European Journal of Physical and Rehabilitation Medicine 2025 June;61(3):449-61
DOI: 10.23736/S1973-9087.25.08995-6

SYSTEMATIC REVIEW

Effects of lower limb botulinum toxin injections on gait functional outcomes in stroke survivors: a systematic review and meta-analysis

Chiara DE SANTIS [1], Stefano DORONZIO [2, 3] *, Maria A. SZCZEPANSKA [2], Gemma LOMBARDI [2, 4], Giovanna CRISTELLA [2], Chiara CASTAGNOLI [2], Teresa BARRETTA [2], Michele PIAZZINI [1], Marco BACCINI [2], Francesca CECCHI [2, 3]

[1]School of Specialization in Physical and Rehabilitation Medicine, University of Florence, Florence, Italy; [2]Unit of Neuromotor Research, IRCCS Don Carlo Gnocchi ONLUS Foundation, Florence, Italy; [3]Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; [4]Department of NEUROFARBA, University of Florence, Florence, Italy

*Corresponding author: Stefano Doronzio, Department of Clinical and Experimental Medicine, University of Florence, Via di Scandicci 269, 50143 Florence, Italy. E-mail: sdoronzio@dongnocchi.it

ABSTRACT

INTRODUCTION: Spasticity is a relatively common complication of stroke. In the lower limb, it generally involves the ankle and the foot, often leading to equinovarus deformity. Botulinum toxin (BoNT) injections are commonly used to manage spasticity, both in the subacute and chronic phase after stroke; however, their effects on function, particularly gait, are uncertain. This systematic review aims to update the current evidence on the effects of BoNT treatment on gait function in stroke survivors.

EVIDENCE ACQUISITION: This systematic review follows the PRISMA guidelines. We searched five databases (PubMed, Embase, Scopus, CINAHL, Web of Science) for Randomized Controlled Trials (RCTs) published in English that investigated the effects of BoNT injections on gait in individuals with stroke compared to any other treatment or no treatment. Two reviewers independently selected the studies, assessed the risk of bias using the PEDro scale, and extracted the results. Standardized mean differences were calculated and, when possible, meta-analyses were performed, using random effects models.

EVIDENCE SYNTHESIS: From a total of 1238 records, 8 studies met the inclusion criteria, all but one study enrolling participants with chronic stroke. Sample sizes ranged from 16 to 468 subjects, for a total of 434 in the experimental groups and 568 in the control groups.. Gait function was assessed using a variety of gait tests, including instrumental gait analysis. Meta-analyses showed no significant effects of BoNT on gait speed, step frequency or step length. One small, underpowered study, with high risk of bias, reported significant improvements of gait speed in individuals with subacute stroke. Other gait-related variables were measured in single small trials, most often finding no differences between BoNT and control interventions.

CONCLUSIONS: Our findings indicate that current evidence shows no effects of BoNT treatment on gait speed, and insufficient evidence on its effects on other gait parameters. Adequately-powered, high-quality trials are needed to verify whether BoNT treatment, beyond reducing spasticity, can positively impact functional outcomes other than gait speed in individuals with chronic post-stroke lower limb spasticity and/or during early stroke recovery.

(*Cite this article as:* De Santis C, Doronzio S, Szczepanska MA, Lombardi G, Cristella G, Castagnoli C, *et al.* Effects of lower limb botulinum toxin injections on gait functional outcomes in stroke survivors: a systematic review and meta-analysis. Eur J Phys Rehabil Med 2025;61:449-61. DOI: 10.23736/S1973-9087.25.08995-6)

KEY WORDS: Botulinum toxins; Hemiplegia; Stroke; Gait; Randomized controlled trial; Meta-analysis.

Introduction

In Europe, stroke affects 600,000 persons/year;[1] stroke incidence and the prevalence of stroke survivors are constantly rising, in line with the aging of the population worldwide and with the improvements of survival rates after a stroke. According to projections of the Global Burden of Disease study, 2015, and to the Eurostat (statistical office of the EU) demographic projections, a 34% increase in total number of stroke events in the EU between 2015 and 2035 is expected.[1]

According to Jorgensen *et al.*,[2] walking function is impaired in two out of three persons with acute stroke and half of them are unable to walk even with assistance; most individuals recover the ability to walk within the first 11 weeks post-stroke, while only 5% of stroke survivors experience further recovery after that time. At the end of rehabilitation, 64% of stroke survivors have independent walking function, 14% are dependent on assistance, and 22% remain unable to walk.[2]

Spasticity and muscle weakness (spastic paresis), both resulting from neurological damage, are common after stroke, and markedly influence motor function, complicating the rehabilitation process.[3] Post-stroke lower limb spasticity generally affects the ankle and the foot, leading to equinovarus deformity, spasms and pain, and affecting balance, stride, gait, mobility.[4] Spasticity may also cause alterations in gait patterns, *e.g.* loss of optimal contact, poor stance phase or loss of heel to toe rockers.[4]

Interventions to reduce spasticity after stroke include various treatments, such as physiotherapy, orthoses, pharmacological treatment, orthopedic surgery and neurosurgery.[5] Among focal pharmacological therapies, botulinum toxin (BoNT) agents are administered by intramuscular injection. Leg spasticity represents the third most commonly treated group with BoNT injections, following arm spasticity and hemispasticity.[6] The most frequently targeted leg muscles for BoNT treatments are gastrocnemius (caput medialis), tibialis posterior, soleus and gastrocnemius (caput lateralis).[6]

Studies on BoNT efficacy usually identify the reduction of muscle tone as the primary outcome. A meta-analysis published in 2016,[7] aimed to assess the benefits of BoNT injection after stroke, and including 7 articles (603 patients), confirmed a statistically significant decrease in muscle tone, observed at week 4 and 12 after treatment compared to controls. BoNT therapy was also associated to increased Lower Limb Fugl-Meyer scores, but no effects were found on gait speed during the whole follow-up period. Indeed, the same review reported a lack of studies investigating functional outcomes after BoNT injections. These shortcomings were also highlighted by a more recent systematic review by Gupta *et al.*[4] evaluating the effecs of lower limb BoNT injections on walking and Quality of Life (QoL) in individuals with stroke. The Authors reported insufficient evidence to support or refute improvement on walking or QoL following BoNT injections, and stressed the need for further well-designed Randomized Clinical Trials (RCTs) targeting these outcomes.

The main objective of this systematic review was to evaluate whether, six years after the recommendations by Gupta *et al.*,[4] the call for large RCTs addressing the functional effects of BoNT treatment for lower limb spasticity in stroke survivors has been met, and to summarize the current evidence on the effects of BoNT treatment on gait function.

Evidence acquisition

Study design, registration and setting

We designed and reported this systematic review, following the PRISMA-P[8] checklist and according to the PRISMA Statement 2020.[9] The study design was registered on PROSPERO under the ID CRD42023423818. The study was carried out by researchers of the joint research PROMISE@LAB.

Search strategy

To establish a search strategy, the PICO[10] model was used (Table I). We searched for RCTs published in English that investigated the effects of BoNT injections on

TABLE I.—*Criteria for eligibility of studies according to the PICO model.*

Patients (P)	Adult Stroke survivors who were able to walk, even with aids, regardless of stroke type, distance from onset, age and gender
Intervention (I)	BoNT injections in lower limb muscles (any preparation, dose, treated muscles)
Control (C)	Placebo or another treatment or no treatment)
Outcome (O)	Gait function (any clinical scale or test measuring kinematic, including spatial-temporal, or kinetic parameters or global walking performance
Study design (S)	Randomized controlled trials English

gait function in individuals with stroke, compared to any other treatment or no treatment. The search was conducted on five databases (PubMed, Embase, Scopus, CINAHL, Web of Science), from inception to May 4th, 2023. Five database-specific strings (Supplementary Digital Material 1: Supplementary Text File 1) were composed, using the Boolean operators and the following keywords, with the relative engine explosion: hemiplegia, stroke, botulinum toxin, gait. No filters were used in the research.

Titles selection

The records obtained by each database were uploaded on RAYYAN (https://rayyan.ai/) and the duplicates removed. Two researchers (CDS and SD) independently screened the obtained records, first by title and abstract and then by full-text. Disagreements were solved by consensus, with the intervention of a third author (MB).

Data extraction

The following data were independently extracted from included articles by two researchers (MS, MB):

- participants: inclusion/exclusion criteria, age, gender, type of stroke, time since stroke, number of subjects enrolled in the experimental and control groups;
- botulinum toxin preparation (Dysport or Botox);
- muscle treated and BoNT units injected in each site in participants assigned to the experimental group;
- intervention delivered to the control group (placebo, other intervention, no intervention);
- time of follow-up assessments;
- outcome measures related to walking, regardless of whether they were considered primary or secondary outcomes, and the specific measurement tools used.

Risk of bias assessment

The methodological quality of the RCTs included in the review was assessed independently by two blinded researchers (CC and SD) using the PEDro scale.[11] The PEDro Scale assesses 10 items related to the study internal validity, each scored as either present (score=1) or absent (score=0), leading to a maximum score of 10. The scale has an additional item related to external validity (eligibility criteria), which is not computed in the total score. A cut point of 6 is usually chosen to rate sufficient quality.[12] Reliability of the PEDro scale has been investigated in both pharmacological and nonpharmacological studies, with similar results in the two fields and Intraclass Correlation Coefficients (ICCs), ranging 0.89-0.91.[13]

Data analysis

Gait-related outcomes were classified according to the measured variable, *i.e.* global gait function, spatial-temporal gait parameters, other kinematic and/or kinetic parameters. Gait speed and step frequency values were converted to meters/second and steps/minute, respectively, when reported in different units. For each outcome, the standardized mean difference (SMD) with 95% confidence interval (CI) was used as the principal measure of effect size. The SMD was calculated for each study using differences in gait parameters between the treatment and control group, divided by the standard deviations of differences pooled from the two groups, at different time points. When possible, for each outcome, pooled estimates were obtained from different studies based on random effects models to account for the heterogeneity of results.[14] Heterogeneity and inconsistency were assessed using the Q statistic and the I2 statistic, respectively.[15] Differences in participants' inclusion criteria, type of control, preparation and dose of BoNT injections, treated muscles, outcome measures and time of follow-up were examined as possible sources of heterogeneity in the results. Data from articles that were sufficiently homogeneous for these characteristics were pooled, with subgroup analyses when indicated. Meta-analyses were conducted separately for each follow-up period. If a study reported data from groups treated with different doses of BoNT, the data from the group with the best outcome were included in the meta-analysis. The statistical analysis was performed with the jamovi (version 2.5) computer software (The jamovi project, 2024. Retrieved from https://www.jamovi.org).

Evidence synthesis

The research on the 5 databases yielded 1238 records. After removal of duplicates, 761 records were screened by title and abstract and 37 full-text articles were assessed for eligibility. Finally, 8 articles were included in the systematic review.[16-23] The flow chart of the study selection process is shown in Figure 1. In two studies,[18, 23] after the last RCT follow-up, an open-label extension of the study was conducted, in which all consenting participants were treated with BoNT injections; only data from the RCT phase of these studies were included in the meta-analysis. For the study with a cross-over design[17] only data collected in the first period were considered. The main features of the included studies are summarized in Table II.[16-23]

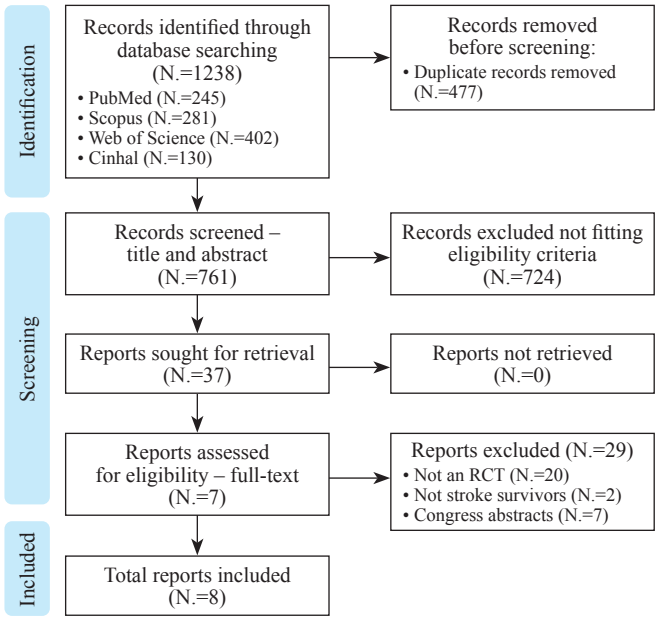

Figure 1.—Flow chart of the process of studies selection.

Participants

One study[22] enrolled participants in the subacute phase (within 6 weeks) following stroke, whereas in all the other studies, participants were in a more chronic phase, at least 3[17, 21, 23] or 6[16, 19, 20] months after the stroke. Sample size ranged from 16[16] to 468[23] subjects, totaling 434 participants in the experimental group and 568 in the control group. Two studies[18, 21] assigned participants who were to receive BoNT injections to 3 and 2 experimental groups, respectively, each receiving a different dose of the drug.

Treated muscles

Triceps surae was treated in all the studies, but only 4 studies[20-23] performed BloNT injection in all its components (medial and lateral gastrocnemius and soleus). In all studies, with the exception of Pittock at al. (2003),[21] other muscles of the lower limb were also treated: tibialis posterior in all the remaining 6 studies, but, in two of them, as an optional target;[16, 18] flexor hallucis longus in 3 studies,[16, 19, 23] in two of them as an optional target;[16, 23] flexor digitorum longus in 3 studies,[17-19, 23] as an optional target in two studies;[17, 23] flexor digitorum brevis in two studies,[19, 23] as an optional target in one study;[23] quadriceps femoris in two studies,[19, 23] limited to rectus femoris and as an optional target in one study;[23] flexor hallucis brevis in one study;[19] and the extensor hallucis longus, as an optional target, in one study.[23]

Preparation

The Botulinum Toxin preparation was Dysport in two studies, where participants in the experimental group received a total of 1000 units,[17] or three different doses of the drug, *i.e.*, 500, 1000 or 1500 units.[21] The other studies all used Botox preparation, with doses ranging from 200 UI to 300 UI.

Follow-up assessments

All studies measured the results after BoNT injections at more time-points, largely variable between studies, ranging from 2 weeks to 4 months. However, most studies planned follow-ups at one, two and three months, so the meta-analyses were conducted including data measured at this time -points, when possible.

Quality assessment

Table III[16-23] shows the results of quality appraisal. Most of the studies achieved the minimum acceptable score to be considered of sufficient quality based on the PEDro scale criteria,[12] but some relevant items (intention-to-treat analysis, blinding of therapists) were rarely met.

Concomitant interventions

In most studies, concomitant rehabilitation was allowed,[16, 18, 20, 21] one study did not mention concomitant interventions at all,[23] and in two studies all participants continued with active physiotherapy[17] or comprehensive rehabilitation.[22]

Gait outcome measures

Gait functioning was selected as primary outcome only in one study[21] and as secondary outcome in three studies,[16, 18, 23] whereas four studies[17, 19, 20, 22] did not differentiate between primary and secondary outcomes. Gait assessment was conducted using a variety of different tools: Two Minutes Walking Test (2MinWT);[21] Ten Meters Walking Test (10MWT);[16, 17, 19, 20, 23] Six Minutes Walking Test (6MinWT);[22] subjective qualitative gait assessment by physicians;[17, 18, 20] laboratory instrumental gait analysis during ground walking[19, 22] or treadmill walking[16] at comfortable speed.

Effects of BoNT injections on gait

Gait speed

This gait parameter was measured in 6 studies, collected by means of the 10MWT[16, 17, 19, 20, 23] or by gait analysis.[22]

TABLE II.—*Synthesis of the studies included in the review.*[16-23]

Study	Time since stroke	Num exp/cntr	BoNT	Muscle (units)	Type of control	Other treatment	Primary outcome	Secondary outcomes	Follow-up (months)
Bollens *et al.*[16]	≥6 months	8/8	Botox	Soleus (200) TP (75) FHL (25)	Tibial neurotomy	Rehab allowed	Ankle stiffness	MAS. MRC, PROM, SIAS, 10MWT, gait analysis	2, 6
Burbaud *et al.*[17]	≥3 months	10/13	Dysport	GA (500-1000) Optional: Soleus (200-400) TP (200-350) FDL (150-300	Placebo	PT (all groups)	AS (ankle), 10MWT, AROM (dorsiflexion), L-FMA, PRS		1, 3
Dunne *et al.*[18]*	≥6 months	28-28/29	Botox	TP (70-100) Soleus (80-125) FDL or GA medialis (50-75)	Placebo	Rehab allowed	AS Adverse events	Self-reported spasm frequency, Pain, AROM, gait PRS	1, 2, 3, 4
Hui-Xian *et al.*[19]	<6 months	23/23	Botox	GA (150), TP (70) Optional: QF (150) FDL (70), FHL (50), FDB (20), FHB (10)	Routine rehab (including drugs and AFO)	Routine rehab (including AFO) in all groups)	MAS, L-FMA, 10MWT, TUG, gait analysis§		0.25, 1, 3
Kaji *et al.*[20]	≥6 months	58/62	Botox	GA medialis and lateralis, Soleus, TP (75 each)	Placebo	Rehab allowed	MAS, gait PRS, 10MWT, NRS of functional disability, adverse events§		0.25, 1, 1.5, 2, 3
Pittock *et al.*[21]**	≥3 months	59-60-60/55	Dysport	GA and Soleus (total units: 500-1000-1500)	Placebo	Rehab allowed	2MinWT	Step length, cadence, RMA (leg-trunk), AROM, PROM, NRS pain 0-4, adverse events	1, 2, 3
Tao *et al.*[22]	<6 weeks	11/12	Botox	GA (100) Soleus and TP (50 each)	Placebo	Routine rehab	L-FMA. MAS, mBI Limited to last follow-up: gait speed, step length, cadence, 6MinWT§		1, 2
Wein *et al.*[23]	≥3 months	233/235	Botox	GA (150) Soleus and TP (75) Optional‡: RF (100), FHL and FDL (50 each), FDB and EHL (25 each)	Placebo	Not reported	MAS	CGI, MTS, pain, GAS (week 8 and 12), 10MWT (week 6 and 12)	0.5, 1, 1.5, 2, 3

TP: tibialis posterior; FHL: flexor hallucis longus; FDL: Flexor digitorum longus; GA: Gastrocnemius medialis; QF: quadriceps femoris; FDB: flexor digitorum brevis; AFO: ankle foot orthosis; FHB: flexor hallucis brevis; PT: physiotherapy; Rehab: Rehabilitation; AS: Ashworth Scale: MAS: modified Ashworth scale; MRC: Medical Research Council 0-5 (muscle strength); PROM: passive range of motion; SIAS: Stroke Impairment Assessment Set; 10MWT: Ten Meters Walking Test; AROM: active range of motion; PRS: Physician Rating Scale of gait quality; L-FMA: lower limb Fugl-Meyer Assessment Scale motor score; TUG: Timed Up and Go test; NRS: Numeric Rating Scale; 2MinWT: Two Minutes Walking Test; mBI: modified Barthel Index; 6MinWT: Six Minutes Walking Test; CGI: Clinical Global Impression of change; GAS: Goal Attainment Scale.
*Two experimental groups; **three experimental groups; §primary outcome not specified; ‡maximum permitted dose in the optional muscles, to a total additional dose not exceeding 100 U.

TABLE III.—*Quality appraisal of the studies included in the review.*[16-23]

	Item1*	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	PEDro score
Study	1	1	0	1	0	0	1	1	1	1	1	7
Bollens *et al.*[16]	1	1	0	1	1	0	0	0	0	1	1	5
Burbaud *et al.*[17]	1	1	1	1	1	0	1	1	1	1	1	9
Dunne *et al.*[18]*	1	1	1	0	0	0	1	1	0	1	1	6
Hui-Xian *et al.*[19]	1	1	1	1	1	1	1	1	0	1	1	9
Kaji *et al.*[20]	1	1	0	1	1	0	1	1	1	1	1	8
Pittock *et al.*[21]**	1	1	0	0	1	0	0	1	0	1	1	5
Tao *et al.*[22]	1	1	1	1	1	1	0	1	0	1	1	8

Item1: eligibility criteria; item2: Randomization; item3: concealed allocation; item4: groups similar at baseline; item5: Blind participants; item6: blind therapists; item7: blind assessors; item8: key outcome obtained from over 85% of participants; item9: intention-to-treat analysis; item10: between-groups comparison; item11: point measures and variability measures reported.
*This item does not count for total PEDro score.

In two studies[17, 19] values were only presented in graphical form, so we extracted them from the graph. One article[23] did not report any values, and only stated that no significant differences were found between control and treated group for this outcome. In one article,[20] results of the 10MWT were reported as the time the participant took to walk 10 meters and we converted them to m/sec. This same study reported data measured at different follow-ups as mean changes from baseline assessment, so we computed gait speed values by subtracting change values from baseline values and used the SD at baseline as denominator for the SMD. We obtained gait speed values from the distance covered during the 2MinWT in the study by Pittock *et al.*[21]

We excluded from the meta-analysis the findings reported by Tao *et al.*,[22] who enrolled participants with subacute stroke (on average, 24 days from onset), and by Bollens *et al.*,[16] who compared the effect of BoNT injections with tibial neurotomy. Pooled data from four studies that enrolled participants in a more chronic phase and compared BoNT treatment with no treatment[20] or placebo[17, 20, 21] showed no differences between groups at both one month (SMD: 0.15; 95% CI: -0.23 - 0.53) and three months post-treatment (SMD: 0.18; 95% CI: -0.29 - 0.65), with significant inconsistency (one month: I2=56.02%; Q=6.821, P=0.078; three months: I2=70,79%; Q=8.891; P=0.031) (Figure 2).[17, 19-21] Pooled estimates were then conducted including only the three studies that compared BoNT treatment with placebo[17, 20, 21] showing no effect of BoNT treatment with no heterogeneity and inconsistency (one month; SMD: -0.05; 95% CI: -0.30 - 0.20; I^2=0%;

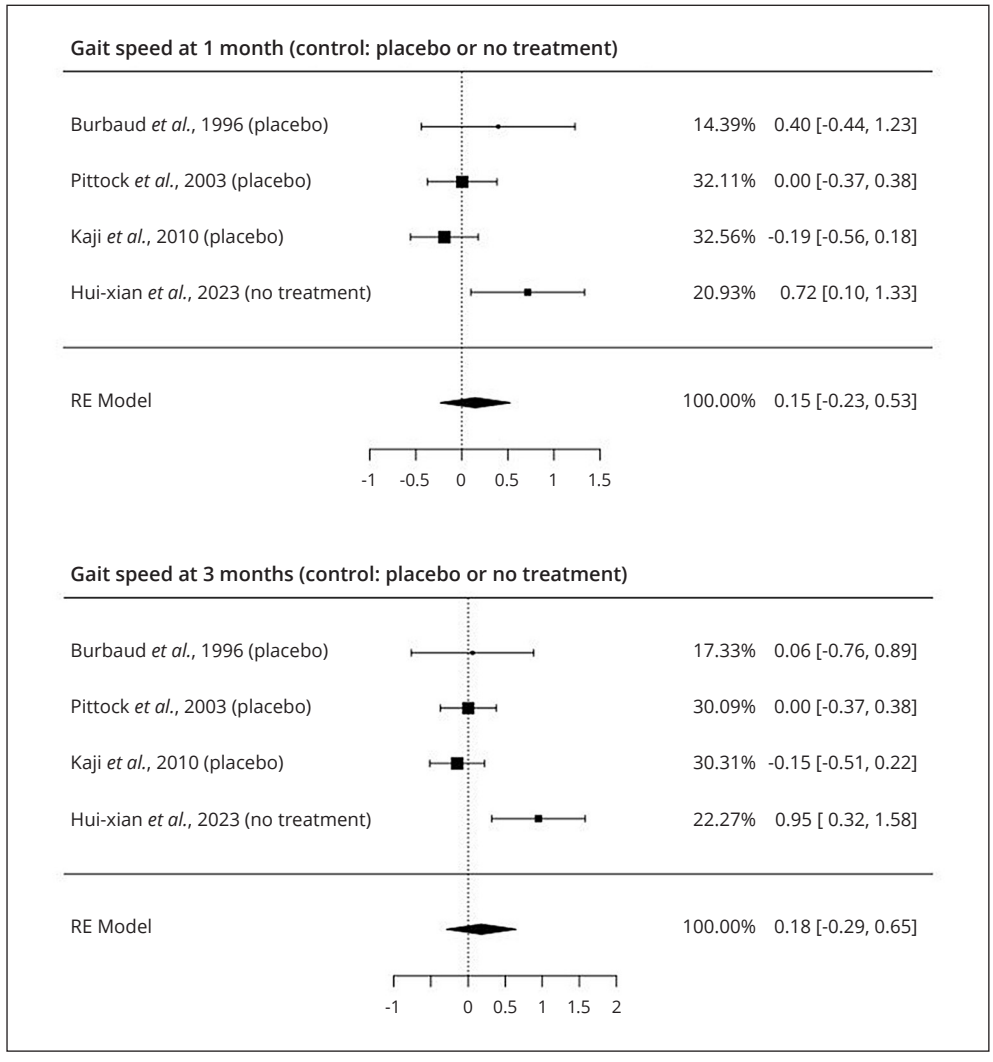

Figure 2.—Forest Plot of results for the outcome *gait speed* found in studies that compared BoNT intervention to placebo or no treatment.[17, 19-21]

Q=1.734, P=0.420; three months; SMD: -0.06; 95% CI: -0.31 - 0.19; I^2=0%; Q=0.400, P=0.819).

Conversely, the study that enrolled subacute stroke participants[22] found that, 2 months after the intervention, participants who received BoNT injections showed significantly higher gait speed than those who received placebo (SMD: 1.52; 95% CI: 0.59-2.45).

When BoNT injections were compared to tibial neurotomy[16] no superiority of either treatment was found (SMD: 0.13; 95% CI: -0.85-1.11).

Step frequency

This parameter was measured only by two studies,[21, 22] conducted on different stroke populations. Therefore, data on step frequency were pooled only including results of three different BoNT doses reported by Pittock *et al.*[21] in participants with chronic stroke. In this population, BoNT was not more effective than placebo, irrespective of the dose injected and the time of follow-up (Figure 3)[21] (1 month: SMD: -0.08; 95%CI: -0.30-0.14; I^2=0%; Q=0.087, P=0.958; 2 months: SMD: -0.07; 95%CI: -0.29-0.15; I^2=0%; Q=0.002, P=0.999; 3 months: SMD: -0.03; 95%CI: -0.25-0.18; I^2=0%; Q=0.281, P=0.869). In individuals with subacute stroke, Tao *et al.*[22] found a non-significant effect favoring BoNT *versus* placebo at 2 months post-intervention (SMD: 0.75; 95%CI: -0.10-1.59).

Other spatial-temporal gait parameters

Step or stride length were measured only in two studies, both enrolling participants with chronic stroke,[19, 21] but the authors reported this parameter differently. One study considered stride length,[19] while the other considered the difference in step length between the less affected and the more affected leg, named step length discrepancy.[21] Therefore, also for this outcome, we pooled only data on different BoNT doses,[21] finding that the discrepancy in step length was not significantly changed after treatment with BoNT compared to placebo at any follow-ups, independently from the dose injected (Figure 4)[21] (1 month: SMD: -0.07; 95%CI: -0.15-0.28; I^2=0%; Q=1.415, P=0.493; 2 months: SMD: -0.03; 95%CI: -0.25-0.19; I^2=0%; Q=0.462, P=0.794; 3 months: SMD: -0.03; 95%CI: -0.25-0.19; I^2=0%; Q=1.639, P=0.441). In contrast, Yu *et al.*[19] found a greater increase in stride length in the BoNT group than in the usual care group, which was progressively more pronounced at subsequent post-treatment assessments (one week: SMD: 0.66; 95%CI: 0.4-1.27; four weeks: SMD: 0.66; 95%CI: 0.4-1.27; eight weeks: SMD: 0.66; 95%CI: 0.4-1.27).

Other gait measures

The following measures were reported by single studies. A Physician Rating Scale was used by Burbaud *et al.*[17] and Dunne *et al.*[18] as the only measure of gait function. The physician viewed video recordings of the patient's gait and rated its quality on a score from 0 to 4[17] or on a Lickert Scale (–1=worse than baseline, 0=same as baseline, +1 better than baseline).[18] The first study reported data only for the BoNT treatment, without comparison with the control intervention. Dunne *et al.*[18] reported that at the three months follow-up the gait of 17/54 and 6/26 participants in the experimental and placebo groups (cumulative data of subjects treated with different doses of BoNT), respectively, was rated as improved compared to the baseline assessment; however, we performed an independent analysis of their data using the chi square test and found that the difference in proportions between the two groups was not significant (P=0.295).

A different Physician Rating Scale focused on foot kinematics and use of assistive devices (total score ranging from -1 to 9) was used as an additional gait measure in the study of Kaji *et al.*.[20] No difference between BoNT and placebo groups were found at any follow-up (one month: SMD: -0.07; 95%CI: -0.43-0.30; two months: SMD: -0.11; 95%CI: -0.48-0.26; three months: SMD: -0.02; 95%CI: -0.39-0.35).

Hui-xian *et al.*[19] measured two additional gait-related variables, *i.e.* the TUG and the peak plantar forefoot pressure on the more affected side during the stance phase of gait. For both variables, significant differences between BoNT and usual care groups were found. The time to completion of the TUG was progressively shorter in group 1 than in group 2 at subsequent follow-ups (one week: SMD: -0.78; 95%CI: -1.38- -0.18; four weeks: SMD: -1.60; 95%CI: -2.27- -0.94; eight weeks: SMD: -1.97; 95%CI: -2.68- -1.27). As for the peak forefoot pressure, it was significantly higher in BoNT group at all assessments after the intervention (one week: SMD: 0.77; 95%CI: 0.18-0.37; four weeks: SMD: 1.03; 95%CI: 0.62- 1.45; eight weeks: SMD: 0.78; 95%CI: 0.18-0.38).

In the study that compared BoNT with tibial neurotomy,[16] instrumental gait analysis was a secondary gait-related outcome in addition to gait speed measured by the 10mWT. Neither kinematic (maximal ankle dorsiflexion at different phases of the gait cycle) nor kinetic (maximal plantar flexion moment of the ankle in stance phase, external work and net energy cost of walking) parameter showed significantly different changes between the two groups either two or six months after the intervention.

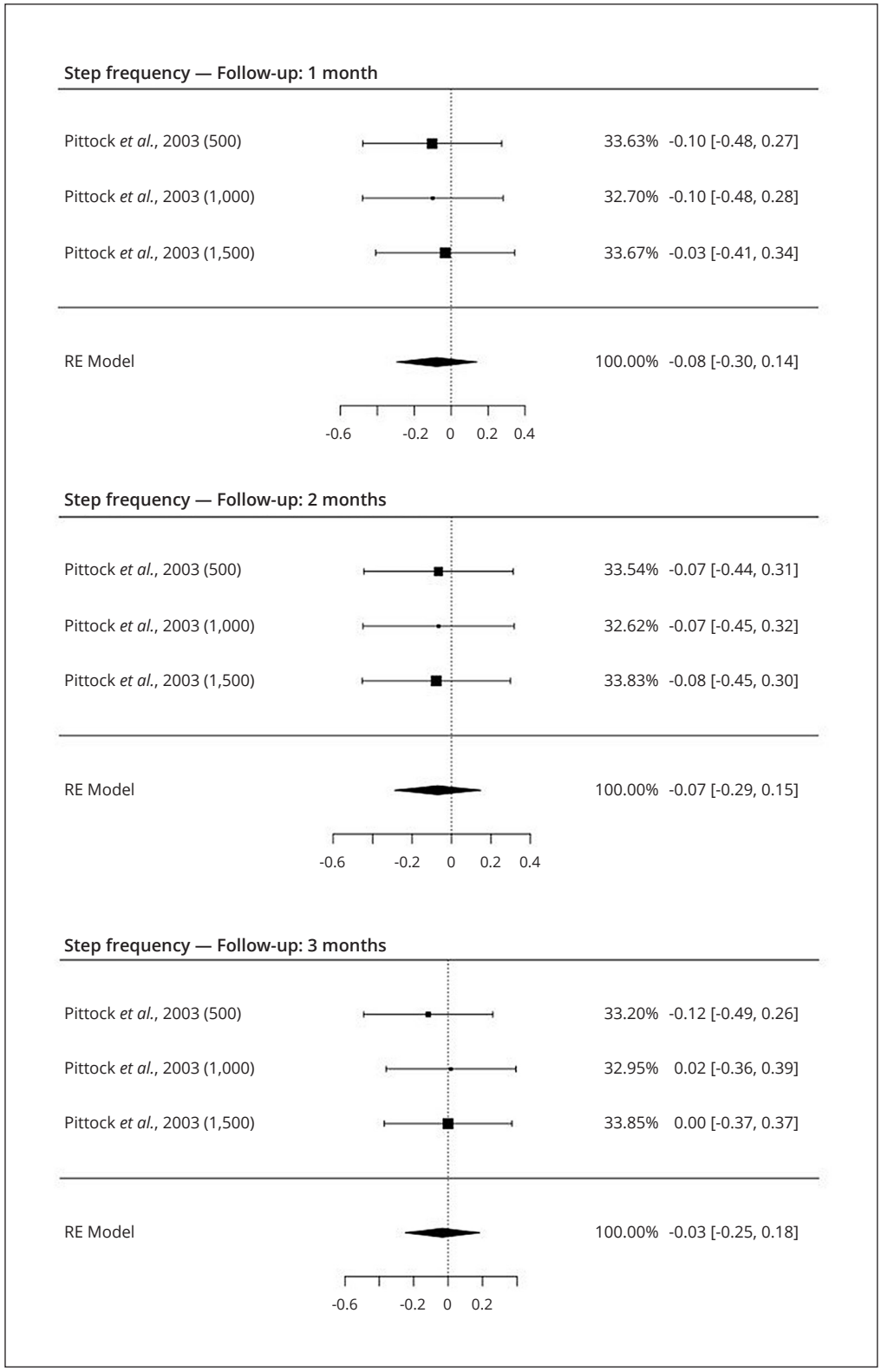

Figure 3.—Forest plot of results for the outcome *step frequency* found in groups treated with different doses of Dysport (numbers in parentheses) compared to the control group.[21]

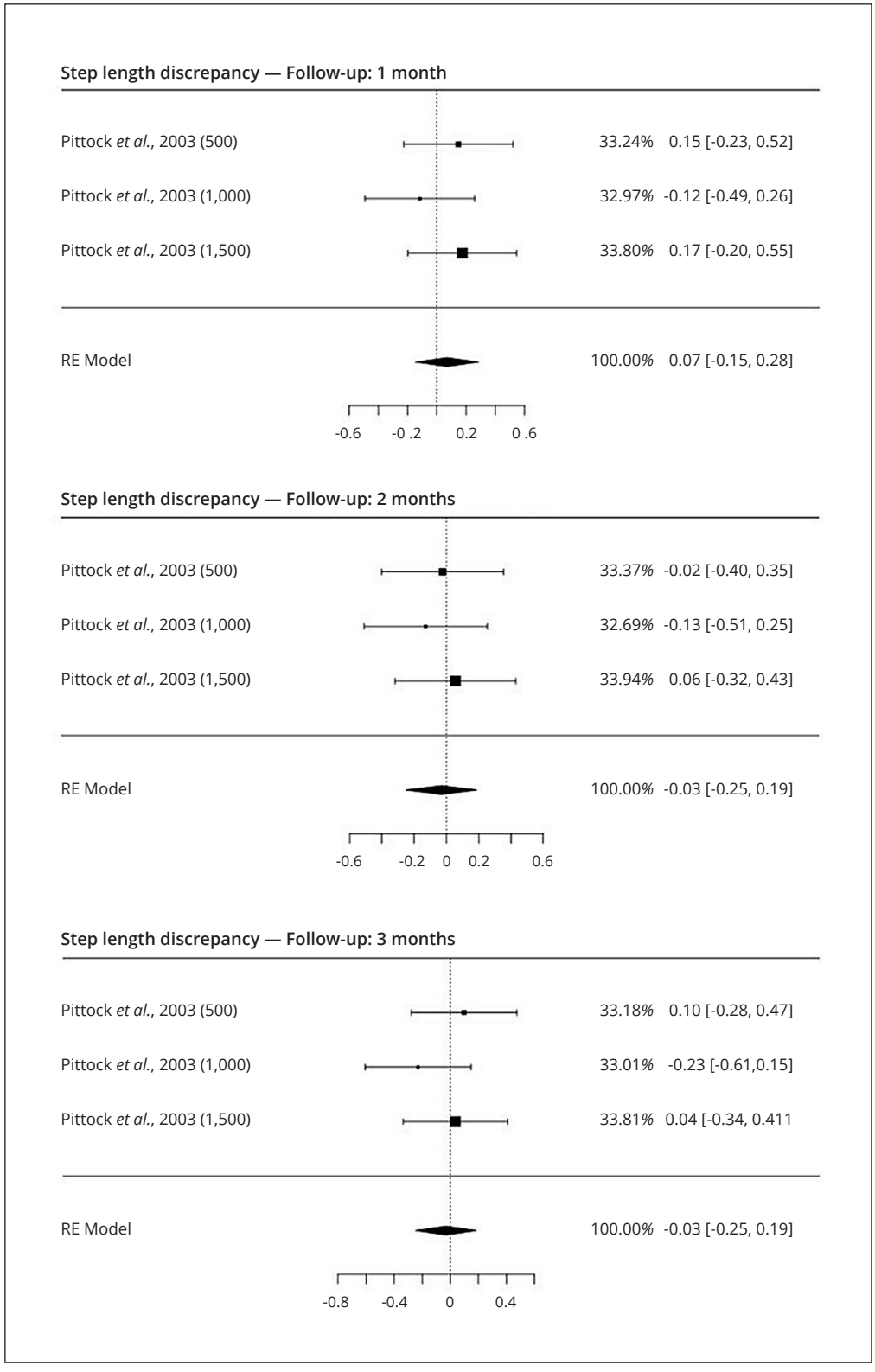

Figure 4.—Forest plot of results for the outcome step length discrepancy (difference in step length between the paretic and the non-paretic limb) found in groups treated with different doses of Dysport (numbers in parentheses) compared to the control group.[21]

Discussion

This systematic review aimed to update the current evidence about the effects of BoNT injections in lower limb muscles on gait function in stroke survivors. Despite the previous recommendations[4, 7] to include functional outcomes in clinical trials, and despite the growing number of trials examining the effects of BoNT on spasticity, very few trials have assessed its impact on gait, and only two of them[19, 23] were published after these recommendations. Gait assessment was conducted using a wide variety of instruments and variables, so it was impossible to obtain robust meta-analytical estimates based on sufficiently large samples of participants, except for gait speed. Unlike Gupta *et al.*,[4] our results allowed a meta-analysis from data on 246 subjects (118 and 128 receiving BoNT treatment or placebo, respectively), finding no effects of BoNT on gait speed. These results are further strengthened by the most powered study (468 participants) by Wien *et al.*[23] This large RCT could not be included in the meta-analysis since the authors did not report values of gait assessment, its results reported no significant difference in gait speed between BoNT and placebo at any follow-up.

It is noteworthy that all the trials on individuals with chronic post-stroke spasticity that were included in our review mentioned walking ability among their inclusion criteria; therefore, the lack of BoNT effects cannot be attributed to the recruitment of individuals too severely impaired, unlikely to achieve walking independent from the considered intervention.[5] Conversely, two underpowered RCTs with moderate to serious risk of bias, reported a large effect on gait speed of BoNT treatment, one in individuals with chronic stroke, compared to usual care[19] and the other in individuals with subacute stroke, compared to placebo.[22] Data from a large multicentre trial with low risk of bias[21] indicate that step frequency is also not affected by BoNT treatment. Other gait-related variables were measured in single, small trials, so we are uncertain whether they are affected by BoNT injections. However, no studies found a significant improvement of quality of gait, assessed through observational gait analysis by clinicians, in individuals with chronic stroke.

Our results confirm, in a larger number of participants and with an updated literature search, the findings of the systematic reviews of Baker *et al.*,[24] Tao *et al.*,[7] Sun *et al.*,[25] and Gupta *et al.*,[4] all selecting only RCTs. The first, including only two RCTs assessing gait speed after BoNT injections into lower limb muscles[20, 21] found a perfect equality of effects between BoNT and placebo with no heterogeneity. The same findings were confirmed by Tao *et al.*,[7] who included an additional RCT (Burbaud *et al.*).[17] The inclusion of one more recent article, by Yu *et al.*[19] in the present meta-analysis did not change the results to any great extent, since this study enrolled a limited number of participants (43 altogether). Indeed, Yu *et al.* is the only study reporting a significant effect of the botulinum toxin on gait speed in chronic stroke, but, contrary to the other trials, it was not placebo-controlled, and presented a serious risk of bias due to the uncertainty about assessors' blinding. Finally, also the results of the large, multicentre study by Wien *et al.*,[23] although not included in the meta-analysis, as the values of gait assessment were not reported, strongly support the absence of BoNT effects on gait speed in people with chronic stroke. Sun *et al.*[25] also found no effect on gait speed in favour of BoNT compared to control, even if the authors pooled data from studies enrolling people with chronic and subacute stroke and even from a study where BoNT treatment was compared to BoNT treatment + a co-intervention (spasmodic muscle therapeutic instrument treatment);[26] the choice of pooling results from subjects with chronic and subacute stroke is also questionable, because faster improvements are expected early after stroke, as an effect of both spontaneous recovery and rehabilitation.[27] Indeed, we found that only one study enrolling subacute stroke participants[22] reported a very large effect on gait speed of BoNT treatment compared to placebo.

The most recent systematic review including only RCTs, by Gupta *et al.*,[4] included 5 placebo-controlled trials, but did not conduct any meta-analysis due to the variability between the trials with regard to the eligibility criteria of participants and the method used to assess gait function. The authors stated that their review was inconclusive in evidencing the efficacy of BoNT on gait function and QoL, stressing the need for large, well-designed RCTs on this topic.

All the RCTs considered in the quoted previous systematic reviews were also included in the present work, except for the trial where all groups received the BoNT treatment[26] and the trial where the experimental group received both BoNT injection and functional electrical stimulation by means of a foot-drop stimulator during walking, that were included in the review by Sun *et al.*[25] and by Gupta *et al.*,[4] respectively.

Reaffirming previous conclusions with additional data helps provides clarity, ultimately helping doctors to make choices based on the latest evidence. This clarity is highly needed, since other previous meta-analyses – some cited in a recent guideline on this topic (28) – that did not restrict the selection of studies to RCTs, reported somewhat different results. Foley *et al.*[13] found a small, significant effect of BoNT injections on gait velocity, but in this re-

view both randomized (N.=5) and pretest-posttest (N.=3) trials were included. Moreover, three of the included RCTs compared BoNT treatment *vs.* BoNT treatment + a co-intervention, or EMG-guided BoNT injection *vs.* non-EMG-guided injection, so these studies were treated as a single-group intervention and only data from the group that received BoNT treatment alone, or non-EMG-guided BoNT treatment were analyzed. Similar results are reported in a more recent review,[28] quoted in the AAPRM guideline by Verduzco-Gutierrez *et al.*,[36] that also included all study designs and found a small but significant effect of BoNT on 10MWT by pooling data from one RCT, one non-randomized trial and four non-controlled studies. Thus, in both reviews the meta-analytic estimate was computed mainly from data of non-controlled studies, and implying a risk of overestimation of the treatment effect.

These shortcomings are also present in the review by Lizama *et al.*,[29] also quoted by Verduzco-Gutierrez *et al.*,[36] who did not conduct any meta-analysis, but, from data of 12 mostly non-randomized or event non-controlled trials, and including also studies where BoNT treatment was provided to both experimental and control groups – reported that spatiotemporal, kinematic, kinetic and electromyographic parameters, collected by means of instrumental gait analysis, can be improved by BoNT treatment, even if gait speed remains unchanged. While this conclusion was mostly derived from non-controlled trials, in our search, we found only one RCT that compared BoNT treatment to usual care and assessed gait function through instrumental gait analysis,[19] not included by Lizama *et al.*, since it was published later. Therefore, we cannot be certain of a real effect of BoNT on these parameters.

It is noteworthy that all the RCTs included in our review reported a significant reduction of spasticity in the BoNT group compared to controls, except for Dunne *et al.*[18] The combined results of reduced spasticity and unchanged walking function indicate that the reduction in muscle tone does not in itself translate into a functional improvement in walking, at least when estimated on the basis of gait speed. This is further supported by the finding of Pittock *et al.*[21] that increasing doses of BoNT produced an increasing reduction in spasticity, but had no effect on walking.

It is possible that, for tone reduction to translate into functional improvements, physiotherapy must be added to BoNT. There is limited evidence of the superiority of BoNT plus physiotherapy intervention over BoNT intervention alone in improving gait function, mostly, but not exclusively from non-randomized trials,[30-32] and also of BoNT plus physiotherapy over physiotherapy alone from a non-randomized trial.[33] However, the studies included in this review provide limited or no information about concomitant physiotherapy treatment. Only in two studies all participants of both groups underwent concomitant rehabilitation,[16, 22] but only the study enrolling subacute patients[22] detailed its type, frequency and intensity. In most studies, concomitant rehabilitation was allowed, but in two of them[18, 21] less than half of the participants were actually receiving physiotherapy concurrently during the trial. Unfortunately, the most powered study[23] did not mention concomitant rehabilitation or physiotherapy at all.

The failure of BoNT treatment in increasing gait speed in chronic stroke survivors does not exclude that BoNT might have other beneficial effects in this population. Indeed, spasticity may induce equinovarus deformity, may cause spasm and pain, and affect balance, transfer, and mobility, leading to an increased risk of complications such as falls and pressure ulcers.[34] However, no study has specifically addressed the potential benefits of treating post-stroke lower limb spasticity to these regards. Also, other gait parameters. like joint kinematics and pattern of foot contact might be affected by BoNT treatment, but, at present, the evidence of such effects on gait is lacking. Actually, one of the included studies, by Dunne *et al.*[18] stated that "*the treatment with BoNT also improved gait quality,*" assessed as improved/unchanged/worsened by a blinded physician observing video recordings of patients' walking before and after injections. However, performing an independent analysis of the data presented in this article, we found that the percentage of individuals rated as improved was not significantly different between the two groups; thus, the purported improvement of gait quality reported by these authors was not supported by their own data.

Of the two studies actually showing a large effect of BoNT on gait speed, that by Tao *et al.* was carried out in a very small number of participants with a recent stroke;[22] their results suggest that early treatment with BoNT might be usefully combined with rehabilitation in patients who develop spasticity. However, the authors did not compare groups at baseline assessment, and only reported measures of spasticity and gait collected at 2-months follow-up. Moreover, although the study is labelled as double-blind RCT, assessors blinding is not explicitly stated. Given the high risk of bias, we cannot be certain that the large differences between groups observed at follow-up are due to BoNT treatment. Adequately powered, high-quality RCTs are recommended to verify whether BoNT injections into lower limb muscles actually improve functional outcomes when administered in the subacute phase in addition to intensive rehabilitation.

Limitations of the study

The results of this review must be interpreted with caution, given the inherent limitations related to the scarcity and, in some cases, low quality of the current literature on this topic. Very few articles were retrieved, and they were not homogeneous in time from stroke, samples size (actually, only one study[23] enrolled more than 50% of the total subjects), toxin preparation used (Dysport *vs.* Botox), follow-up time, gait outcome measures, BoNT dosage and targeted muscles. The variability or the latter features, however, was expected. Conceivably, the choice of the muscles to be treated with BoNT injections depends on the clinical assessment and most studies, in fact, provided BoNT treatment tailored to the clinical presentation. However, all studies injected the triceps surae, one of the muscle groups of the lower limb where spasticity that interferes with gait function predominates. BoNT dosage, at least in part, depends on the muscle that is treated, and in most studies, dosage ranged 200-300 units (as Botox units). Moreover, the two studies that assessed the effects on gait of different BoNT dosages, actually did not find any significant difference among groups treated with different doses, and we conservatively included in the analysis data from the group with the best outcome. The BoNT preparation (Dysport, Botox) is also a relevant feature, but the data were not heterogeneous, so we decided against aggregating studies that used different BoNT preparations separately. With regard to gait speed, the results consistently showed that BoNT injections have no effects, regardless of the injected muscles, dosage and preparation.

Despite these limitations, therefore, our results indicate that the use of BoNT injections in chronic stroke survivors with lower limb spasticity should be carefully evaluated on a case-by-case basis, taking into account the physician expertise, the variability in patient response and the limited evidence of consistent functional benefits on gait parameters. According to the Clinical Practice Guideline for Stroke Rehabilitation in Korea,[35] BoNT is recommended in stroke patients for reducing spasticity with a high level of evidence. Botulinum toxin A is also recommended in the AAPM&R clinical recommendations for the management of focal spasticity of the upper and lower limbs, with a grade of A classification.[36] Neither guideline specifically refers to treatment-induced functional improvements, merely recommending their use to reduce spasticity. Tone reduction, however, must have an impact on function to induce a meaningful positive change for the person. NICE guideline on stroke rehabilitation[37] are much more restrictive and state that there is insufficient clinical evidence to recommend botulinum toxin A for spasticity of the lower limb. The NICE guidelines[37] also point out the lack of cost-effectiveness evidence for BoNT treatment, a key issue, given the high costs of this treatment.

Conclusions

Compared to the most recent previous systematic review of RCTs by Gupta *et al.*,[4] our study identified three additional RCTs investigating the effects of toxin on gait parameters, including a well-powered study that enrolled nearly 500 participants. Results of our meta-analysis showed that BoNT injections have no effect on gait speed in persons with chronic post-stroke lower limb spasticity. Insufficient evidence was found of benefits of BoNT treatment on functional parameters other than gait speed. Further large RCTs are needed to investigate whether, beyond the reduction of spasticity, BoNT treatment may positively impact functional outcomes other than gait speed, *e.g.* joint kinematics and kinetics, energetic cost of walking, and risk of falls, and to clarify the effects of BoNT in individuals with recent stroke.

References

1. Stevens E, Emmett E, Wang Y, McKevitt C, Wolfe C. The Burden of Stroke in Europe. Stroke Alliance for Europe 2017;131.

2. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil 1995;76:27–32.

3. Urrutia R, Miren Gutiérrez-Muto A, Sanz-Morère CB, Gómez A, Politi AM, Lunardini F, *et al.* Spasticity evaluation with the Amadeo Tyromotion device in patients with hemispheric stroke. Front Neurorobot 2023;17:1172770.

4. Gupta AD, Chu WH, Howell S, Chakraborty S, Koblar S, Visvanathan R, *et al.* A systematic review: efficacy of botulinum toxin in walking and quality of life in post-stroke lower limb spasticity. Syst Rev 2018;7:1.

5. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: physiology, assessment and treatment. Brain Inj 2013;27:1093–105.

6. Dressler D, Altavista MC, Altenmueller E, Bhidayasiri R, Bohlega S, Chana P, *et al.* Consensus guidelines for botulinum toxin therapy: general algorithms and dosing tables for dystonia and spasticity. J Neural Transm (Vienna) 2021;128:321–35.

7. Wu T, Li JH, Song HX, Dong Y. Effectiveness of Botulinum Toxin for Lower Limbs Spasticity after Stroke: A Systematic Review and Meta-Analysis. Top Stroke Rehabil 2016;23:217–23.

8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.*; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

10. Roever L. PICO: model for clinical questions. Evid Based Med Pract 2018;115:2.

11. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 2009;55:129–33.

12. Moseley AM, Herbert RD, Sherrington C, Maher CG. Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). Aust J Physiother 2002;48:43–9.

13. Foley NC, Bhogal SK, Teasell RW, Bureau Y, Speechley MR. Estimates of quality and reliability with the physiotherapy evidence-based database scale to assess the methodology of randomized controlled trials of pharmacological and nonpharmacological interventions. Phys Ther 2006;86:817–24.

14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

16. Bollens B, Gustin T, Stoquart G, Detrembleur C, Lejeune T, Deltombe T. A randomized controlled trial of selective neurotomy versus botulinum toxin for spastic equinovarus foot after stroke. Neurorehabil Neural Repair 2013;27:695–703.

17. Burbaud P, Wiart L, Dubos JL, Gaujard E, Debelleix X, Joseph PA, *et al*. A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. J Neurol Neurosurg Psychiatry 1996;61:265–9.

18. Dunne JW, Gracies JM, Hayes M, Zeman B, Singer BJ; Multicentre Study Group. A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. Clin Rehabil 2012;26:787–97.

19. Yu HX, Liu SH, Wang ZX, Liu CB, Dai P, Zang DW. Efficacy on gait and posture control after botulinum toxin A injection for lower-limb spasticity treatment after stroke: A randomized controlled trial. Front Neurosci 2023;16:1107688.

20. Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M; GSK1358820 Spasticity Study Group. Botulinum toxin type A in poststroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. J Neurol 2010;257:1330–7.

21. Pittock SJ, Moore AP, Hardiman O, Ehler E, Kovac M, Bojakowski J, *et al.* A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis 2003;15:289–300.

22. Tao W, Yan D, Li JH, Shi ZH. Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients. J Phys Ther Sci 2015;27:759–62.

23. Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R. OnabotulinumtoxinA for the Treatment of Poststroke Distal Lower Limb Spasticity: A Randomized Trial. PM R 2018;10:693–703.

24. Baker JA, Pereira G. The efficacy of Botulinum Toxin A for limb spasticity on improving activity restriction and quality of life: a systematic review and meta-analysis using the GRADE approach. Clin Rehabil 2016;30:549–58.

25. Sun LC, Chen R, Fu C, Chen Y, Wu Q, Chen R, *et al.* Efficacy and Safety of Botulinum Toxin Type A for Limb Spasticity after Stroke: A Meta-Analysis of Randomized Controlled Trials. BioMed Res Int 2019;2019:8329306.

26. Ding X, Huang L, Wang Q, Liu Y, Zhong J, Chen H. Clinical study of botulinum toxin A injection combined with spasmodic muscle therapeutic instrument on lower limb spasticity in patients with stroke. Exp Ther Med 2017;13:3319–26.

27. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci 2004;22:281–99.

28. Varvarousis DN, Martzivanou C, Dimopoulos D, Dimakopoulos G, Vasileiadis GI, Ploumis A. The effectiveness of botulinum toxin on spasticity and gait of hemiplegic patients after stroke: A systematic review and meta-analysis. Toxicon 2021;203:74–84.

29. Cofré Lizama LE, Khan F, Galea MP. Beyond speed: gait changes after botulinum toxin injections in chronic stroke survivors (a systematic review). Gait Posture 2019;70:389–96.

30. Roche N, Zory R, Sauthier A, Bonnyaud C, Pradon D, Bensmail D. Effect of rehabilitation and botulinum toxin injection on gait in chronic stroke patients: a randomized controlled study. J Rehabil Med 2015;47:31–7.

31. Fujita K, Miaki H, Hori H, Kobayashi Y, Nakagawa T. How effective is physical therapy for gait muscle activity in hemiparetic patients who receive botulinum toxin injections? Eur J Phys Rehabil Med 2019;55:8–18.

32. Cinone N, Letizia S, Santoro L, Facciorusso S, Armiento R, Picelli A, *et al.* Combined Effects of Isokinetic Training and Botulinum Toxin Type A on Spastic Equinus Foot in Patients with Chronic Stroke: A Pilot, Single-blind, Randomized Controlled Trial. Toxins (Basel) 2019;11:210.

33. Uchiyama Y, Koyama T, Wada Y, Katsutani M, Kodama N, Domen K. Botulinum Toxin Type A Treatment Combined with Intensive Rehabilitation for Gait Poststroke: A Preliminary Study. J Stroke Cerebrovasc Dis 2018;27:1975–86.

34. Brainin M, Norrving B, Sunnerhagen KS, Goldstein LB, Cramer SC, Donnan GA, *et al.*; International PSS Disability Study Group. Poststroke chronic disease management: towards improved identification and interventions for poststroke spasticity-related complications. Int J Stroke 2011;6:42–6.

35. Kim DY, Ryu B, Oh BM, Kim DY, Kim DS, Kim DY, *et al.*; KSNR Stroke CPG Writing Group. Clinical Practice Guideline for Stroke Rehabilitation in Korea-Part 1: Rehabilitation for Motor Function (2022). Brain Neurorehabil 2023;16:e18.

36. Verduzco-Gutierrez M, Raghavan P, Pruente J, Moon D, List CM, Hornyak JE, *et al.* AAPM&R consensus guidance on spasticity assessment and management. PM R 2024;16:864–87.

37. Evidence reviews for interventions for spasticity: Stroke rehabilitation in adults (update): Evidence review P. London: National Institute for Health and Care Excellence (NICE); 2023.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Chiara De Santis and Stefano Doronzio contributed substantially to data extraction; Stefano Doronzio and Chiara Castagnoli performed the quality assessment. Teresa Barretta and Maria Anna Szczepanska contributed to results extraction. Michele Piazzini, Gemma Lombardi, and Giovanna Cristella were responsible for writing, review, and editing. Marco Baccini provided the conceptualization, methodology, conflicts resolution, evidence synthesis, writing review, and project administration. Francesca Cecchi contributed to the conceptualization, methodology, writing (draft and review), and supervision. All authors read and approved the final version of the manuscript.

History

Manuscript accepted: June 13, 2025. - Manuscript revised: May 14, 2025. - Manuscript received: March 11, 2025.

Supplementary data

For supplementary materials, please see the HTML version of this article at www.minervamedica.it