse events were uncommon, and the rate did not differ significantly between the groups; none of the serious adverse events were considered by the investigators to be attributable to the study treatment. At six months, 70% of patients who received onabotulinumtoxinA and 71% of patients treated with solifenacin had adequate symptom control, as defined by a PGSC score of four or five. At six months, all oral medications were discontinued. Within one month of discontinuing oral medication, significantly fewer women in the solifenacin group than in the onabotulinumtoxinA group had adequate control of symptoms (50 vs 62%; *P*=0.006). At 12 months, more patients treated with onabotulinumtoxinA continued to have adequate control of symptoms compared to patients treated with solifenacin (38 vs 25%; *P*=0.61).
Duthie et al[59] Botulinum toxin injected into the detrusor muscle (dose not reported) vs lifestyle modification vs bladder retraining	SR (19 RCTs) Adults with idiopathic or neurogenic OAB syndrome regardless of whether they also had stress incontinence The majority of included studies involved	N=not reported Duration not reported	Primary: Patient perception of improvement or cure, satisfaction with treatment, number of leakage episodes, frequency and volume of voids, urodynamic measures and clinician findings and QOL	Primary: Urinary frequency was improved in patients treated with botulinum toxin at both the four to six week and 12 week follow up points. The mean difference was a reduction in urinary frequency of -6.50 episodes per day (95% CI, -8.92 to - 4.07) at four to six weeks. At 12 weeks, the mean difference in urinary frequency was -3.37 episodes per day (95% CI, -5.15 to -1.59). An improvement in incontinence episodes occurred with botulinum toxin at both four to six week and 12 weeks. The mean difference was a reduction in incontinence episodes of -1.58 episodes per day (95% CI, - 2.16 to -1.01) at four to six weeks. At 12 weeks, the mean difference was a reduction of - 2.74 episodes per day (95% CI, -4.47 to -1.01). The change in PVR was significantly higher in the placebo group compared

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vs pharmacologic therapy vs surgery vs bladder instillation techniques vs neuromodulation	participants with neurogenic OAB, often due to spinal cord injury or MS.		Secondary: Not reported	to the botulinum toxin group (70.22 mL; 95% CI, 30.63 to 109.81). Both the UDI-6 and the IIQ-7 symptom scores showed improvement following treatment with botulinum toxin. Botulinum toxin treatment significantly improved some of the domains of the KHQ, including impact on life, incontinence impact, and incontinence severity measures compared to placebo. At all time points, treatment with botulinum toxin was associated with significant improvements I-QOL score compared to placebo. One trial compared 300 units of intravesical botulinum toxin type A with instillation of resiniferatoxin. There was a significant decrease in rates of incontinence with botulinum toxin compared to resiniferatoxin at six, 12 and 18 months. There was also a significant increase in PVR in the botulinum toxin A treatment group at all time points. Secondary: Not reported
Treatment of Urinary Incontinence Due to Detrusor Overactivity Associated with a Neurologic Condition (e.g., Spinal Cord Injury, Multiple Sclerosis)				
Schulte-Baukloh et al[60] OnabotulinumtoxinA 300 units injected into the detrusor muscle The total number of units to be administered was divided among 30 injections into the detrusor muscle, avoiding the trigone.	OL Patients with MS who were suffering from OAB symptoms, such as frequency, urgency, and UUI that was resistant to antimuscarinic drugs	N=16 6 months	Primary: Urodynamic measurements and subjective QOL outcomes Secondary: Not reported	Primary: Daytime urinary frequency was significantly reduced from baseline with onabotulinumtoxinA at four weeks, three and six months, as was nighttime urinary frequency (P<0.05 for all). The MVV was significantly lower following treatment with onabotulinumtoxinA at four weeks (P<0.05); however, there were no significant improvements at three and six months. Treatment with onabotulinumtoxinA significantly reduced pad usage at four weeks (P<0.05) and three months (P<0.05); however, there was no reduction in pad use at month six (P=NS). Significant improvements from baseline in RV and MCC occurred with onabotulinumtoxinA treatment at four weeks (P<0.005 for both) and three months (P≤0.05 for both) but not six months (P=NS for both). The overall questionnaire scores indicated significant improvements on all

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				three assessed instruments, including the UDI-6, the SSI, and the SII after one and three months of treatment with onabotulinumtoxinA. Subjectively, the symptoms worsened by the six month evaluation. Secondary: Not reported
Khan et al[61] OnabotulinumtoxinA 300 units injected into the detrusor muscle The total number of units to be administered was divided among 40 injections into the detrusor muscle, including the bladder base and trigone.	OL, PRO, SC Patients with a confirmed diagnosis of MS with NDO who had not responded to behavioral therapy or to at least two medications	N=137 Exact duration not reported; mean, 29 months	Primary: Proportion of patients reporting continence, UDI-6, IIQ-7 and EQ-5D scores Secondary: Not reported	Primary: Four weeks following treatment with onabotulinumtoxinA, 76% of patients reported continence compared to 83% of patients who reported incontinence at baseline (*P* value not reported). Of the patients who received onabotulinumtoxinA treatment, 72% received a second treatment, and 47, 25, 14 and 5% returned for treatments three through six, respectively. There was no statistically significant difference in the intervals of onabotulinumtoxinA administration (*P*=0.50). Of the 28% of patients who did not receive a second treatment after greater than 12 months of follow-up, 18% had not yet reported the return of OAB symptoms, 2% elected alternate treatment, 1.5% were lost to follow-up and 6.5% elected no further intervention due to MS progression and inability or unwillingness to perform CISC. The mean difference in UDI-6 and IIQ-7 scores for injections one through four was 38.2 to 46.2 (*P*<0.0001 for both), 33.5 to 40.1 (*P*<0.0001 for both), 38.6 to 41 (*P*<0.0001 for both), and 33.7 to 41.6 (*P*<0.0001 and 0.0003, respectively). There were no calculations for injections five or six due to the small patient number. The overall EQ-5D index did not change significantly four weeks after treatment. A total of 110 patients (87%) reported some or extreme problems with mobility on EQ-5D. Secondary: Not reported
Herschorn et al[62] OnabotulinumtoxinA 300	DB, MC, PC, PRO, RCT	N=57 36 weeks	Primary: Change in urinary incontinence	Primary: Treatment with onabotulinumtoxinA was associated with statistically significant reductions from baseline in daily urinary incontinence episodes at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
units injected into the detrusor muscle vs placebo The total number of units to be administered was divided among 30 injections into the detrusor muscle, avoiding the trigone. Antimuscarinics were discontinued at week three and could be resumed at 50% of the previous dose at week four and at the full dose at week six.	Patients 18 to 75 years of age with NDO secondary to spinal cord injury or MS who had urinary incontinence (one or more episodes per day) despite current antimuscarinic treatment		episodes per day at six weeks Secondary: Changes in urodynamics and questionnaire scores at six weeks, daily frequency of urinary incontinence episodes, urodynamics and questionnaire scores at other time points	six weeks compared to treatment with placebo (1.3±1.3 vs 4.8±2.9; *P*<0.0001). Secondary: Statistically significant improvements in all urodynamic parameters occurred at six weeks with onabotulinumtoxinA compared to placebo (*P*<0.05 for all). Patients treated with onabotulinumtoxinA experienced improvements in ICIQ and I-QOL scores compared to placebo. On ICIQ question one (urinary incontinence frequency) significant improvements with onabotulinumtoxinA extended to 24 weeks. At 24 and 36 weeks 65.2 and 33.3% of patients in the onabotulinumtoxinA, respectively, reported fewer than three leakage episodes weekly compared to 3.8% at baseline. Complete continence was achieved in 10.7% of patients treated with onabotulinumtoxinA compared to zero patients treated with placebo. At six week six, significantly fewer patients treated with onabotulinumtoxinA compared to placebo experienced urinary incontinence while asleep (39 vs 72%; *P*<0.05), when physically active or exercising (29 vs 66%; *P*<0.01) and for no obvious reason (29 vs 55%; *P*<0.05). Significantly greater improvements from baseline in I-QOL total scores were seen at six, 24 and 36 weeks with onabotulinumtoxinA compared to placebo.
Cruz et al[63] OnabotulinumtoxinA 200 units injected into the detrusor muscle vs onabotulinumtoxinA 300 units injected into the detrusor muscle vs	DB, MC, PC, RCT Patients 18 to 80 years of age with ≥14 urinary incontinence episodes per week due to NDO from spinal cord injury or MS (clinically stable for at least three	N=275 At least 52 weeks	Primary: Change from baseline to six weeks in urinary incontinence episodes per week Secondary: Changes from baseline in MCC, $P_{detmaxIDC}$, I-QOL total score, ($V_{PmaxIDC}$), DC and MVV	Primary: By six weeks, the mean weekly urinary incontinence episodes were significantly reduced in both the onabotulinumtoxinA 200 (-21.8) and 300 unit (-19.4) groups compared to placebo (-13.2; *P*<0.01 for both comparisons), with no clinically relevant differences between onabotulinumtoxinA dose groups. The proportion of patients who achieved ≥50%, ≥75%, or 100% reductions in weekly urinary incontinence episodes was significantly higher with onabotulinumtoxinA compared to placebo (*P*<0.001). By six weeks, 7.6, 38.0 and 39.6% of patients treated with placebo, 200 and 300 units of onabotulinumtoxinA, respectively, achieved complete continence.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo The total number of units to be administered was divided among 20 injections into the detrusor muscle, avoiding the trigone and dome. Those taking antimuscarinics at baseline were to maintain the same regimen during the study.	months before screening and an EDSS score of ≤6.5); patients were not adequately managed by antimuscarinic agents			Secondary: Patients treated with onabotulinumtoxinA experienced significantly greater increases in MCC, $V_{pmaxIDC}$, and DC, and decreases in $P_{detmaxIDC}$ at week six, with no differences between onabotulinumtoxinA doses (*P*<0.001 for all except DC) There were greater proportions of patients with no IDC at six weeks in the onabotulinumtoxinA 200 and 300 unit groups compared to the placebo group (64.4 and 59.5% vs 17.4%; *P* value not reported). Patients treated with onabotulinumtoxinA experienced significant increases in the MVV (*P*<0.001) and I-QOL total summary scores at six weeks compared to patients treated with placebo (*P*<0.001).
Mehta et al[64] Botulinum toxin A 100 to 150 units injected into the detrusor muscle vs control (placebo in all studies except one, in which lidocaine was used) injected into the detrusor muscle	MA (8 RCTs) Studies of patients ≥18 years of age in which ≥50% of the study population had experienced a spinal cord injury and received botulinum toxin A injected into the detrusor sphincter with the aim of treating voiding dysfunction	N=129 Duration not reported	Primary: PVR, detrusor pressure, UP and QOL and adverse events Secondary: Not reported	Primary: Botulinum toxin A was associated with significant improvements in PVR compared to the control group at one month (SMD, 1.119±0.140; 95% CI, 0.844 to 1.394; *P*<0.001) three months (SMD, 0.772±0.135; 95% CI, 0.507 to 1.037; *P*<0.001) and six months (SMD, 0.379±0.169; 95% CI, 0.048 to 0.711; *P*<0.025). One month following injection, the treatment effect represented an actual, average decrease in PVR from 252 to 153 mL. One month following injection, there was a moderate treatment effect on detrusor pressure with botulinum toxin A injection compared to the control group (SMD, 0.570±0.217; 95% CI, 0.145 to 0.995; *P*=0.009), while a large effect size was seen on UP (SMD, 0.896±0.291; 95% CI, 0.327 to 1.466; *P*=0.002). The average detrusor pressure decreased from 88.7 to 20.46 cmH_2O, and the UP improved from 119.7 to 102.3 cmH_2O. Adverse events were generally mild with botulinum toxin A and included mild muscular weakness, transitory paresis of limbs, transitory autonomic dysreflexia and urethral bleeding. Two studies evaluated QOL and the results demonstrated that overall quality of life improved from -0.68±.27 to 0.66±0.19 (*P*<0.05), based on I-QOL. The results of one study demonstrated an improvement on the IIQ-7 questionnaire (*P*=0.001), indicating that a decrease in urination difficulty led to improvement in the general QOL of the individual.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Treatment of Upper Limb Spasticity in Adults				
Kaji et al[65] OnabotulinumtoxinA 300 units injected intramuscularly vs placebo Injections consisted of 75 units of onabotulinumtoxinA or placebo per muscle into each of the following: medial head of the gastrocnemius, lateral head of the gastrocnemius, and soleus muscle and tibialis posterior muscle (divided into three sites per muscle).	DB, MC, PC, PG, RCT Patients 20 to 80 years of age who weighed ≥50 kg and had a stroke at least six months prior to treatment and had equinus deformity (plantar flexion of the ankle) as demonstrated by a score of more than three for ankle flexors on the MAS	N=120 12 weeks	Primary: AUC of the change from baseline in the MAS ankle score Secondary: MAS score, gait scale (Physician's Rating Scale), gait speed and CGI score	Primary: The ankle MAS AUC was significantly lower in the onabotulinumtoxinA group compared to the placebo group (mean difference, -3.428; 95% CI, -5.841 to -1.016; *P*=0.006). Secondary: The ankle MAS score was significant lower in the onabotulinumtoxinA group compared to the placebo group at four, six and eight weeks (*P*<0.001 for all). There was a slight increase from baseline in the Physician's Rating Scale gait score for both groups; however, the difference between groups was not significant at any time point (*P*≥0.688 for all). Similarly, there were no statistically significant differences between the treatment groups at any time point with regard to gait speed (*P*≥0.209). There was a significantly greater increase in the CGI score in the onabotulinumtoxinA group compared to the placebo group at four, six and eight weeks (*P*≤0.048 for all). No significant between-group differences were noted in the CGI scores by the patient and by the physical or occupational therapist at any time point.
Kaji et al[66] OnabotulinumtoxinA 120 units injected intramuscularly vs onabotulinumtoxinA 200 units injected intramuscularly vs	DB, MC, PC, PG, RCT Patients 20 to 80 years of age weighing ≥40 kg with a stroke at least six months prior to treatment, focal spasticity of both the wrist and fingers,	N=109 12 weeks	Primary: AUC of the change from baseline in MAS wrist scores in higher dose group Secondary: AUC of the change from baseline in MAS wrist scores in lower dose group, DAS and	Primary: There was a significantly greater improvement in the AUC of the change from baseline in the MAS wrist score with the higher onabotulinumtoxinA dose compared to placebo (mean difference, -6.830; 95% CI, -10.567 to -3.093; *P*<0.001). Secondary: The mean AUC was smaller in the lower onabotulinumtoxinA dose group compared to the placebo group (-10.036 vs -6.227); however, the difference was not statistically significant (*P*=0.215). There was a significantly greater reduction from baseline in the MAS wrist score at every time point in the higher onabotulinumtoxinA dose group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo The total number of units to be administered was divided among the flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus and flexor digitorum superficialis to improve wrist and finger flexion.	MAS score of three or four for wrist flexors, two or higher for finger flexors and DAS score of two or higher for at least one of four areas of functional disability		CGI scores and MAS scores for the wrist, finger and thumb	compared to the placebo group ($P \leq 0.01$ for all time points), while no significant difference was noted at any time point in the lower-dose onabotulinumtoxinA group compared to the placebo group ($P \geq 0.09$ at all time points). Patients treated with the higher onabotulinumtoxinA dose experienced a significant improvement in MAS finger score at all time points evaluated compared to patients treated with placebo ($P \leq 0.016$ for all time points), while a significant improvement was only apparent at six weeks in the lower onabotulinumtoxinA dose group compared to the placebo group ($P = 0.015$). Greater decreases in the MAS thumb score were noted with both doses of onabotulinumtoxinA compared to the placebo group (*P* values not reported). There was a significant decrease in the DAS score for limb position for patients treated with the higher onabotulinumtoxinA dose compared to the placebo group at all time points ($P \leq 0.022$), while a significant decrease was noted only at six and eight weeks in the lower onabotulinumtoxinA dose group compared to placebo group ($P \leq 0.031$). In the score for dressing, a significant improvement was noted in the higher onabotulinumtoxinA dose group compared to the placebo group at six, eight and 12 weeks ($P \leq 0.038$), while a significant improvement was noted only at four weeks in the lower onabotulinumtoxinA dose group compared to the placebo group ($P = 0.035$). No significant differences between groups were noted at any time point in the scores for hygiene and pain.
Simpson et al[67] OnabotulinumtoxinA up to 500 units injected intramuscularly vs tizanidine 2 to 36 mg daily	AC, DB, MC, PC, RCT Patients 18 to 85 years of age with prior stroke or traumatic brain injury at least three months	N=60 24 weeks	Primary: Change from baseline in the wrist MAS at visit four Secondary: Change from baseline in DAS, Modified Frenchay	Primary: Patients randomized to receive treatment with onabotulinumtoxinA experienced a statistically significant reduction from baseline in wrist MAS score compared to patients treated with tizanidine or placebo (-1.32±0.89 vs -0.22±0.88 and -0.68±1.00, respectively; $P \leq 0.08$ compared to both). Secondary: The cosmetic component of the DAS was significantly improved with onabotulinumtoxinA at six weeks compared to tizanidine or placebo (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All injections in the wrist flexors (flexor carpi radialis and ulnaris) consisted of 50 units, while the remainder of upper-extremity muscles, from the shoulder to fingers, could be injected per the investigator's discretion, based on subject's disability, to a maximum total dose of 500 units.	earlier, and spasticity of the wrist, (score of more than three for wrist flexor tone on the MAS) and difficulty with hygiene or dressing, pain or malposition of the wrist, as evidenced by a score of more than two on DAS		Scale, 10 meter walking speed, contralateral grip strength, finger tap test and cognitive evaluations	1.00±1.00 vs 0.12±0.93 and -0.16±1.01; *P*<0.003 for both). There were no significant differences between the treatments with regard to other DAS domains. There were no other statistically significant differences in any secondary outcomes. The results of the impact of the treatments on Modified Frenchay Scale scores were not available at the time of publishing.
Rosales et al[68] Botulinum toxin A injected intramuscularly (Botox® 200 to 360 units per injection or Dysport® 500 to 1,500 units per injection) vs placebo	SR (9 RCTs) Adult patients with hemiplegic stroke and moderate to severe muscle spasticity of the upper or lower extremities as defined by MAS at least three months after cerebrovascular event	N=464 4 to 6 weeks	Primary: Change in MAS score for spasticity Secondary: Proportion of patients experiencing at least a one point change in MAS from baseline in the upper and lower limbs, patient or caregivers perception of GAS and adverse events	Primary: The mean change from baseline in MAS score favored treatment with botulinum toxin A compared to placebo at four to six weeks following treatment (WMD, 0.87; 95% CI, 0.52 to 1.22). Secondary; Patients treated with botulinum toxin A were more likely to achieve a change in MAS score of at least one point compared to treatment with placebo (OR, 4.5; 95% CI, 2.79 to 7.25). Patients receiving treatment with botulinum toxin A were more likely to experience an improvement in GAS score (self reported or by caregiver) compared to the placebo group (OR, 5.85; 95% CI, 3.12 to 10.95). There was no statistically significant difference between botulinum toxin A and placebo treatments with regard to the risk of adverse events (OR, 0.84; 95% CI, 0.55 to 1.28).
Elia et al[69] Botulinum toxin A injected	SR (11 RCTs) Patients ≥15	N=782 12 weeks	Primary: Change in Ashworth scores in	Primary: Treatment with botulinum toxin A (Dysport®) significantly improved Ashworth scores from baseline compared to placebo four weeks following injection of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
intramuscularly (Botox® or Dysport®; dose not reported) vs botulinum toxin B injected intramuscularly (dose not reported) vs placebo	years of age with post-stroke spasticity assessed by the normal, modified or expanded versions of the Ashworth scale		each upper or lower limb joint, patients with at least a two-point reduction in Ashworth scores observed at three to six weeks, or eight to 12 weeks following treatment Secondary: Improvement in GAS, AUC of Ashworth scores, functional disability, pain, QOL measured by validated scales and serious adverse events	500 or 1,000 units. The injection of 1,500 units did not significantly improve Ashworth scores compared to placebo. In addition, patients were more likely to experience an improvement of at least two points on the Ashworth score when treated with Dysport® 500 units (OR, 0.22; 95% CI, 0.06 to 0.81) or 1,000 units (OR, 0.22, 95% CI, 0.09 to 0.52) compared to placebo. The 1,500 unit dose was not significantly more effective compared to placebo. There was no significant reduction in spasticity at four, eight or 12 weeks with any dose of Dysport® (500, 1,000 or 1,500 units) compared to placebo, as evaluated by the number of patients achieving a two point or greater reduction in Ashworth score. Only one trial evaluated this outcome. Treatment with botulinum toxin A was associated with statistically significant improvements in elbow spasticity (WMD, -0.95; *P*<0.001), wrist spasticity (WMD, -1.35; *P*<0.001) and finger flexor spasticity (WMD, -1.07; *P*<0.0001) compared to treatment with placebo. After three to six weeks of treatment with botulinum toxin A, there were statistically significant reductions in Ashworth scores compared to placebo for elbow spasticity (SMD, -0.80; 95% CI, -1.32 to -0.28), wrist spasticity (SMD, -0.83; 95% CI, -1.13 to -0.53) and finger flexor spasticity (SMD, -0.76; 95% CI, -1.13 to -0.39). At nine to 12 weeks, significant improvements were maintained with botulinum toxin A treatment compared to placebo with regard to elbow spasticity (SMD, -80; 95% CI, -1.32 to -0.28), wrist spasticity (SMD, -0.83; 95% CI, -1.13 to -0.53) and finger flexor spasticity (SMD, -0.76; 95% CI, -1.13 to -0.39). Treatment with botulinum toxin B did not significantly improve upper limb spasticity at the elbow (WMD, -0.81; *P*=0.16), wrist (WMD, -1.43; *P*=0.07) and finger flexor (WMD, -1.12; *P*=0.10) after three to six weeks of treatment. Similarly, no statistically significant improvements were reported at any upper limb site nine to 12 weeks following botulinum toxin B treatment (*P*>0.05 for all). Secondary: Clinician's judgment concerning GAS was in favor of botulinum toxin A

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment in three trials; but not botulinum toxin B for any trials evaluated. Measures of disability were available in nine botulinum toxin A studies (three using Botox® and six using Dysport®), but an overall quantitative analysis could not be performed, due to different assessment instruments and scoring systems used between studies. Two studies reported a significant improvement in disability following treatment with botulinum toxin A. One study reported an increase in the number of patients with reduced disability, as measured with the DAS, compared to placebo. The second study reported an improvement in Action Research Arm test and Barthel index following treatment with 500 units of Dysport®, but worsening with the 1,000 unit dose. The QOL was assessed by validated scales in two trials. There was a nonsignificant improvement in the Rand 36-item health survey and a significant improvement in the SF-36 in patients treated with the lowest botulinum toxin A (Botox® 90 units). Botulinum toxin A was well tolerated. The incidence of adverse events was not higher with botulinum toxin A compared to placebo. In one trial, severe adverse events occurred in 12 of 65 (18.4%) patients treated with botulinum toxin A and three of 26 (11.5%) patients treated with placebo. No serious adverse events were considered treatment-related by the study investigators. In one study of botulinum toxin B, dry mouth was more common in the treatment group compared to placebo.
Foley et al[70] Botulinum toxin A injected intramuscularly (Botox®, Dysport® and Xeomin®; doses not reported) vs placebo or non-pharmacologic measures	MA (10 RCTs) Patients ≥18 years of age, of whom ≥60% were recovering from either a first or subsequent stroke, presenting with moderate to	N=1,000 Up to 24 weeks	Primary: DAS score, Action Research Arm Test score and Barthel index Secondary: Not reported	Primary: In patients with upper limb spasticity following stoke, the overall treatment effect size following botulinum toxin A injection was 0.536±0.094 (95% CI, 0.352 to 0.721), indicating a favorable benefit with botulinum toxin A compared to placebo. Patients treated with botulinum toxin A experienced a statistically significant improvement in DAS score compared to patients treated with placebo (SMD, 0.688; 95% CI, 0.454 to 1.012; *P*<0.0001). Botulinum toxin A was associated with significant improvements in motor function as evident by Action Research Arm Test scores compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	severe spastic upper limb hemiplegia			placebo treatment (SMD, 0.406; 95% CI, 0.85 to 0.73; *P*=0.013). There were no statistically significant improvements in Barthel index scores, a measurement of generalized disability, in patients treated with botulinum toxin A compared to treatment with placebo (SMD, 0.372; 95% CI, -0.002 to 0.0746; *P*=0.051). Secondary: Not reported

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SC= single center, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ADL=activities of daily living, AUC=area under the curve, BSDI=blepharospasm disability index, CIC=clean intermittent catheterization, CISC=clean intermittent self-catheterization, CGI-clinician global impression, DAS=disability assessment scale, DC=detrusor contraction, DLQI=dermatology life quality index, EDSS=expanded disability status scale, EMG=electromyography, EQ-5D=Euroqol group 5 domains, GAS=goal attainment scaling, HDSS=hyperhidrosis disease severity scale, HIT-6=headache impact test-6, ICIQ=international consultation on incontinence questionnaire, IGA=investigator global assessment, IGAE=investigator global assessment of efficacy, IIQ-7=incontinence impact questionnaire 7 items, I-QOL=incontinence quality of life, IUSS=Indevus urgency severity scale, JRS=Jankovic rating scale, KHQ=King health questionnaire, LOCF=last observation carried forward, LS=least squares, MAS=modified Ashworth scale, MCC=maximum cystometric capacity, MIDAS=migraine disability assessment score, MIQ=migraine impact questionnaire, MSQ=migraine specific quality of life, MOS-QOL=medical outcomes study quality of life, MS=multiple sclerosis, MVV=mean void volume, NDO=neurogenic detrusor overactivity, NNH=number needed to harm, NNT=number needed to treat, OAB=overactive bladder, OABq=overactive bladder questionnaire, $P_{detmaxIDC}$= pressure during first involuntary detrusor contraction, PD=pupillary distance, PEGR=subject evaluation of global response, PGA=physician global assessment, PGI=patient global impression, PGSC=patient global symptom control, PFDI-SF=pelvic floor distress inventory short form, PFIQ-SF=pelvic floor incontinence questionnaire short form, PVR=post void residual, QOL=quality of life, RV=residual volume, SD=standard deviation, SE=standard error, SF-36=short form 36 questions, SGA=subjects global assessment, SII=symptom impact index, SMD=standardized mean difference, SSI=symptom severity index, SSRI=serotonin selective reuptake inhibitor, TCA=tricyclic antidepressant, TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale, UDI-6=urinary distress inventory, UP=urethral pressure, UTI=urinary tract infection, UUI=urge urinary incontinence, VAS=visual analog scale, $V_{PmaxIDC}$= volume at first involuntary detrusor contraction, WMD=weighted mean difference

Special Populations

Table 4. Special Populations[3-6,10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
AbobotulinumtoxinA	No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
IncobotulinumtoxinA	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
OnabotulinumtoxinA	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <18 years of age have not been established with the exception of cervical dystonia (>16	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	years of age) and blepharospasm and strabismus (>12 years of age).				
RimabotulinumtoxinB	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

Adverse Drug Events

The most common adverse events associated with the botulinum toxin products are listed in Table 5. The adverse events below are reported across all indications for each product. For the incidences of adverse events as they relate to their specific indications, please consult the product-specific prescribing information.

Table 5. Adverse Drug Events (%)[3-6,10]

Generic Name	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
Cardiovascular				
Chest pain	-	-	-	>2
Edema	-	-	-	>2
Hypertension	-	-	2	-
Peripheral edema	-	-	-	>2
Vasodilation	-	-	-	>2
Central Nervous System				
Anxiety	-	-	3 to 10	>2
Chills	-	-	-	>2
Confusion	-	-	-	>2
Dizziness	<4	-	2 to 10	3 to 6
Drowsiness	-	-	2 to 10	-
Fall	-	-	3	-
Fatigue	12	-	<3	-
Fever	-	-	2 to 10	>2
Gait disturbance	-	-	3	-
Headache	2 to 11	<7	5 to 10	10 to 16
Hyperesthesia	-	-	-	>2
Migraine	-	-	4	>2

Generic Name	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
Somnolence	-	-	-	>2
Tinnitus	-	-	-	>2
Tremor	-	-	-	>2
Vertigo	-	-	<1	>2
Dermatological				
Abscess	-	-	-	>2
Allergic dermatitis	-	✔	-	-
Allergic reactions	-	✔	-	>2
Contact dermatitis	2 to 3	-	-	-
Cyst	-	-	-	>2
Diffuse skin rash	-	-	✔	-
Injection site reaction	3	-	-	-
Injection site swelling	2 to 3	-	-	-
Pruritus	-	-	3 to 10	>2
Endocrine				
Blood glucose elevated	✔	-	-	-
Gastrointestinal				
Constipation	-	-	4	-
Diarrhea	-	8	-	-
Dyspepsia	-	-	-	<10
Gastrointestinal disorder	-	-	-	>2
Nausea	2	✔	<10	3 to 10
Stomatitis	-	-	-	>2
Vomiting	-	-	-	>2
Genitourinary				
Bacteriuria	-	-	4	-
Blood urine present	2	-	-	-
Dysuria	-	-	4 to 9	-
Hematuria	-	-	4	-
Residual urine volume	-	-	3	-
Urinary retention	-	-	6 to 17	-
Urinary tract infection	-	-	18 to 49	>2
Infection/Infestation				
Bronchitis	2 to 3	-	<3	-
Cystitis	-	-	-	>2
Infection	-	-	3 to 10	13 to 19
Influenza/flu symptoms	2 to 3	-	2 to 10	6 to 9
Pharyngitis	-	-	3 to 10	-
Pneumonia	-	-	-	>2
Upper respiratory tract infection	3	5	-	-
Vaginal moniliasis	-	-	-	>2
Viral infection	-	-	-	>2
Musculoskeletal				
Arthralgia	-	-	-	<7
Arthritis	-	-	-	>2
Asthenia	-	-	2 to 10	<6
Back pain	-	-	2 to 10	3 to 7
Dysphagia	15 to 39	13	<1	10 to 25
Facial pain	-	<1	-	-

Generic Name	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
Hernia	-	-	-	>2
Hypertonia	-	-	2 to 10	-
Injection site discomfort	13 to 22	-	2 to 10	-
Injection site pain	2 to 5	>5	3 to 10	12 to 16
Jaw pain	-	-	<1	-
Joint disorder	-	-	-	>2
Muscle atrophy	1	-	-	-
Muscle spasm	-	✔	2	-
Musculoskeletal stiffness	-	-	2 to 10	-
Muscle weakness	16 to 56	7	4	-
Musculoskeletal pain	7	9	3	-
Myalgia	-	✔	3	-
Myasthenia	-	-	-	3 to 6
Neck pain	>5	7	3 to 10	<17
Pain in extremity	-	-	5 to 9	-
Pain related to cervical dystonia/torticollis	-	-	-	4 to 10
Pharyngolaryngeal pain	2 to 3	-	-	-
Torticollis	-	-	-	<8
Ophthalmic				
Abnormal vision	-	-	-	>2
Amblyopia	-	-	-	>2
Blepharospasm	-	<1	-	-
Diplopia	-	-	2 to 10	-
Dry eye	-	16	<6	-
Ectropion	-	-	✔	-
Entropion	-	-	✔	-
Eye disorder	7 to 18	<1	-	-
Eyelid edema	2	<1	<1	-
Eyelid ptosis	2	<19	2 to 21	-
Keratitis	-	-	✔	-
Lacrimation	-	-	✔	-
Lagophthalmos	-	-	✔	-
Photophobia	-	-	✔	-
Superficial punctate keratitis	-	-	6	-
Visual impairment	-	12	-	-
Respiratory				
Breathing difficulties	3	-	-	-
Cough	2 to 3	-	2 to 10	3 to 7
Dyspnea	-	5	2 to 10	>2
Lung disorder	-	-	-	>2
Rhinitis	-	-	2 to 10	1 to 5
Sinusitis	2	-	-	-
Other				
Accidental injury	-	-	-	<5
Dysarthria	-	✔	-	-
Dysphonia	6 to 28	-	-	-
Dry mouth	13 to 39	16	2 to 10	3 to 34
Ecchymosis	-	-	-	>2

Generic Name	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
Facial paresis	5 to 11	<1	2	-
Glossitis	-	-	-	>2
Hypercholesterolemia	-	-	-	>2
Hypersensitivity	-	✔	-	-
Injection site hematoma	-	<1	-	-
Injection site hemorrhage	-	-	3 to 10	-
Irritation, unspecified	-	-	✔	-
Malaise	-	-	-	>2
Nasopharyngitis	10	5	-	-
Neoplasm	-	-	-	>2
Nonaxillary sweating	-	-	3 to 10	-
Otitis media	-	-	-	>2
Taste perversion	-	-	-	>2
Tooth disorder	-	-	-	>2

✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 6. Contraindications[3-6,10]

Contraindication	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
Infection at proposed injection site(s)	✔	✔	✔	✔
Known allergy to cow's milk protein	✔	-	-	-
Known hypersensitivity to any botulinum toxin preparation or any components of the formulation	✔	✔	✔	✔
Potential for immunogenicity from therapeutic proteins	✔	-	-	-
Urinary tract infection or urinary retention	-	-	✔	-

Black Box Warning for AbobotulinumtoxinA[3]

WARNING
Distant Spread of Toxin Effect: The effects of abobotulinumtoxinA and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

Black Box Warning for IncobotulinumtoxinA[4]

WARNING
Distant Spread of Toxin Effect: The effects of incobotulinumtoxinA and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These

WARNING
symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

Black Box Warning for OnabotulinumtoxinA[5]

WARNING
Distant Spread of Toxin Effect: The effects of onabotulinumtoxinA and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

Black Box Warning for RimabotulinumtoxinB[6]

WARNING
Distant Spread of Toxin Effect: The effects of rimabotulinumtoxinB and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

Warnings/Precautions

Table 7. Warnings and Precautions[3-6,10]

Warning/Precaution	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
Autonomic dysreflexia; may occur in patients treated for detrusor overactivity associated with a neurologic condition	-	-	✔	-
Bronchitis; more frequent in patients with reduced lung function treated for upper limb spasticity	-	-	✔	-
Corneal exposure; reduced blinking from injections may lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders	-	✔	✔	-
Dysphagia and breathing difficulties following treatment for cervical dystonia	✔	✔	✔	✔
Facial anatomy in the	✔	-	-	-

Warning/Precaution	Abobotulinum-toxinA	Incobotulinum-toxinA	Onabotulinum-toxinA	Rimabotulinum-toxinB
treatment of glabellar lines; use caution administering to patients with surgical alterations to facial anatomy				
Human albumin; theoretical risk for transmission of viral diseases	✔	✔	✔	✔
Hypersensitivity reactions have been reported	-	✔	✔	-
Injections in or near vulnerable anatomic structures; serious adverse events have been reported	-	-	✔	-
Intradermal immune reaction; risk is unknown	✔	-	-	-
Not interchangeable with other botulinum toxins	✔	✔	✔	✔
Patients with compromised respiratory status; monitor pulmonary function	-	-	✔	-
Preexisting neuromuscular disorders; increased risk of adverse events from typical doses	✔	✔	✔	✔
Ptosis; risk increased when treated for glabellar lines	-	✔	-	-
Retrobulbar hemorrhages; hemorrhages sufficient to compromise retinal circulation have occurred	-	-	✔	-
Spread of toxin effect; effects may be observed beyond the site of local injection	✔	✔	✔	✔
Urinary retention; only treat patients willing and able to initiate catheterization post-treatment, if required	-	-	✔	-
Urinary tract infection; use caution in overactive bladder patients with multiple recurrent infections	-	-	✔	-

Drug Interactions

Patients receiving concomitant treatment with botulinum toxins and aminoglycosides or other agents interfering with neuromuscular transmission should be closely monitored because the effect of the botulinum toxin may be potentiated. Use of antimuscarinic drugs after administration of botulinum toxins may potentiate systemic anticholinergic events such as blurred vision.[3-6,10]

The effect of administering different botulinum neurotoxin products concomitantly or within several months of each other is unknown. Excessive weakness may be exacerbated by subsequent administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of botulinum toxin products.[3-6]

Dosage and Administration

The potency (in units) of various botulinum toxin products is specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one botulinum toxin cannot be compared to or converted into units of any other botulinum toxin product. Treatment with any botulinum toxin should not be administered more frequently than every 12 weeks.

Table 8. Dosing and Administration[3-6,10]

Generic Name	Adult Dose	Pediatric Dose	Availability
AbobotulinumtoxinA	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia: Injection: initial, 500 units IM; adjust dose in 250 unit increments according to patient response	Safety and efficacy in children <18 years of age have not been established.	Powder for solution for injection: 300 units 500 units This medication is administered by a medical professional.
IncobotulinumtoxinA	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia: Injection: initial,120 units IM; maintenance,120 to 240 units IM Treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA: Injection: initial, equivalent dose as the previous onabotulinumtoxinA dose; if previous dose unknown, administer 1.25 to 2.50 units per injection site; maximum; 35 units IM per eye	Safety and efficacy in children <18 years of age have not been established.	Powder for solution for injection: 50 units 100 units This medication is administered by a medical professional.
OnabotulinumtoxinA	Prophylaxis of headaches in adult patients with chronic	Treatment of strabismus and	Powder for solution for injection:

Generic Name	Adult Dose	Pediatric Dose	Availability
	migraine: Injection: initial, 155 units IM; maximum, 360 units IM Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia: Injection: 50 units IM per injection site Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Injection: 100 units IM into the detrusor muscle Treatment of severe primary axillary hyperhidrosis: Injection: 50 units IM per axilla Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders: Injection: initial, 1.25 to 2.50 units IM per injection site; maximum, 5 units per injection site (the cumulative 30-day dose should not exceed 200 units) Treatment of upper limb spasticity in adults: Injection: up to 50 units IM per injection site Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis): Injection: 200 units IM into the detrusor muscle	blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in children ≥12 years of age: Injection: initial, 1.25 to 2.50 units IM per injection site; maximum, 5 units per injection site (the cumulative 30-day dose should not exceed 200 units) Safety and efficacy in children <18 years of age have not been established for all other indications with the exception of cervical dystonia (>16 years of age).	100 units 200 units This medication is administered by a medical professional.
RimabotulinumtoxinB	Treatment of adults with cervical dystonia to reduce the severity of abnormal head	Safety and efficacy in children have not been established.	Solution for injection: 2,500 units (0.5 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	position and neck pain associated with cervical dystonia: Injection: initial, 2,500 to 5,000 units IM; botulinum toxin-naïve patients should receive a lower initial dose		5,000 units (1 mL) 10,000 units (2 mL) This medication is administered by a medical professional.

IM=intramuscularly

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
European Federation of Neurological Societies: **Guidelines on Diagnosis and Treatment of Primary Dystonias (2011)**[11]	Recommendations for treatment: • Botulinum toxin A (or type B if there is resistance to type A) can be considered initial treatment for primary cranial (excluding oromandibular) or cervical dystonia. • Botulinum toxin A is effective for writer's cramp and is possibly effective in other types of upper limb dystonia, but controlled dose adjustments are needed because of frequent muscle weakness. • Botulinum toxin A is probably effective for adductor-type laryngeal dystonia, but there is insufficient evidence to support efficacy in abductor-type laryngeal dystonia and in muscular tension dysphonia. • Repeated treatments with botulinum toxins are safe and efficacious; however, doctors and patients should be aware that excessive cumulative doses may be dangerous, particularly in children. • Botulinum toxin injections can be performed by direct inspection; electromyography (EMG) or ultrasound-assisted targeting may improve clinical outcomes. • Avoid administering botulinum toxins to patients affected by a disorder of neuromuscular transmission or in presence of local infection at the injection site. • Currently recommended dosage should not be exceeded.
American Academy of Neurology: **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 (2008)**[12]	Blepharospasm • For patients with blepharospasm, botulinum toxin injection is probably effective with minimal adverse events. Following dosage conversion, onabotulinumtoxinA and incobotulinumtoxinA are likely equally efficacious, and onabotulinumtoxinA and abobotulinumtoxinA are possibly equally effective. • Botulinum toxin injection should be considered as a treatment option for blepharospasm, although the evidence supporting use in blepharospasm is suboptimal. Hemifacial spasm • Botulinum toxin is possibly effective with minimal adverse events in the treatment of hemifacial spasm. • Following dosage conversion, onabotulinumtoxinA and incobotulinumtoxinA are likely equally effective. • The evidence supporting use in hemifacial spasm is suboptimal. Cervical dystonia

Clinical Guideline	Recommendations
	• Botulinum toxin is established as safe and effective for the treatment of cervical dystonia. Botulinum toxin has a longstanding and widespread use in the treatment of cervical dystonia, a condition without effective alternative medical therapies. • Botulinum toxin injection should be offered as a treatment option to patients with cervical dystonia. • Botulinum toxin is likely to be more effective and better tolerated in patients with cervical dystonia compared to trihexyphenidyl. <u>Focal limb dystonia</u> • Treatment of focal limb dystonia with botulinum toxin presents challenges, in achieving sufficient neuromuscular blockade to improve dystonic movements without inducing excessive muscle weakness. Many clinicians advocate EMG or nerve stimulation to optimize needle localization for injection; however, further data are needed to establish this recommendation. • Botulinum toxin should be considered as a treatment option for focal upper extremity dystonia. <u>Laryngeal dystonia</u> • Botulinum toxin should be considered as a treatment option for adductor spasmodic dysphonia. • There is conflicting evidence supporting the use of botulinum toxin in abductor spasmodic dysphonia. <u>Tics</u> • Treatment with botulinum toxin is possibly effective for the treatment of motor tics. • There are insufficient data to determine the effectiveness of botulinum toxin in phonic tics. • There are no data to compare the efficacy of botulinum toxin and neuroleptics in the treatment of tic disorders. <u>Tremor</u> • Botulinum toxin injection in forearm muscles is probably effective in reducing the tremor amplitude in patients with essential hand tremor. Benefits must be considered against adverse events of muscle weakness associated with botulinum toxin injection. • Currently available data are insufficient to draw a conclusion on the use of botulinum toxin in the treatment of head and voice tremor.
American Academy of Neurology: **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**	<u>Upper and lower extremity spasticity</u> • Botulinum toxin is effective in the treatment of adult spasticity of the upper and lower limb to reduce muscle tone and improve passive function. • Data suggest that botulinum toxin is probably effective in improving active function. • There are inadequate data to determine if electrical stimulation or EMG techniques for optimal muscle localization improve outcomes. • Botulinum toxin should be offered to reduce muscle tone and improve passive function in adults with spasticity, and should be considered to improve active function. • There is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection.

Clinical Guideline	Recommendations
Neurology (2008)[13]	Spasticity due to cerebral palsy in children • Botulinum toxin injection in the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy. • Botulinum toxin injection should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery. • Botulinum toxin injection should be considered as a treatment option in children with upper extremity spasticity. • As in adult spasticity, there is lack of consensus on what constitutes meaningful functional gain following treatment for spasticity. While many clinicians, patients, and caregivers find the results of botulinum toxin treatment for spasticity gratifying, botulinum toxin is not approved for the treatment of spasticity in children.
American Heart Association/American Stroke Association: **Comprehensive Overview of Nursing and Interdisciplinary Rehabilitation Care of the Stroke Patient: A Scientific Statement From the American Heart Association (2010)[72]**	Spasticity • Left untreated, spasticity can lead to contracture, and activity limitations and participation restrictions will vary dramatically depending on spasticity location(s) and severity (e.g., from difficulties cleaning a palm to problems with ambulation). • Spasticity should be treated if it causes pain or affects mobility, activities of daily living or sleep. Indirect management of spasticity involves addressing conditions that may exacerbate spasticity (e.g., urinary tract infections, fecal impaction or pressure sores). A combination of physical and pharmacological modalities usually is necessary. Physical approaches include range-of motion exercises; heat, cold, and electric stimulation; and splinting. • Oral medications for spasticity of cerebral origin include dantrolene and tizanidine. Phenol or botulinum toxin injections may be used to target specific muscles or muscle groups. • For severe spastic hemiplegia, intrathecal baclofen also may be used. • Currently, neurosurgical procedures (e.g., selective dorsal rhizotomy, dorsal root entry zone lesions) lack clinical trial evidence.
American Heart Association/American Stroke Association: **Management of Adult Stroke Rehabilitation Care: A Clinical Practice Guideline (2005)[73]**	Spasticity • Spasticity and contractures should be treated with antispastic positioning, range of motion exercises, stretching, splinting, serial casting or surgical correction. • Tizanidine, dantrolene and oral baclofen are recommended for spasticity resulting in pain, poor skin hygiene or decreased function. Tizanidine should be used specifically for chronic stroke patients. • Diazepam or other benzodiazepines are not recommended for use during the stroke recovery period due to deleterious effects on recovery as well as sedation and adverse events. • Treatment with botulinum toxin or phenol/alcohol may be recommended for selected patients with disabling or painful spasticity or spasticity resulting in poor skin hygiene or decreased function. • Intrathecal baclofen is recommended for chronic stroke patients with spasticity resulting in pain, poor skin hygiene or decreased function. • Consider neurosurgical procedures, such as selective dorsal rhizotomy or dorsal root entry zone lesion, for spasticity resulting in pain, poor skin hygiene or decreased function.
American Academy of Neurology:	Axillary hyperhidrosis, palmar hyperhidrosis, gustatory sweating, drooling in neurodegenerative diseases and hyperlacrimation

Clinical Guideline	Recommendations
Assessment: Botulinum Neurotoxin 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 (2008)[18]	• Botulinum toxin is considered to be safe and effective for the treatment of axillary hyperhidrosis, probably safe and effective for palmar hyperhidrosis and in drooling in patients with Parkinson's disease and is possibly effective for gustatory sweating. • There is insufficient evidence to support the effectiveness of botulinum toxin in hyperlacrimation. • Botulinum toxin should be considered as a treatment option to patients with axillary hyperhidrosis. • Botulinum toxin should be considered as a treatment option for palmar hyperhidrosis and drooling. • Botulinum toxin may be considered for gustatory sweating. • While there are no head-to head comparisons of botulinum toxin with other treatment options in hyperhidrosis or drooling, many clinicians offer botulinum toxin to patients with axillary hyperhidrosis unresponsive to topical treatment and to patients with palmar hyperhidrosis as an alternative to iontophoresis or sympathectomy. • Use botulinum toxin with caution in patients with amyotrophic lateral sclerosis, as dysphagia or worsening weakness may occur. <u>Detrusor sphincter dyssynergia (DSD), neurogenic detrusor overactivity (NDO)</u> • Botulinum toxin is safe and effective for the treatment of NDO in adults. • Data on the use of botulinum toxin for DSD are conflicting. Botulinum toxin is probably safe and effective for the treatment of DSD in patients with spinal cord injury. • On the basis of one study, botulinum toxin does not provide significant benefit for the treatment of DSD in patients with multiple sclerosis. • Botulinum toxin should be offered as a treatment option for patients with NDO. • Botulinum toxin should be considered for DSD in patients with spinal cord injury. <u>Low back pain</u> • Botulinum toxin is possibly effective for the treatment of chronic predominantly unilateral low back pain. • Botulinum toxin may be considered as a treatment option for patients with chronic predominantly unilateral low back pain. <u>Headache</u> • Based on available clinical trial data, botulinum toxin injection is likely ineffective in the treatment of episodic migraine. • Based on inconsistent results from clinical trials, there is insufficient evidence to support or refute a benefit of botulinum toxin for the treatment of chronic daily headache. • Based on the results of clinical trials, botulinum toxin injection is probably ineffective for patients with chronic tension-type headaches. • Botulinum toxin injections should not be considered in patients with episodic migraine or chronic tension-type headaches; however, it is possible that under-dosing and suboptimal muscle selection may account for some of the reported failures in clinical trials.
American Urological Association:	<u>First-line treatments</u> • Behavioral therapies (e.g., bladder training, bladder control strategies,

Clinical Guideline	Recommendations
Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults (2012)[14]	pelvic floor muscle training and fluid management) are considered first-line treatment in all patients with overactive bladder (OAB). • Behavioral therapies may be combined with antimuscarinic therapies. Second-line treatments • Clinicians should offer oral antimuscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium as second-line therapy. No one agent is recommended over another. • If both an immediate-release (IR) and an extended-release (ER) formulation are available, then ER formulations should be prescribed over IR formulations due to lower rates of dry mouth. • Transdermal oxybutynin (patch or gel) may be offered. • If a patient experiences an inadequate response or unacceptable adverse events with one antimuscarinic medication, then a dose reduction or a switch to a different antimuscarinic medication is indicated. • Antimuscarinics should not be used in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist. Antimuscarinics should be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. • Clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative antimuscarinics. • Use caution when prescribing antimuscarinics to patients who are using other medications with antimuscarinic properties or in the elderly, frail OAB patient. • Patients who are not responsive to behavioral and medical therapy should be referred to a specialist if they desire additional therapy. Third-line treatments • Sacral neuromodulation may be considered a third-line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. • Peripheral tibial nerve stimulation may be considered as third-line treatment in a carefully selected patient population. • Clinicians may offer intradetrusor onabotulinumtoxinA as third-line treatment in carefully selected and thoroughly counseled patients who are refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary.
European Association of Urology: **Guidelines on Assessment and Nonsurgical Management of Urinary Incontinence (2012)[15]**	Antimuscarinic drugs • Offer IR or ER formulations of antimuscarinic drugs as initial drug therapy for adults with urgency urinary incontinence (UUI). • If IR formulations of antimuscarinic drugs are unsuccessful for adults with UUI, offer ER formulations or longer-acting antimuscarinic agents. • Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth. • Evaluate efficacy and any adverse events for patients on antimuscarinic medication for UUI in the first 30 days. • When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of cognitive adverse events, especially in those receiving

Clinical Guideline	Recommendations
	cholinesterase inhibitors. • Avoid using oxybutynin IR in patients who are at risk of cognitive dysfunction. • Consider use of trospium chloride in patients known to have cognitive dysfunction. Use solifenacin, tolterodine and darifenacin with caution in patients with cognitive dysfunction. • Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction. <u>Duloxetine</u> • Duloxetine should not be offered to women or men who are seeking a cure for incontinence. • Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms. • Duloxetine should be initiated using dose titration because of high adverse event rates. <u>Intravaginal estrogen</u> • Women using systemic oestrogen should be counseled that they have an increased risk for developing urinary incontinence or worsening of their existing incontinence. • Offer post-menopausal women with urinary incontinence local oestrogen therapy, although the ideal duration of therapy and best delivery method are unknown. • Advise post-menopausal women who are taking oral oestrogens that they have an increased risk for developing urinary incontinence or worsening of their existing urinary incontinence. <u>Desmopressin</u> • Desmopressin may be used in patients requiring occasional short-term relief from urinary incontinence; however, this use is off-label. • Do not use desmopressin for long-term control of urinary incontinence. <u>Intravesical injection of botulinum toxin A</u> • Offer botulinum toxin A intravesical injections to patients with UUI refractory to antimuscarinic therapy. • Warn patients of the possible need to self-catheterize and the associated risk of urinary tract infection; ensure that they are willing and able to do so.
European Association of Urology: **Guidelines on Neurogenic Lower Urinary Tract Dysfunction (2012)**[16]	<u>Drug treatment</u> • Antimuscarinic therapy for NDO is safe and effective for long-term use. • Outcomes for NDO can be maximized by considering a combination of antimuscarinic agents. • Alternative ways of administration of antimuscarinic agents (transdermally and intravesically) should be considered to reduce adverse events. • α-blockers may help to decrease bladder outlet resistance and may be a preventive measure in spinal cord injury to prevent autonomic dysreflexia. • The mainstay of treatment for overactive detrusor is antimuscarinic drug therapy. • Lower urinary tract rehabilitation may be effective in selected cases

Clinical Guideline	Recommendations
	(patients not suffering from a complete spinal cord lesion). • Any method of assisted bladder emptying should be used with the greatest caution. Intravesical drug treatment • Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce NDO. • Sphincterotomy is the standard treatment for DSD. • Bladder neck incision is effective in a fibrotic bladder neck.
National Institute for Health and Clinical Excellence: **Management of Lower Urinary Tract Dysfunction in Neurological Disease (2012)**[17]	Behavioral treatment • For patients with neurogenic lower urinary tract dysfunction, behavioral management programs should be considered (e.g., timed voiding, bladder retraining or habit retraining). • When choosing a behavioral management program, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment. Antimuscarinics • Antimuscarinic drugs should be offered to patients with spinal cord disease (e.g., spinal cord injury or multiple sclerosis) who have symptoms of OAB such as increased frequency, urgency and incontinence. • In patients with conditions affecting the brain (e.g., cerebral palsy, head injury or stroke) with symptoms of an OAB, antimuscarinic drugs should be considered. • Antimuscarinic drug treatment should be considered in patients with urodynamic investigations showing impaired bladder storage. • Residual urine volume should be monitored in patients not using intermittent or indwelling catheterization after beginning treatment. • Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections and may precipitate or exacerbate constipation. Botulinum toxin A • Bladder wall injection with botulinum toxin A should be offered to adult patients with spinal cord diseases (e.g., spinal cord injury or multiple sclerosis) and symptoms of OAB and an inadequate response to or poorly tolerated antimuscarinic drugs. • Bladder wall injection with botulinum toxin A may be considered for children and young people with spinal cord disease and symptoms of OAB for who antimuscarinic drugs were ineffective or poorly tolerated. • Bladder wall injection with botulinum toxin A may be considered in adults with spinal cord disease with urodynamic investigations showing impaired bladder storage for whom antimuscarinic drugs were ineffective or poorly tolerated. • Consider bladder wall injection with botulinum toxin A for children and young people with spinal cord disease with urodynamic investigations showing impaired bladder storage and for whom antimuscarinic drugs were ineffective or poorly tolerated. • A catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after botulinum toxin A treatment. The patient must be able and willing to manage such a regimen should urinary retention develop after the treatment.

Clinical Guideline	Recommendations
	• Monitor residual urine volume in patients who are not using a catheterization regimen during treatment with botulinum toxin A. • Monitor upper urinary tract in patients at risk of renal complications (e.g., those with high intravesical pressures on filling cystometry) during treatment. • People should be offered repeated botulinum toxin A injections and have prompt access to repeat injections when symptoms return.
American Academy of Ophthalmology: **Preferred Practice Patterns Committee. Esotropia and Exotropia (2012)**[19]	Botulinum toxin A • Chemodenervation by injection of botulinum toxin A into one or more extraocular muscles induces a temporary weakness by pharmacologic blockade of the neuromuscular junction. • While the mechanism of long-term ocular realignment in children is unknown, it likely results from contracture of the direct antagonist combined with motor and sensory adaptations that allow restoration of some degree of binocularity. • Favorable prognostic indicators include good vision in each eye, absence of restricted eye movement, a small to moderate angle of esotropia, and the potential for binocular vision. • Injections may be an alternative to conventional extraocular muscle surgery in selected patients, but its value in managing infantile esotropia has not been definitively established. • Disadvantages of treatment include: frequent need for injection (especially with larger preoperative angles), iatrogenic ptosis (may increase the risk for amblyopia) and the need for general anesthesia.
American Headache Society/American Academy of Neurology: **Guidelines for Prevention of Episodic Migraines (2012)**[74]	Drugs recommended for use • The following medications have been established as effective in the prophylaxis of migraines and should be offered to patients requiring treatment: divalproex/sodium valproate, metoprolol, petasites (butterbur), propranolol, timolol and topiramate. • The following medications are probably effective and should be considered for patients requiring migraine prophylaxis: amitriptyline, fenoprofen, feverfew, histamine, ibuprofen, ketoprofen, magnesium, naproxen, riboflavin, venlafaxine and atenolol. • The following medications have been deemed as possibly effective and may be considered for patients requiring migraine prophylaxis: candesartan, carbamazepine, clonidine, guanfacine, lisinopril, nebivolol, pindolol, flurbiprofen, mefenamic acid, coenzyme Q10, and cyproheptadine. • Please note the role of botulinum toxin A is not described within this guideline as it is not recommended for use in patients with episodic migraines.

Conclusions

There are currently four botulinum toxin products approved by the Food and Drug Administration (FDA). AbobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®) and onabotulinumtoxinA (Botox®) are botulinum toxin type A products, while rimabotulinumtoxinB (Myobloc®) is the only botulinum toxin B product.[3-6] Botulinum toxin inhibits neurotransmission between peripheral nerve endings and muscle fibers, thereby weakening or paralyzing skeletal muscle.[2] As a result, botulinum toxin has been proven to be beneficial for the treatment of conditions in which the goal of therapy is to reduce contraction of striated or smooth muscle, including blepharospasm, cervical dystonia, strabismus and upper limb spasticity. The potency (in units) of one botulinum toxin product is specific to the preparation and assay method utilized by the manufacturer and units of biological activity of one product cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay

method.[3-6] In adults with cervical dystonia, results of head-to-head studies have not demonstrated a statistically significant difference between botulinum toxin products with regard to improvements in Toronto Western Spasmodic Torticollis Rating Scale total or subscale scores for symptomatic improvement.[37-39] In studies comparing incobotulinumtoxinA and onabotulinumtoxinA in patients with blepharospasm, similar improvements in Jankovic Rating Scale scores and other clinical outcomes have been reported.[28,29,30,43] OnabotulinumtoxinA may have a longer duration of action compared to abobotulinumtoxinA, with a similar duration of action as incobotulinumtoxinA and rimabotulinumtoxinB.[29,30,38,44] The labeling for each product indicates that administration of botulinum toxin should not occur more frequently than every 12 weeks.[3-6]

Treatment guidelines recommend botulinum toxin A as first-line treatment for primary cranial or cervical dystonia, and botulinum toxin B may be used if there is resistance to botulinum toxin A. Botulinum toxin should also be considered for the treatment of blepharospasm, although the evidence supporting use its use is suboptimal.[11,12] In adults with spasticity of the upper and lower limb, botulinum toxin reduces muscle tone, improves passive function and may improve active function.[13] Specifically, in post-stroke patients, oral medications for spasticity of cerebral origin include dantrolene and tizanidine. Botulinum toxin injections may be used to target specific muscles or muscle groups or in patients with disabling or painful spasticity or spasticity resulting in decreased function.[72,73] In nonneurogenic urinary incontinence, intravesical injections of botulinum toxin A are considered a third-line treatment option for patients with urgency urinary incontinence that is refractory to behavioral modifications and antimuscarinic therapy. Botulinum toxin A injections in the detrusor are considered the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor overactivity; however, antimuscarinic therapy remains the preferred initial treatment option. [14-18] In patients with esotropia or exotropia, injections of botulinum toxin A may be an alternative to conventional extraocular muscle surgery in selected patients; however, the value in managing infantile esotropia has not been established.[19]

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