TABLE E-1 Studies Reporting the Use of BoNT-A Treatment for Lower-Extremity Spasticity in Patients with Cerebral Palsy

Author	Year	Number of Patients	Dosage	Drug	Method(s) of Evaluation*	Conclusions and/or Outcomes
Koman et al.[6]	1994	12 (6 treatment, 6 control)	Initial 1 to 2 U/kg with titration up	Botox	Physician Rating Scale	Five of six patients receiving BoNT-A improved versus two of six placebos
Corry et al.[35]	1998	20 (10 treatment, 10 control)	6 to 8 U/kg Botox, 15 U/kg Dysport	Botox or Dysport	Ashworth Scale, gait analysis, Physician Rating Scale	BoNT-A and casting provided similar outcomes
Flett et al.[36]	1999	18 (8 BoNT-A, 10 plaster)	4 to 8 U/kg	Botox	Ankle dorsiflexion, GMFM, Modified Ashworth Scale	BoNT-A and casting provided similar outcomes
Sutherland et al.[37]	1999	20 (10 treatment, 10 control)	Total 4 U/kg	Botox	Electromyography, gait analysis, plantar flexor strength, range of motion	Peak ankle dorsiflexion in stance and swing significantly improved in BoNT-A subjects
Wissel et al.[38]	1999	33 (16 high-dose, 17 low-dose)	40-80 U/muscle or 20-40 U/muscle	Botox	Ashworth Scale, gait analysis	200 U BoNT-A per leg was superior compared with 100 U
Koman et al.[14]	2000	114 (56 treatment, 58 control)	Total 4 U/kg	Botox	Gait analysis, quantification of muscle denervation by nerve conduction, range of motion	BoNT-A group demonstrated improved gait function and partial denervation of the injected muscle
Barwood et al.[39]	2000	16 (8 treatment, 8 control)	Total 8 U/kg (2 U/kg at 4 sites)	Botox	Analgesia dosage, hospital stay, pain score	BoNT-A was superior to placebo for reduction in pain, analgesic requirements, and length of hospital admission following surgery
Ubhi et al.[40]	2000	40 (22 treatment, 18 control)	25 U/kg for diplegia and 15 U/kg for hemiplegia	Dysport	GMFM, passive ankle dorsiflexion, physiological cost index, video gait analysis	BoNT-A provided superior functional outcomes
Love et al.[41]	2001	24 (12 treatment, 12 control)	2.8 to 4.7 U/kg per muscle	Botox	GMFM, parental satisfaction	BoNT-A provided superior functional outcomes

Desloovere et al.[42]	2001	34 (17 casting before BoNT-A, 17 casting after BoNT-A)	Mean 24.4 U/kg for diplegia and 16.4 U/kg for hemiplegia	Botox	Gait analysis	Casting after injections provided some enhanced benefits in proximal joints
Boyd et al.[43]	2001	39 (19 treatment, 20 control)	4 U/kg per muscle	Botox	GMFM	BoNT-A provided greater improvement in the total scores from baseline
Detrembleur et al.[44]	2002	12 (6 managed with BoNT-A + electrical stimulation, 6 managed with BoNT-A)	2 to 5 U/kg per muscle	Botox	Deep tendon reflex scale, Modified Ashworth Scale, Physician Rating Scale, range of motion	Electrical stimulation did not improve outcomes compared with BoNT alone
Polak et al.[45]	2002	48 (23 managed with 8 U/kg, 25 managed with 24 U/kg)	8 or 24 U/kg	Dysport	Gastrocnemius muscle length	24 U/kg body weight was more effective and lasted longer than 8 U/kg
Baker et al.[46]	2002	125 (36 managed with 10 U/kg, 28 managed with 20 U/kg, 30 managed with 30 U/kg, 31 control)	10, 20, or 30 U/kg	Dysport	GMFM, dynamic gastrocnemius shortening	All doses were superior to placebo; the 20 U/kg group had most pronounced improvement in dynamic measures
Reddihough et al.[47]	2002	49 (22 managed with BoNT-A + physiotherapy, 27 managed with physiotherapy)	8 to 20 U/kg distributed between two to six muscle groups	Botox	GMFM, Modified Ashworth Scale, parental questionnaire, range of movement, Vulpe Assessment Battery	Significant increase in fine motor rating and parents' rating of the treatment
Bottos et al.[48]	2003	20 (10 managed with	15 to 20 U/kg per muscle	Dysport	Ashworth Scale, gait analysis, GMFM, range	BoNT-A + casting provided more marked and enduring

		BoNT-A + casting, 10 managed with BoNT-A)			of movement	results
Kay et al.[49]	2004	20 (10 managed with BoNT-A + casting, 10 managed with casting)	8 U/kg divided between sites	Botox	Active and passive ankle dorsiflexion, GMFM, Modified Ashworth Scale	Serial casting alone provided superior results for fixed equinus contractures
Sätilä et al.[50]	2005	19 (9 proximally injected, 10 distally injected)	3 U/kg per site (12 U/kg for diplegics, 6 for hemiplegics)	Botox	Active and passive ankle dorsiflexion, Modified Ashworth Scale	Outcomes were similar for two different injection sites
Ackman et al.[51]	2005	39 (12 managed with BoNT-A, 13 managed with BoNT-A + casting, 14 managed with placebo + casting)	4 U/kg per muscle	Botox	Gait analysis	BoNT-A without casting was less effective in the short and long-term management of dynamic equinus
Mall et al.[52]	2006	61 (33 treatment, 28 control)	30 U distributed	Dysport	Knee-knee distance, GMFM, Modified Ashworth Scale	BoNT-A was superior to placebo
Hazneci et al.[53]	2006	43 (22 managed with BoNT-A, 21 managed with splinting)	300 U distributed	Botox	Knee-knee distance, GMFM, Modified Ashworth Scale, passive hip abduction	BoNT-A was superior to splinting alone
Scholtes et al.[54]	2007	46 (23 treatment, 23 control)	4 to 6 U/kg per muscle	Botox	Edinburgh Visual Gait Analysis Interval Testing scale, muscle length and spasticity	BoNT-A + rehabilitation improved gait, increased muscle length, and decreased spasticity

Hawamdeh et al.[55]	2007	60 (40 treatment, 20 control)	Range 6 to 12 U/kg (increase by factor of 5 for Dysport)	Botox or Dysport	GMFM, muscle tone, passive ankle dorsiflexion range of motion	Long-term BoNT-A + therapy reduced spasticity and improved functional mobility
Bjornson et al.[56]	2007	33 (17 treatment, 16 control)	12 U/kg distributed	Botox	National Centers for Medical and Rehabilitation Research Domains	Excellent safety profile; measurable physiological and mechanical effects may not be appreciated by patients or families
Newman et al.[57]	2007	12 (6 managed with immediate casting, 6 managed with delayed casting)	10 U/kg per muscle	Dysport	Range of motion with use of the Tardieu Scale	Delayed serial casting provided better outcomes
Graham et al.[58]	2008	91 (47 treatment, 44 control)	4 U/kg per muscle	Botox	Hip displacement/migration percentage	Possible benefit for hip displacement shown for hip bracing with BoNT-A

*GMFM = gross motor function measurements.

TABLE E-2 Studies Reporting the Use of BoNT-A Treatment for Upper-Extremity Spasticity in Cerebral Palsy

Author	Year	Number of Patients	Dosage	Drug	Method(s) of Evaluation*	Conclusions and/or Outcomes
Corry et al.[59]	1997	14 (7 treatment, 7 control)	2 to 6 U/kg for Botox or 8 to 9 U/kg for Dysport	Botox or Dysport	Hand grasp-and-release score, range of movement	Large variation in outcomes suggests BoNT-A may be useful in some patients
Fehlings et al.[60]	2000	30 (15 treatment, 15 control)	2 to 6 U/kg per muscle	Botox	Ashworth Scale, Quality of Upper-Extremity Skills Test	BoNT-A provided superior upper-extremity functional outcomes
Speth et al.[61]	2005	20 (10 BoNT-A + therapy, 10 therapy)	2 to 3 U/kg above the elbow, 1 to 2 U/kg in the forearm	Botox	Ashworth Scale, Melbourne assessment of upper-limb function, nine-hole peg test, PEDI	BoNT-A reduced impairment but there was no significant difference in functional outcome
Wallen et al.[62]	2007	72 (20 BoNT-A + OT, 20 BoNT-A, 17 OT, 15 control)	0.5 to 2 U/kg per muscle	Botox	Goal Attainment Scale, Canadian Occupational Performance Measure	Occupational therapy enhanced functional outcomes
Russo et al.[63]	2007	43 (21 treatment, 22 control)	Muscle tone specific, max 12 U/kg	Botox	Assessment of Motor and Process Skills, Goal Attainment Scale, Modified Ashworth Scale, PEDI, Pediatric Quality of Life, Tardieu Scale	BoNT-A improved body structure, activity participation, and self-perception
Kawamura et al.[64]	2007	39 (18 low dose, 21 high dose)	High dose, 0.6 to 3 U/kg per muscle; low dose, 0.3 to 1.5 U/kg per muscle	Botox	PEDI, grip strength, Quality of Upper Skills Test	No difference in hand and arm function between low and high dose
Lowe et al.[65]	2007	42 (21 BoNT-A, 21 delayed BoNT-A)	0.5 to 2 U/kg per muscle	Botox	Adverse events, Canadian Occupational Performance Measure, Goal Attainment Scale, PEDI, Quality of Upper-Extremity Skills Test	No adverse events; BoNT-A safe for upper-extremity spasticity treatment

*Additional methods of evaluation were used for some studies; OT = occupational therapy; PEDI = Pediatric Evaluation of Disability Inventory Self Care Domain; U = units.

TABLE E-3 Commonly Treated Muscles with Associated Deformities and Recommended Localization and Dosage*

Affected Joint	Deformity	Muscles Frequently Involved	Localization Technique	Lateral Gastrocnemius Dosage Ratio
Upper extremity				
Shoulder	Internal rotation	Subscapularis	EMG control or ultrasound guidance	1.02
		Pectoralis major	Palpation under stretch	0.76
		Latissimus dorsi	Palpation under stretch	0.16
Elbow	Flexion	Biceps brachii	Palpation under stretch	1.22
		Brachioradialis	Palpation under stretch	0.39
Forearm	Pronation	Pronator teres	EMG control or ultrasound guidance	0.23
		Pronator quadratus	EMG control or ultrasound guidance	0.07
Wrist	Flexion	Flexor carpi radialis	Palpation under stretch	0.1
		Flexor carpi ulnaris	Palpation under stretch	0.14
Finger	Flexion	Flexor digitorum profundus	EMG control or ultrasound guidance	0.12
		Flexor digitorum superficialis	EMG control or ultrasound guidance	0.12
		Flexor pollicis longus	EMG control or ultrasound guidance	
Thumb	Thumb-in-palm	Adductor pollicis	EMG control or ultrasound guidance	
		First dorsal interosseous	EMG control or ultrasound guidance	
		Abductor brevis	EMG control or ultrasound guidance	
Lower extremity				
Hip or pelvis	Flexion	Iliopsoas	EMG control or ultrasound guidance	
		Rectus femoris	Palpation with or without stretch	
	Abduction	Gluteus medius	Palpation with or without stretch	
		Tensor fasciae latae	Palpation with or without stretch	
	Subluxation, scissoring, or adduction	Iliopsoas	EMG control or ultrasound guidance	
		Adductor longus	Palpation with or without stretch	
		Adductor brevis	Palpation with or without stretch	
Knee	Extension	Rectus femoris	EMG control or ultrasound guidance	
		Lateralis vastus	Palpation with or without stretch	
		Medialis vastus	Palpation with or without stretch	
	Flexion	Semimembranosus	Palpation with or without stretch	0.98
		Semitendinosus	Palpation with or without stretch	0.7
		Gracilis	Palpation with or without stretch	0.32

	Equinus	Gastrocnemius (medial)	Palpation with or without stretch	1.48
		Gastrocnemius (lateral)	Palpation with or without stretch	1
		Soleus	Palpation with or without stretch	2.63
		Posterior tibialis	EMG control or ultrasound guidance	0.66
		Anterior tibialis	Palpation with or without stretch	0.84
		Peroneals (longus and brevis)	Palpation with or without stretch	

*EMG = electromyography.

TABLE E-4 Treatment of Chronic Radial Epicondylitis with BoNT-A*

Author	Year	Level of Evidence	Number of Patients	Dosage	Drug	Clinical Outcome
Placzek et al.[66]	2007	Level-I prospective randomized double-blind placebo-controlled multicenter study	132 total enrollment: 70 BoNT-A, 62 Placebo	60 units	Dysport	BoNT-A treated group demonstrated significant improvement in pain scores and patient satisfaction over the placebo group
Hayton et al.[67]	2005	Level-II prospective randomized double-blind placebo-controlled single-center study	40 total enrollment: 19 BoNT-A, 21 Placebo	50 units	Dysport	Three months following the injections, there was no significant difference between the BoNT-A group and the placebo group in grip strength, pain, and health-related quality of life
Wong et al.[68]	2005	Level-I prospective randomized double-blind placebo-controlled multicenter study	60 total enrollment: 30 BoNT-A, 30 Placebo	60 units	Dysport	BoNT-A-treated group demonstrated significant improvement in pain scores over the placebo group. There was no statistical difference in grip strength between groups
Placzek et al.[69]	2004	Level-IV retrospective case series	16 BoNT-A	60 units	Dysport	BoNT-A treatment resulted in significant improvement in pain scores and clinical scores
Keizer et al.[70]	2002	Level-II prospective, randomized single-center study	40 total enrollment: 20 BoNT-A, 20 surgery (Hohmann release)	30-40 units	Botox	Except for sick leave at 3 months, there were no significant differences (pain, ROM) between the BoNT-A treated group and the surgery group
Morre et al.[71]	1997	Level-IV retrospective case series	14 BoNT-A	20-40 units	Botox	BoNT-A treatment led to pain relief of more than 50% in 9 patients and total pain relief in 4 patients

*ROM = range of motion.

TABLE E-5 Treatment of Congenital Talipes Equinovarus Deformity with BoNT-A

Author	Year	Level of Evidence	Number of Patients (feet)	Dosage	Drug	Clinical Outcome
Mitchell et al.[72]	2004	Level-IV retrospective case series*	3 (3 feet)	10 units	Botox	All three patients experienced correction of their deformities following the injections and casting. For one patient, a tibialis anterior transfer was performed to address the forefoot adductus deformity.
Alvarez et al.[29]	2005	Level-II prospective single center study	51 (73 feet)	10 units/kg in the triceps surae muscle complex: gastrocnemius 3-6 units/kg, soleus 2-3 units/kg	Botox	One of 73 feet required surgical release; 9 required a second course of manipulation and casting including BoNT-A if necessary; and 63 of 73 required no additional casting.
Delgado et al.[73]	2000	Level-IV retrospective case series	4 (7 feet)	2 units/kg -11.6 units/kg	Botox	Although all patients experienced significant improvement after BoNT-A injections, two patients required additional surgical intervention.

*BoNT-A injections for recurrent talipes equinovarus deformity following surgical correction.

TABLE E-6 Treatment of Plantar Fasciitis with BoNT-A

Author	Year	Level of Evidence	Number of Patients	Dosage	Drug	Clinical Outcome
Babcock et al.[74]	2005	Level-II prospective, randomized, double-blind, placebo-controlled single center study	27 (43 feet)	70 units divided in two doses: 40 units in the tender region of the heel and 30 units in the most tender point of the arch	Botox	Compared with placebo injections, the BoNT-A group significantly improved in pain scores, Maryland foot scores, pain relief scores, and pressure algometry response.
Placzek et al.[75]	2005	Level-IV retrospective case series	9 (9 feet)	200 units injected subfascially in four different directions	Dysport	Significant reduction in acute pain and pain progression without any adverse events such as muscle weakness or systemic reaction.
Placzek et al.[76]	2006	Level-IV retrospective case series	25 (25 feet)	200 units injected subfascially in four different directions in 19 patients and 100 units subfascially in 6 patients	Dysport	A significant reduction in maximum and continuous pain scores was seen 2 weeks after injection in both groups (100 vs. 200 units). Clinically, the maximum and continuous pain reduction was better in patients treated with 200 units of BoNT-A.