

Supplementary Materials: Contribution of Single-Fiber Evaluation on Monitoring Outcomes Following Injection of Botulinum Toxin-A: a Narrative Review of the Literature

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Table S1. Jitter normal value reference for each study.

Authors	OO	Frontal	EDC	BB	TA	Other muscles
Sanders et al. 1986 [1]	<30	<30	<34	<30	US	
Lange et al. 1987 [2]	US	US	<34	US	US	
Olney et al. 1988 [3]	US	US	US	<28.9 ± 10.9	US	
Lange et al. 1991 [4]	US	US	Reference elsewhere [122]			
Girlanda et al. 1992 [5]	US	US	No reference, Comparison to baseline value	US	US	
Garner et al. 1993 [6]	US	US	Reference elsewhere [122]	US	Reference elsewhere [122]	
Girlanda et al. 1996 [7]	No reference, Comparison to baseline value	US	US	US	US	
Bogucki et al. 1999 [8]	<50 years: 27 ≥50 years: 29	US	US	US	US	
Bakheit et al. 1997 [9]	US	US	< 57	US	US	
Bhatia et al. 1999 [10]	US	US	US	US	US	
Schweizer et al. 1999 [11]	US	US	US	US	US	Thyroarythenoid US
Tang et al. 2000 [12]	US	US	Not precisely defined: “normal before injection”, pre-injection value written: 29.9 and 28.5	US	No precision “the changes were similar”	
Roche et al. 2008 [13]	<30	US	<40	US	US	
Osio et al. 2010 [14]	US	US	Reference elsewhere [60]	US	US	
Schnitzler et al. 2011 [15]	<10% of pairs exceeded 30 µs Or mean jitter <19 µs	US	<10% of pairs exceeded 40 µs Or mean jitter <24 µs	US	US	
Alimohammadi et al. 2014 [16]	<34	US	US	US	US	
Punga et al. 2015 [17]	US	Contralateral frontalis: US	US	US	US	
Ruet et al. 2015 [18]	Mean jitter <20 µs Individual jitter <30 µs	US	Mean jitter <25 µs Individual jitter <40 µs	US	US	
Szuch et al. 2017 [19]	US	US	Mean jitter: Voluntary SFEMG: <43,8 Stimulated SFEMG: <25	US	US	

Lispi et al. 2018 [20]	US	US	US	US	US	Injected EDB and contralateral: US
Leonardi et al. 2019 [21]	US	US	US	US	US	Deltoid: US
Timmermans et al. 2019 [22]	US	US	US	US	US	
Punga et al. 2020 [23]	US	US	US	US	US	Deltoid: US
Eleopra et al. 2020 [24]	US	US	US	US	US	ADM: US

US: unspecified.

Table S2. Study characteristics.

Authors	Population Age (years)-Sex by patient Number of patient by pathology (n)	BoNT-A Brand Name ® Number of injections Dose Previous injection	Muscle(s) studied	SFEMG Device used Calculation jitter methodology	Interval between BoNT-A and SFEMG Jitter MCD in µs; By patient and muscle
Sanders et al. 1986 [1]	age and sex US BSP n = 4	Botox® 1 injection except #1 with 2 injections All patients: 12.5 MLU Previous: US	OO EDC Frontal BB	Device: US ; Standard electrode No description	#1 D -5; OO: 30; Frontal: 24; EDC: 30 D 1: OO: 90; Frontal: 21; EDC: US D 2: OO:106; Frontal: 56; EDC: US D 51: OO: 305; Frontal: 56; EDC: 27 D 147: OO: 114; Frontal: 49; EDC: US D 51 after the second one: OO: 123; Frontal: 90; EDC: 50 D 158 after the second one: OO: 93; Frontal: 37; EDC: 32
					#2 D 53: OO: 300; Frontalis: >300; EDC: 44 D 188: OO: 83; Frontalis: 97; EDC: 33
					#3 D 0: OO: 43; EDC: 30 D 3: OO: >300; EDC: 30 D 60: OO: US; EDC: 37
					#4 D 42: EDC: 40; BB: 66 D 100: EDC: 34; BB: 26
Lange et al. 1987 [2]	#1/51/F #2/58/F #3/42/F #4/49/F #5/62/M Dystonic disorders n=3 torticollis n = 1 oromandibular dystonia n = 1	Botox® (MLU) 2 injections for #1 and #2 #1: 285; 450 #2: 372; 687 #3: 100 #4: 302.5 #5: 245 First injection	EDC	Standard electrode Peak-to-peak amplitude >200 µV, rise time <300 µs, 20 pairs	#1: Before injection: 28 2 W after the 1 st one: 49.2 4 Mt after 2 nd one: 41 #2: 6 W after the 1 st one: 37 3 W after 2 nd one: 36 #3: 2 W after the 1 st injection: 27.1 #4: 3 W after the 1 st injection: 54.2 #5: 6 W after the 1 st injection: 65.2

Olney et al. 1988 [3]	#1/48/F #2/53/F #3/64/F #4/46/F #5/62/M #6/31/M Torticollis n=6	One injection 280 UI First injection	BB	Dantec 1500; 13K87 Standard electrode Peak-to-peak amplitude >200 μ V, rise time <300 μ s, constant shape over time. 50 to 100 consecutive discharges of each 20 pairs of voluntarily activated single muscle fibers; commercially available jitter meter	#1: W 0: 26; W 2: 25; W 4: 29 #2: W 0: 28; W 2: 32; W 4: 39 #3: W 0: 30; W 4: 27 #4: W 0: 27; W 8: 41 #5: W 0: 30; W 10: 46 #6: W 0: 33; W 12: 46
Lange et al. 1991 [4]	Torticollis n = 42	Botox® n = 23 Pb n = 19 One injection Doses BoNT-A (U) 140, 150, 165 (detailed elsewhere [99]) First injection	EDC n = 36 BB n = 4 TA n = 2	Standard electrode Computer programs TECA Mystro and Nicolet Viking Peak-to-peak amplitude >200 μ V, rise time <300 μ s, constant shape over time. At least 50 consecutive discharges of each 20 pairs of voluntarily activated	Before injection (n = 42) EDC 21-30 (for both groups) BB 21.7 TA 28.8 Pb 25.7 2 W (n = 42) EDC BoNT-A 43.6 Pb 26.5 <i>unchanged from preinjection p < 0.05</i> BB: US TA: US 12 W (n = 27) EDC 35.5 Pb 24.5 BB: US TA: US
Girlanda et al. 1992 [5]	Sex US #1 #2 #3 BSP #4 HSF #5 spasmodic torticollis with 2 nd dosage doubled	Botox® #1 #2 #3 #4 20 U #5 65 U 2 sessions of injection First injection	EDC	Standard electrode 20 pairs Electromyograph BASIS EPM (OTE BIOMEDICA)	D 45 after the 1 st injection: 32.6 D 45 after 2 nd injection: 40 D 1, 4, 7, 14, 30 after 1 st injection and D 1, 4, 7, 14, 30, 60 and 90 after 2 nd injection: US for each patient, data represented on figure
Garner et al. 1993 [6]	#1/46/F/Perioral dystonia #2/40/F/Torticollis #3/31/M/Torticollis #4/66/M/Torticollis #5/39/M/HSF #6/58/F/MGS #7/45/M/Torticollis #8/57/F/Torticollis	First injection One injection (ng): #1: 5 #2: 22.5 #3: 15 #4: 20 #7: 15 #8: 20 #5: 2 #6: 6	EDC all patients Alternatively, right and left sided muscles Except #5 only right + TA for #1 #7	Standard electrode MEDELEC MS 20 Peak-to-peak amplitude >500 μ V, rise time less than 250 μ s 20 fiber pairs	Details given for maximum MCD #1: EDC: D 13: 142; TA: D13: 129 #2: D 7: 121 #3 D: US: <i>normal</i> #4: D 6: 54.5 #5: D US: <i>normal</i> #6: D 11: 50.2 #7: EDC: D 7: 66.9; TA: D5: 48 #8: D 3: 156
Girlanda et al. 1996 [7]	Age US; 3F/3M BSP n = 6	Botox® 20 units One injection No detail about injection past history	Bilateral OO	Mystro Medelec MS25 Standard electrode 20 pairs Electrophysiological investigator blinded to treatment	Baseline: BoNT-A: normal (<30 μ s); Pb: around 25 μ s, [20 μ s- 30 μ s] W 1: BoNT-A: mean 75 μ s, [50 μ s-100 μ s], p < 0.02; Pb: mean 35 μ s [25 μ s-42 μ s]; <i>non- significantly</i> W 2: BoNT- A: mean 150 μ s, [50 μ s-

						250μs], p < 0.01; Pb: mean 41 μs [32μs-48μs], p < 0.01 Mt 1: BoNT-A: mean 125 μs, [50 μs-175μs], p < 0.02; Pb: between 36 and 38 μs, p < 0.02 Data detailed in figures
Bogucki et al. 1999 [8]	#1/45/F/MGS #2/67/F/BSP #3/64/F/HSF #4/71/M/BSP #5/41/F/BSP #6/84/F/BSP #7/47/F/HSF #8/59/F/HSF #9/65/F/HSF #10/58/F/MGS #11/72/F/BSP #12/51/F/BSP #13/73/F/MGS #14/69/F/BSP #15/42/M/BSP #16/63/M/MGS BSP n = 8; MGS n = 4; HSF n = 4	Dysport® 120 UI/ muscle One injection Bilateral for BSP One side for HSF First injection	OO	Mk2 Dantec 13K87, Denmark Standard electrode Slight voluntary contraction of OO 20 pairs		Before injection: 22.7 ± 2.5; n = 16 Early remission (D 7-14; mean 9.9 ± 2.2): 99.9 ± 50.1; n = 15/16 Late remission (D 23-57; mean 35.6 ± 11.6): 96.3 ± 35.1; n = 15/16 When dystonic movements occurred (D 57-265; mean 116.7 ± 52.5): 59.8 ± 18.8; n = 13/16 decrease in jitter was noted compared to pretreatment (p < 0.0005), 1 st (p < 0.015) and 2 nd (p < 0.002) posttreatment analysis
Bakheit et al. 1997 [9]	#1/67/F/MS #2/34/F/MSA with torticollis	Dysport® #1 250 U for left leg #2 750 U 250 in right SCM and left splenius capitis - 500 in left trapezius	EDC	Standard electrode		Interval US #1 ranged from 92.6 to 408 #2 US
Bhatia et al. 1999 [10]	#1/45/F/Cervical dystonia #2/57/F/Symptomatic hemidystonia #3/32/F/Symptomatic hemidystonia	Dysport® One injection #1: 650 UI: SCM 300, Left splenius capitus 300, Right splenius capitus 200 History of 650 UI Dysport® at 12-14 intervals weeks between November 1989 and 1995 #2: Total dose 900 UI Dysport® Previous: March 1989 – October 1991: 30 months of injections, total dose at each visit ranged from 350 -800 UI at intervals of 10-12W #3: History: Since January 1988, at 8 and 10 W intervals with an average dose of 600 UI at each visit October 1990 in addition to usual injections further dose of 200UI	#1 1 st SFEMG right EDC 2 nd SFEMG right EDC Deltoid iliopsoas 3 rd SFEMG right EDC #2 Right EDC and BB #3 US	Standard electrode #1 10 pairs		#1 W 2: 93.6 Mt 4: No precise data: <i>excessive jitter</i> Mt 9: Normal 20.1 #2 Mt 2: BB: normal; EDC: no data precision: <i>3/11 pairs showed abnormal jitter</i> #3 Mt2: No data: normal

		given into left gastrocnemius			
Schweizer et al. 1999 [11]	73/Sex US SFEMG studied n = 10 BoNT-A injection for spasmodic dysphonia n = 1	periodically injected since 1990 dose US	laryngeal muscles	CNE	7 Mt after the last injection: 40.7
Tang et al. 2000 [12]	Patients injected Botox® n=192; CBTX-A® n=593 only 40 SFEMG 5-82/28F/12M HSF n=17; BSP n = 8 MGS Syndrome n = 2 Cervical dystonia n = 13 Botox® n = 18 CBTX-A® n = 22	Botox® 99.4 UI (30-300) CBTX-A 107.3 UI (30- 300 UI)	EDC TA	Counterpoint MKII Dantec Standard electrode	Before: normal for both Botox® and CBTX-A® W 2-3: Botox®: EDC 29.9 to 36.2 (+21%, p<0.01); CBTX-A®: EDC 28.5 to 36.4 (+27%, p<0.01 W 5-8 and Mt 4-5: Data shown in figure only
Roche et al. 2008 [13]	Patients from a cohort of 187 patients Dysport® n = 33 Botox® n = 233) 25-59 #1/25/M/MS #2/32/F/Paraplegia #3/42/F/Hemiplegic #4/59/F/Hemiplegic	Dysport® #1 1000 UI #21500 UI #3 1000 UI #4 1000 UI One injection for all Previous: #1 Botox®400 UI/ Dysport®1000 UI #2 Botox®500 UI #3 Botox®300 UI #4 Botox®400 UI / Dysport® 1000 UI	#1 EDC #2 EDC #3 OO #4EDC	Nicolet Viking II electromyography Standard electrode Stimulated technique frequency of 10 Hz Peak-to-peak amplitude > 200 µV, rise time < 300 µs, constant shape over time. 100 consecutive discharges of each 20 pairs of stimulated single muscle fibers	#1: D34: 31.1; Mt 3: 25.2 #2: D27: 54.22; Mt 3: 23.8 #3: D30: 31.31 #4: D31: 33.09
Osio et al. 2010 [14]	BoNT-1 group n = 14 Pb group n = 10 BoNT-A group M/F = 0.2 Pb group M/F = 0.3 Obesity n = 24	Botox® 200 UI One injection First injection	Right EDC	Voluntary contraction No data for all devices except the needle: <i>single fiber needle Oxford Instruments</i> 20 pairs registered Calculation methodology not detailed refer to a bibliographic reference [25]	BoNT-A n = 14/14 Pb n = 9/10 (1 refused SF) Pretreatment: BoNT-A 29.12; SD 4.38; Pb 29.44; SD 3.64 D 8: BoNT-A 29.59; SD 3.55 Pb 27.67; SD 3.84 Jitter change (post-pre) 95% confidence interval BoNT-A -1.85; 2.79; p = 0.674 Pb -5.73; 2.17; p = 0.330 EDC 17/18: mean jitter 18.9 µs OO: mean 22.2 µs D 26 ± 8 after injection Details of each patient (D)
Schnitzler et al. 2011 [15]	42.1 ± 14.4; sex US #1/60; #2/29; #3/29; #4/50; #5/63; #6/28 #7/39; #8/56; #9/38; #10/50; #11/22; #12/43; #13/34; #14/64; #15/47; #16/26; #17/23; #18/65; #19/38; #20/57; #21/24 8F/13M Medullary lesion with neurogenic overactive bladder n = 21	Botox® 300UI One injection First injection n = 2/21 N = 19/21 Mean number of injections prior to study inclusion: 2.6 ± 1.7 (0-6 injections) Average interval between BoNT-A injections Mt 6 ± 1 (Mt 4- 12)	EDC n = 18/21 OO n = 3/21: #5; #13; #17	Viking EMG II Stimulated SFEMG Peak-to-peak amplitude >200 µV, rise time <300 µs, constant shape over time, 100 consecutive discharges of 20 pairs	Details of each patient #1: D 29: 24.90; #2: D30: 15.90; #3: D14: 21.05; #4: D24: 24.17; #5: D50: 25.90; #6: D 25: 19.50; #7: D 15: 21.20; #8: D 21: 23.40; #9: D 24: 15.50; #10: D 30: 19.09; #11: D 17: 22.15; #12: D 34: 37.50; #13: D 34: 20; #14: D 24: 17.17; #15: D 22:

						23.47; #16: D 36: 20.90; #17: D24: 20.8; #18: D 28: 18.45; #19: D 24: 15.60; #20: D 25: 15.20; #21: D 22: 15.30
						Baseline: mean 28 (23- 32) whole group W 2: for 12 intervention subjects, increased to 35 (30-39), $p < 0.001$ Pb: 29 -Individual (only detailed for W 0-2) Baseline Pb: Median 28.7; Mean 28.8 ± 1.7 5 UI: Median 25.8; Mean 25.8 ± 3.1 10 UI: Median 28.1 Mean 28.1 ± 0.8 20 UI: Median 29.1; Mean 29.1 ± 2.7 W 2 Pb: Median 29.3; Mean 29.3 ± 2.4 5 UI: Median 33.9; Mean 33.9 ± 4.2 10 UI: Median 34.4 Mean 35.1 ± 2.7 20 UI: Median 37.1; Mean 36.4 ± 2.5 -Mean change between W 0-2 Pb group 1.9 ± 11.6 % p = 0.76 5 UI group 32.8 ± 23.8 % $p = 0.070$ 10 UI group 24.9 ± 10.6 % $p = 0.018$ 20 UI group 26.1 ± 16.8 % $p = 0.053$
Alimohammadi et al. 2014 [16]	Age US; 16F/0M Healthy n = 16	<i>Vistabel</i> Each group n = 4 5 UI 10 UI 20 UI Pb group One injection First injection	OO	Keypoint Medtronic Slight voluntary contraction, 20 pairs		
Punga et al. 2015 [17]	33-52/5F; Sex US Visible glabellar frown lines at rest n = 5	<i>Vistabel</i> Onabotulinumtoxin A Total dose : 2.5 UI n= 1; 5 UI n = 3; 10 UI n = 1; One injection First injection	contralateral frontalis muscle	Keypoint Medtronic 20 pairs		28 range 25-32 34 range 27-39 $p = 0.05$
Ruet et al. 2015 [18]	Age & Sex US SFEMG n = 35 patients presented side effects after BoNT-A injection, categorized into: Fatigue group n = 15; age 48 ± 14 Pseudo-botulism group n = 20; age 41 ± 11 Control group n = 17; age 43 ± 13 Botulism group n = 3; age 53 ± 24	Botox® / Dysport® Fatigue group 10/4 * Pseudo-botulism group 15/4 * Control group 17/0	EDC/OO Fatigue group 8/7 Pseudo-botulism group 11/9 Control group 15/2	Neuropack M1 20 pairs		Fatigue group: D 36 ± 21 EDC 20.5 ± 2.8 (15.0 – 33.1) OO 20.8 ± 3.17 (16.6 – 31.6) Pseudo-botulism group: D 42 ± 24 EDC 42.2 ± 24.4 (21.5 - 110.9) OO 21.7 ± 8.7 (13.8 - 31.3) Control group: D 24 ± 8

					EDC 20.9 ± 7.2 (15.2 – 37.5) OO 22.9 ± 2.9 (20 – 25.9) EDC: Jitter significantly higher in the pseudo-botulism group than in the control ($p < 0.001$) and fatigue group ($p = 0.0005$) No difference between fatigue and control group OO: no significant difference between groups
Szuch et al. 2017 [19]	Age & Sex US N = 1 right foot dystonia with iatrogenic botulism (head drop, bulbar and systemic weakness in Parkinson's disease)	Botox® 4 M from previous one Total 600 UI 5 th injection: EHL 50; FDL 150 Gastrocnemius 150 Peroneus longus 150 Soleus 100 Previous injections: 1 st and 2 nd "preparation and dose unknown" 3 rd 400 UI time US 4 th 600 UI 5M later	Left EDC	Nicolet Viking IV Voluntary SFEMG Upper limit 43.8 + Stimulated SFEMG Upper limit 25 Methodology not detailed	Voluntary SFEMG: D 21 8 pairs with mean jitter 66.24 (norm set at 43.8 μ s) Stimulated SFEMG: D 21 16 pairs with mean 52.74 (norm set below 25 μ s)
Lispi et al. 2018 [20]	Age US; 2F/8M mean 53 Healthy n = 10	Incobotulinumtoxin A Merz® 15 UI each patient One injection First injection	EDB bilaterally	Medelec Synergy using a concentric needle described elsewhere [26]	Baseline: 28 ± 7.5 W1: 33 ± 6.7 W2: 45 ± 9.2 W3: 55 ± 8.1 W4: 111 ± 10.1 W 6: 120 ± 9.5 W 8: 142 ± 6.3 W 10: 110 ± 11.3 W 12: 66 ± 8.5
Leonardi et al. 2019 [21]	#1/48/F/MS #2/32/M/CP	#1 Botox®: 400 UI 2 Mt later: 600 UI 5 Mt later: 400 UI #2 : Dysport®: 1500 UI	#1 left deltoid #2 EDC	US	#1: Mt 5: 111.4 #2: D 10: 75.6
Timmermans et al. 2019 [22]	43/M	Azzalure® 84 UI Previous Similar injection 2 years earlier	Left OO	US	W 6: 112
Punga et al. 2020 [23]	#1/55/F/wrinkles #2/46/M/migraine	#1 Dose: no data Previous injections Also received regular BONT-A injections at a beauty clinic #2 14 treatments of 155 UI of Dysport® divided between a total of 31 points (≈ 3 UI/injection point)	#1 Left OO Left frontalis Left Deltoid #2 Left OO	CNE Voluntary technique No device cited	#1: 1 Mt and a few days OO 125 μ s, 60% increased jitter, Frontalis: No precise data: increased jitter 70% Mt 2: OO: 62 μ s; Frontalis: jitter was increased Deltoid 25 μ s, normal #2: W 2: OO: 37 μ s; increased jitter 38% Mt 4: Jitter analysis in the left OO [...] also normal

				Before
				BoNT-A 25.5 (13)
				BoNT-B 25.5 (11)
				BoNT- C 24.5 (12)
				BoNT-F 25 (12)
				Placebo 26 (13)
				W 2
				BoNT-A 89 (35)
				BoNT-B 78 (38)
				BoNT- C 80 (30)
				BoNT-F 108 (25)
				Placebo 28 (14)
				W 4
				BoNT-A 72.5 (25)
				BoNT-B 69 (18)
				BoNT- C 69 (26)
				BoNT-F 90 (30)
				Placebo 30 (11)
				W 6
				BoNT-A 67 (19)
				BoNT-B 71 (22)
				BoNT- C 65 (27)
				BoNT-F 84 (29)
				Placebo 24 (15)
				W 8
				BoNT-A 52 (22)
				BoNT-B 63 (28)
				BoNT- C 55 (18)
				BoNT-F 51 (20)
				Placebo 27 (13)

In italics: cited from original text#: Patient; *: missing data; ADM: abductor digiti minimi; BB: biceps brachialis; BSP: blepharospasm; CBTX-A®: Chinese type A botulinum toxin; CP: cerebral palsy; D: day; EDB: extensor digitorum brevis; EDC: Extensor digitorum communis; EHL: extensor hallucis longus; F: female; FDL: flexor digitorum longus; FDP: flexor digitorum profundus; FDS: flexor digitorum superficialis; FHL: flexor hallucis longus; FRC: flexor carpi radialis; HSF: hemifacial spasm; HSP: Hereditary spastic paraparesis; M: male; MCD: Mean consecutive difference; MGS: Meige Syndrome; MLU: Mouse lethal unit; MS: multiple sclerosis; MSA: multiple system atrophy; Mt: Month; MU: Mouse unit: 2.5 ng of Botox® = 1 U = mouse LD50 (99); OO: orbicularis muscle; Pb: placebo; SCM: sternocleidomastoid; SD: standard deviation; TA: tibialis anterior; TS: triceps solear; UI: international unit; US: unspecified; W: week.

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