WORLDWIDE SURVEY OF CLINICIAN PRACTICE ON USE OF ADJUNCTIVE THERAPIES FOLLOWING BOTULINUM TOXIN INJECTION FOR SPASTICITY

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Objective: Non-pharmacological adjunctive therapies can be used alongside botulinum toxin injection to enhance its efficacy. The objective of this global study was to determine the current practice and perception among clinicians of the use of adjunctive therapies after botulinum toxin injections for the treatment of limb spasticity.

Methods: A questionnaire with 22 questions on clinical practice demographics, self-reported use and clinician opinion on barriers to the use of complementary therapies, and priorities for future research was translated into 7 languages and distributed worldwide through national and international professional associations concerning (neuro)rehabilitation.

Results: A total of 527 clinicians from 52 countries responded to the survey. Most commonly used physical interventions were: active exercise programmes at home (81%), stretching programmes at home (81%), and splinting (70%), followed by active movement exercises (65%) and within 30 min of botulinum toxin injection and constraint induced movement therapy (63%). The main barriers reported by clinicians to provision of these interventions were clinicians' lack of time, limited financial resources, and lack of evidence. Future research should focus primarily on immediate active movement exercises and passive stretching. Conclusion: Worldwide, clinicians often recommend adjunctive therapies after a botulinum toxin injection to reduce spasticity. The most commonly used physical interventions among clinicians were active exercises at home, stretching at home, and splinting. Lack of evidence, time and financial constraints were identified as barriers to providing these interventions.

LAY ABSTRACT

A neurological injury, such as a stroke, traumatic brain injury or spinal cord injury, may cause muscle stiffness, a condition known as spasticity. Among available treatments for spasticity, botulinum toxin, a neurotoxin injected into the muscle, is used in cases of focal spasticity. Adjunctive therapies are therapies other than drugs that are used to enhance the efficacy of a treatment, such as botulinum toxin. The aim of this worldwide survey of clinicians was to determine the current clinical practice and perception of the use of adjunctive therapies following botulinum toxin injections. The results showed that the most frequently prescribed adjunctive therapies were active exercises at home, stretching at home, and splinting. The main barriers reported by clinicians to provision of these interventions were clinicians' lack of time, limited financial resources, and lack of evidence.

Key words: muscle spasticity; botulinum toxin; healthcare survey; muscle stretching exercise; exercise therapy; splint; electric stimulation; extracorporeal shockwave therapy.

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Patients with central nervous system (CNS) disorders such as stroke, traumatic brain injury, multiple sclerosis, cerebral palsy or spinal cord injury frequently present with a spastic paresis syndrome. This syndrome includes a muscle, joint and connective tissue disorder in which shortening and stiffness of the muscles are

accompanied by a loss of stretch, largely due to the neurological disorder. Such neurological disorders to implementation (8). cause stretch paresis and spastic muscle overactivity (SMO), including spasticity, spastic dystonia, and spastic co-contraction (1). SMO negatively affects the patient's passive (hygiene and increased caregiver burden) and active (walking, manipulating objects) function and quality of life. Therefore, a large consensus orts adequate SMO treatment (2). SMO treatment is multimodal, including rehabilitation, orthosis, chemodenervation with alcohol, phenol or botulinum toxin (BoNT) and surgery. In the treatment of focal SMO, BoNT is usually considered as the first-line treatment with the highest level of evidence. BoNT is a neurotoxin that blocks the release of acetylcholine from the pre-synaptic nerve endings, inducing a decrease in muscle tone. BoNT acts as early as 1 week after injection, with peak effects at 4–6 weeks and a duration of effect ranging between 2 and 6 months. Patients frequently complain about insufficient and short duration of effect and symptom re-emergence between injections, supporting rapid reinjection, increased dosage and/or application of an adjunctive therapy (3). Adjunctive therapy is defined as the application of a non-pharmacological treatment after BoNT injection in order to enhance the effect of BoNT. Most physical interventions mentioned as possible adjunctive therapy are effective on their own and are recommended as best practice in neurorehabilitation (4). It is of interest to determine whether the application of such interventions in combination with BoNT injection could improve outcomes. Recent literature supports the fact that adjunctive therapy may be effective to increase BoNT effect and improve spasticity outcomes (5, 6) based on the Physiotherapy Evidence Database (PEDro) scale and according to Sackett's levels of evidence (7). An additional decrease in Modified Ashworth Scale by at least 1 grade was observed after the application of neuro-muscular electrical stimulation (EStim), constraint induced movement therapy (CIMT) and physical therapy (both level 1) as well as casting and dynamic splinting (level

2) (5, 6). There is also a level 1 evidence that casting

is more effective than adhesive taping for outcomes

including spasticity, range of motion and gait, and

that extracorporeal shock wave therapy (ESWT) is

better than EStim for outcomes including spasticity

and pain (6). An international consensus recommends

adjunctive therapies as best practice on the optimal

use of BoNT within a multidisciplinary context (4).

The choice of adjunctive procedures should be made according to individual needs and treatment goals (4). A recent survey conducted in Canada revealed

that physicians frequently use adjunctive therapies in

combination with BoNT injection. Financial and time

constraints were identified among clinicians as barriers

The aim of this survey was to enlarge the Canadian survey worldwide to understand current clinical practice in the use of adjuvant therapies after BoNT injection, barriers to the use of adjuvant therapy among clinicians, and future research priorities in this area.

METHODS

Survey design

This international online survey was conducted between November 2019 and April 2020. The structure and contents of the survey were based on the survey used in the Canadian study (8). Eight authors translated the survey in his/her native language. No validation process was used.

The survey comprised 22 questions that related to participant and clinical practice demographics, clinician self-reported use of adjunctive therapies, and clinician opinions on barriers to use of adjunctive therapies and future research priorities (Appendix 1). The survey fulfils the e-survey guidelines (Appendix 2) (9). The survey was hosted online by UBC Survey Tool.

Recruitment and survey participants

The survey was conducted in compliance with relevant codes of conduct and data protection legislation (see privacy statement appendix 1). Ethics committee approval was obtained in author and co-authors countries from the Comité d'éthique du C.H.U. UCL Namur, Sit Godine, Belgium (Reference number: 21/2019), 5479 - Santa Casa de Misericórdia de São Paulo, Brazil (Reference number: 5991219.0.0000.5479), University of British Columbia (UBC) Clinical Research Ethics Board, Canada (Reference number: H18-01840), Hopitaux Universitaires Henri Mondor IRB, France (Reference number, ID-RCB: 2022-A01342-41), Azienda Osepdaliera Universitaria Integrata (AOUI) of Verona, Italy, Bioethics Committee at the District Medical Chamber in Gdańsk, Poland (Reference number: KB - 2/19), King's College London, United Kindom (Reference number: Minimal Risk Ethical Review MRA-18/19-9101). The survey was sent via the national and international scientific societies concerning (neuro)rehabilitation (see Acknowledgments member mailing lists). All participants provided informed consent to participate. Clinicians (medical doctors and physical therapists) practising BoNT injections for spasticity were invited to complete the survey.

Data analysis

All questionnaires were analysed for frequency of responses and reported as the number of responses.

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Data were expressed as median and percentage values unless otherwise indicated. Subgroup analyses were performed with Fisher's exact χ^2 tests to compare responses between clinicians working in academic vs non-academic, community, and private settings, as well as clinicians working in multidisciplinary teams vs solo practice (clinician only). Post hoc subgroup analysis was performed with a Bonferroni test to compare responses between low/middle-income and high-income countries (10). Statistical significance was set at p < 0.05. Statistical analysis was performed using SPSS, version 20 (IBM Corporation, Armonk, NY, USA).

RESULTS

Completed questionnaires were received from 527 clinicians across 57 countries in 6 continents. The participation rate (ratio of unique visitors who agreed to participate/unique first survey page visitors) was 99.4%, and the completion rate (ratio of users who completed the survey/users who agreed to participate) was 75.5% (398 completed surveys). Clinician and practice demographics are shown in Table I.

Table I. Characteristics of clinicians who responded to the survey (n=527)

Clinician's characteristics	
Age, years, median (range)	45 (29-90)
Length of clinical experience, years, median (range)	18 (1-55)
Length of BoNT use experience, years, median (range)	10 (1-35)
Sex, n (%)	
Male	164 (31)
Female	279 (53)
Not specified	84 (16)
Specialty, n (%)	
Physical Medicine & Rehabilitation	300 (57)
Neurology	59 (11)
Physical therapy	73 (14)
Other	95 (18)
Setting, n (%)	
Academic	228 (43)
Non-academic	162 (31)
Community or private practice	95 (18)
Not specified – other	42 (8)
Multidisciplinary team, n (%)	
Monodisciplinary	71 (14)
Multidisciplinary	354 (67)
Not specified	102 (19)
Area, n (%)	
North America	10 (2)
South America	52 (10)
Europe	281 (53)
Africa	44 (8)
Asia	38 (7)
Oceania	23 (4)
Not specified	87 (17)
Countries by income, n (%)	
High-income	333 (63)
Middle-income	109 (20)
Low-income	1 (<1)
Not specified	84 (16)

BoNT: botulinum toxin.

The distribution of clinicians in high- and low/ middle-income countries was significantly different, with more physiotherapists in high-income countries and fewer physicians in physical and rehabilitation medicine in low/middle-income countries (see Fig. 1). No significant difference was found in the distribution of specialists working in an academic or non-academic and multidisciplinary or solo setting

Table II shows the frequency of use of adjuvant treatments by the respondents, as well as the barriers among clinicians to the use of adjuvant treatments. The 3 most frequently used adjunctive therapies are: active exercise programme at home (81%), stretching programme at home (81%), and splinting (70%).

After subgroup analysis, the following statistically significant differences were obtained for the frequency of adjuvant treatments: of the participants who prescribe splints, 95.1% work in a multidisciplinary setting vs 86.4% in a solo setting. The same was true for CIMT: 67.1% work in a multidisciplinary setting vs 49.2% working solo (see Table III). The following treatments were used more frequently in a non-academic/private practice compared with an academic hospital: stretching programme at home (98.2% vs 87.7%), active exercise programme at home (97.3% vs 87.9%), TENS (Transcutaneous Electrical Nerve Stimulation) (47.3% vs 26.2%) and motorized arm ergometry (42.7% vs 27.1%) (see Table IV). There was a similar trend regarding the difference in frequency of TENS use between middle- and high-income countries: 49.4% of participants from middle-income countries used TENS compared with 27.3% of participants from high-income countries. In addition, magnesium supplementation (23.9% vs 9.1%) and dietary change recommendations (e.g. reducing sugar intake to optimize blood sugar control) (42.2% vs 19.3%) were used more frequently in middle-income countries compared with highincome countries (see Table V).

Lack of time, lack of financial resources and insufficient scientific evidence are the main barriers among clinicians to the use of adjuvant therapies (see Table II). Especially for adjuvant treatment used immediately after BoNT injections (immediate active movement, stretching, EStim and ESWT) and for the less-used adjuvant therapies, lack of evidence is the biggest barrier. The statement that "the patient does not want the adjuvant treatment" was the least frequently identified as a barrier.

Subgroup analysis showed a significant difference between the barriers mentioned by clinicians from low/middle-income countries vs high-income countries for zinc supplementation and casting of the upper limb (see Table VI). Participants from middle-income

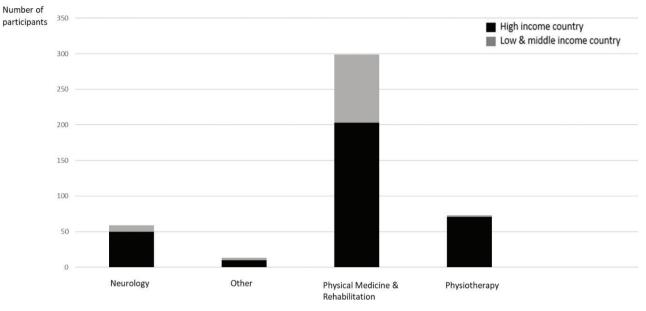


Fig. 1. Specialties of clinicians who responded to the survey, and proportions of respondents in high- and low/middle-income countries.

countries mentioned clinician constraints (28.7% vs 7.5%, p = 0.00005) as a barrier for zinc supplementation significantly more than those from high-income countries. On the other hand, they mentioned lack of evidence for zinc supplementation (29.9% vs 55.4%, p = 0.00225) and adjunctive therapy time constraints (0% vs 16.7%, p = 0.0017), clinician constraints (1.7% vs 23.1%, p = 0.0002) and financial constraints (0% vs 17.3%, p = 0.0012) for casting of the upper limb signifi-

cantly less than those from high-income countries. For the other subgroups (multidisciplinary setting vs solo setting, and non-academic/private practice vs academic hospital) there were no significant differences.

Clinicians indicated a need for more evidence for the use of any adjuvant therapy after BoNT injections. They particularly indicated that future research should prioritize treatments that can be applied immediately after BoNT injection (see Fig. 2).

Table II. Adj	iunctive ther	any use a	and harriors	amona	liniciane
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					Perceived b	parriers to use
Adjunctive therapy	п	Clinician use n (%)	Most commonly reported barrier	n (%)	Lack of evidence n (%)	Patient does not want n (%)
Active exercise programme at home	369	300 (81)	Time constraints	56 (15)	11 (3)	47 (13)
Stretching programme at home	371	299 (81)	Time constraints	68 (18)	30 (8)	38 (10)
Splinting	368	256 (70)	Financial - Patient resources	53 (14)	47 (13)	47 (13)
Immediate active movement	387	252 (65)	Clinician time constraints	98 (25)	84 (22)	20 (5)
			Time constraints	91 (23)		
CIMT	366	231 (63)	Time constraints	75 (20)	32 (9)	46 (12)
Immediate stretching	399	235 (59)	Time constraints	135 (34)	107 (27)	22 (5)
			Clinician time constraints	131 (33)		
Lower extremity casting	358	209 (58)	Clinician time constraints	63 (17)	20 (6)	44 (12)
FES	365	204 (56)	Financial – Clinician /clinic resources	95 (26)	49 (13)	14 (4)
Delayed EStim	365	177 (48)	Lack of evidence	77 (21)	77 (21)	15 (4)
Upper extremity casting	360	172 (48)	Clinician time constraints	57 (16)	29 (8)	44 (12)
Taping	347	160 (46)	Lack of evidence	105 (30)	105 (30)	19 (5)
Immediate EStim	389	120 (31)	Lack of evidence	119 (30)	119 (30)	9 (2)
TENS	364	117 (32)	Lack of evidence	110 (30)	110 (30)	19 (5)
Motorized arm ergometry	365	117 (32)	Financial – Clinician /clinic resources	121 (33)	46 (13)	7 (2)
Dietary changes	365	91 (25)	Lack of evidence	123 (34)	123 (34)	23 (6)
Segmental muscle vibration	363	46 (13)	Lack of evidence	128 (35)	128 (35)	7 (2)
Magnesium supplementation	366	46 (12)	Lack of evidence	158 (43)	158 (43)	6(1)
			Financial – clinician/clinic resources	85 (22)		
Delayed ESWT	367	39 (11)	Lack of evidence	111 (30)	111 (30)	4(1)
Immediate ESWT	382	32 (8)	Lack of evidence	134 (35)	134 (35)	5 (1)
			Financial – clinician/clinic resources	85 (22)		
Zinc supplementation	366	16 (4)	Lack of evidence	159 (43)	159 (43)	4 (<1)

n: number of participants, CIMT: Constrained Induced Movement Therapy, ESWT: Extracorporeal Shockwave Therapy, FES: Functional Electrical Stimulation, TENS: Transcutaneous electrical nerve stimulation.

Table III. Subgroup analyses: statistically significant differences for use of adjunctive therapy between multidisciplinary and solo working settings

		Multidisciplinary	working setting	Solo work	ing setting	
Adjunctive therapy	п	No % (<i>n</i>)	Yes % (n)	No % (n)	Yes % (n)	<i>p</i> -value
Splinting	368	4.9% (15)	95.1% (294)	13.6% (8)	86.4% (51)	0.011
CIMT	366	32.9% (101)	67.1% (206)	50.8% (30)	49.2% (29)	0.008

n: number of participants, CIMT: Constrained Induced Movement Therapy

Table IV. Subgroup analyses: statistically significant differences for use of adjunctive therapy between academic vs non-academic/ private practice

		Academi	c hospital	Non-academic/		
Adjunctive therapy	п	No % (n)	Yes % (n)	No % (n)	Yes % (n)	<i>p</i> -value
Stretching programme at home	243	12.3 (16)	87.7 (114)	1.8 (2)	98.2 (111)	0.002
Active exercise programme at home	243	12.1 (16)	87.9 (116)	2.7 (3)	97.3 (108)	0.006
TENS	240	73.8 (96)	26.2 (34)	52.7 (58)	47.3 (52)	0.001
Motorized arm ergometry	239	72.9 (94)	27.1 (35)	57.3 (63)	42.7 (47)	0.011

n: number of participants, TENS: Transcutaneous electrical nerve stimulation.

DISCUSSION

In the context of this study we considered a range of physical interventions as adjuncts to BoNT administration for reduction of spasticity. However, in rehabilitation programmes in general, physical interventions are the core components of treatment, and if spasticity is a limiting factor, management (including BoNT) may be used to mitigate spasticity and aid progression.

We present here the first worldwide survey on clinicians' practice patterns and perceptions on the use of adjunctive therapies following BoNT injection for limb spasticity. The survey responders had a large experience, with a median 10 years of experience of BoNT use in the management of SMO from all aetiologies. Stroke is the most frequently mentioned pathology, which is consistent with the fact that stroke is also the most common cause of spasticity (11). The responders worked in countries located in 6 continents with different incomes (high and low/middle level). The typical responder was a physical medicine and rehabilitation specialist, working in an academic and multidisciplinary team and coming from European and/or a high-income country. Physical therapists represented 14% of the responders, probably due to the fact that physical therapists in the UK are able to inject BoNT. This may also explain the high number of physical therapist responders in countries with a high-income level.

The 3 most frequently prescribed adjunctive therapies were active exercise programme at home, stretching programme at home, and splinting. Notably, the order of the top 3 and most of the other adjunctive therapies were the same as that reported in a Canadian survey with 48 responders. However, the frequency of the top 3 most frequently prescribed adjunctive therapies was higher in the Canadian survey, with a 94–100% rate compared with a 70–81% rate in the current survey (8). This may

 Table V. Subgroup analyses: statistically significant differences for use of adjunctive therapy between high-income country vs low-/

 middle-income country

		High-income		Low-/mide		
Adjunctive therapy	n	No % (<i>n</i>)	Yes % (n)	No % (n)	Yes % (n)	<i>p</i> -value
TENS	364	72.7 (200)	27.3 (75)	50.1 (45)	49.4 (44)	0.000
Magnesium supplementation	366	90.9 (249)	9.1 (25)	76.1 (70)	23.9 (22)	0.000
Dietary change recommendations	365	80.7 (222)	19.3 (53)	57.8 (52)	42.2 (38)	0.000
(e.g. reducing sugar intake to						
optimize blood sugar control)						

n: number of participants, TENS: Transcutaneous electrical nerve stimulation.

Table VI. Subgroup analyses: statistically significant differences for barrier for adjunctive therapy between high-income country vs low-/middle-income country

Adjunctive Therapy	п	Barrier	п	High-income % (n)	Low-/middle-income % (n)	<i>p</i> -value
Zinc supplementation	327	Clinician constraints	43	7.5 (18)	28.7 (25)	0.00005
		Lack of evidence	159	55.4 (133)	29.9 (26)	0.00225
Casting Upper Extremity	445	Adjunctive therapy time constraints	54	16.7 (54)	0 (0)	0.0017
		Clinician constraints	77	23.1 (75)	1.7 (2)	0.0002
		Financial constraints	56	17.3 (56)	0 (0)	0.0012

n: number of participants.

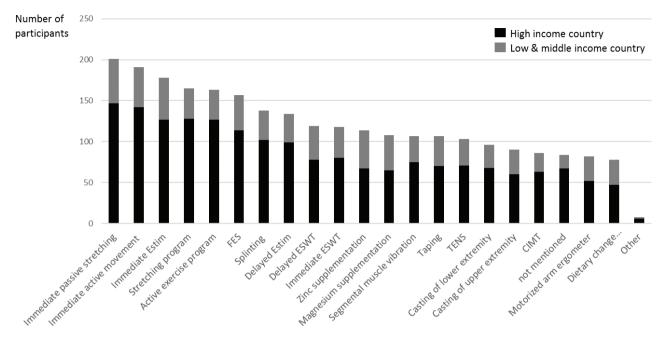


Fig. 2. Future research priorities regarding adjunctive therapies following botulinum toxin injection for spasticity reported by clinicians in high- and low/middle-income countries.

CIMT: Constrained Induced Movement Therapy, ESWT: Extracorporeal Shockwave Therapy, FES: Functional Electrical Stimulation, TENS: Transcutaneous electrical nerve stimulation.

be due to the fact that the current survey included responders from all 6 continents and from low/middle-income countries. Subgroup analysis showed some differences in the frequency of use of some adjunctive therapies. However, globally, no large differences were observed between used adjunctive therapies. This supports the theory that clinical practice after BoNT injection is largely uniform within the rehabilitation community. In the current survey, nearly two-thirds of the patients injected with BoNT were given a recommendation for immediate stretching at home, an active movement programme, splinting, or CIMT. There is evidence for the effect of CIMT and splinting as adjunctive treatments after BoNT injection, namely: the additional use of CIMT (level 1 according to Sackett's levels of evidence) and dynamic splinting (level 2) results in an improvement in Modified Ashworth Scale scores of at least 1 grade. (4-6). In addition, there is some evidence to support the use of EStim and ESWT (12, 13). However, immediate and delayed EStim, and, most of all, ESWT are less frequently or almost never recommended. The cost of the device is a possible explanation for the low use rate of ESWT. and EStim is cheaper and can be easily applied even in middle-income countries (14).

Surprisingly, the 2 most frequently prescribed adjunctive therapies (active movement and stretching exercise) are not the ones with the highest level of evidence (15). Also, compared with other available adjuvant therapies, the 3 most prescribed therapies (active movement, stretching exercises, and splints) had the lowest compliance rates (16). Although patient compliance with some adjuvant therapies (e.g. home exercise programmes) is estimated at 50% (16), patient willingness does not appear to be a barrier to clinicians prescribing adjuvant therapies. The main barriers reported by clinicians to provision of these interventions were clinicians' lack of time, limited financial resources, and lack of evidence.

The top 3 barriers reported by clinicians to the use of adjuvant therapies are patient and clinician time constraints, financial resources and lack of evidence. The most frequently reported barrier reported by clinicians to the implementation of adjunctive therapies was a lack of evidence highlighting the need for future research, including high-level randomized controlled trials and other relevant study designs. Logically, the lack of evidence was more frequently reported in the lessfrequently prescribed adjunctive therapies, supporting the fact this was the main reason for non-prescription. The other barriers reported by clinicians were the patient and clinician time constraints and financial resources. Notably, time constraint was the main barrier to the implementation of the 2 most frequently recommended adjunctive therapies. Financial barrier was the main limitation for 5 adjunctive therapies (splinting, FES, ESWT, magnesium supplementation and motorized arm ergometry). Whether or not clinicians worked in an academic setting or a multidisciplinary team had little influence on the perceived barriers. Clinicians working in high-income countries reported more

barriers for casting upper extremities. They perceived more time and clinician constraints. Surprisingly, they also mentioned more financial constraints. In addition, lack of evidence was more frequently indicated as a barrier to zinc supplementation in high-income countries. Nevertheless, globally, no large differences were observed between perceived barriers whether the clinicians worked in a high- or low/middle-income country.

Overall, this survey shows that clinicians often use adjuvant therapies in combination with BoNT injections to optimize the treatment of SMO.

Study limitations

This study has several limitations. Although the number of responders was high, the survey represents only a proportion of the clinicians treating spasticity worldwide. Furthermore, the completion rate was 75.5% (398 out of 527 clinicians fully completed the survey questionnaire). Thus, nearly 25% of clinicians did not answer all items. The survey was questioning clinicians about the use and perceived barriers to use of adjunctive therapies. We did not collect the rate of persons who effectively received or refused the adjunctive therapy. There may be discrepancies between these 2 rates, supporting a future prospective observational study collecting these dates. Finally, responders treated several aetiologies resulting in SMO, including cerebral palsy, which may have different scientific evidence and practice.

Future research

Clinicians particularly indicated that future research should prioritize treatments that can be applied immediately after BoNT injection. This may indicate that they believe it would be more feasible to perform these treatments in the clinic immediately after BoNT injection, rather than referring the patient elsewhere for treatment.

Conclusion

Overall, this survey shows that, worldwide, clinicians often use adjunctive therapies after a botulinum toxin injection to reduce spasticity. The most commonly used physical interventions among clinicians were active exercises at home, stretching at home, and splinting. Lack of evidence, time and financial constraints were identified as barriers to providing these interventions.

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Conflicts of interests

FS has received honoraria from Allergan and Merz, MS has received honoraria from Allergan, SA has received honoraria and grant funding from Ipsen and honoraria from Allergan and Merz. JJ has received honoraria from Ipsen, Merz and Abbvie/Allergan for services as speaker, scientific advisor, researcher, and trainer. TD has received grants from Allergan and Merz. AI, MN, JM, NB, EC, MN, ES and PM have no conflicts of interest to declare.

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