Clinical Drug Investigation (2018) 38:991–1000
https://doi.org/10.1007/s40261-018-0701-x

REVIEW ARTICLE

Safety Profile of High-Dose Botulinum Toxin Type A in Post-Stroke Spasticity Treatment

Alessio Baricich[1] · Alessandro Picelli[2] · Andrea Santamato[3] · Stefano Carda[4] · Alessandro de Sire[5] · Nicola Smania[2] · Carlo Cisari[1] · Marco Invernizzi[1]

Published online: 12 September 2018

Abstract

Botulinum toxin type A (BoNT-A) is considered the gold standard for the treatment of focal post-stroke spasticity (PSS). However, a recently published study estimated that a significant percentage of patients affected by PSS could benefit from higher doses of BoNT-A than those permitted by current directives in the countries studied. Several studies have reported the use of high doses of BoNT-A in the management of patients affected by severe PSS; however, the most important adverse effect of this drug might be systemic diffusion of the toxin, which could potentially be related to its dose. Even if systemic toxicity is a rare event, fear of systemic toxicity is still the most relevant concern regarding use of high doses. The aim of our narrative review was to show the state of the art on the use of high doses of BoNT-A in patients affected by PSS in order to define the safety profile, focusing on both clinical and instrumental assessment of systemic effects. Current evidence from the literature suggests that higher doses of BoNT-A are effective in reducing spasticity of upper and lower limbs after stroke, with rare occurrence of mild adverse effects. The use of high doses seems to be an effective and safe therapeutic option to reduce multifocal or generalized PSS in selected patients. In particular, the potential role of higher doses in order to improve the functional outcome of these patients should be noted.

Key Points

Botulinum toxin type A (BoNT-A) is currently considered the gold standard for the treatment of focal post-stroke spasticity (PSS). However, it has been suggested that a significant percentage of affected patients could benefit from doses higher than those permitted by current directives in the countries studied.

Several studies have reported the results of use of higher doses of BoNT-A in PSS and clinical and instrumental evaluations suggest that this could be an effective and safe treatment in selected patients affected by severe PSS.

Further research should focus on the potential role of high doses of BoNT-A in improving the functional outcome of the affected patients.

✉ Alessio Baricich
alessio.baricich@med.uniupo.it

1 Physical Medicine and Rehabilitation, Department of Health Sciences, Università del Piemonte Orientale, viale Piazza d'armi 1, 28100 Novara, Italy

2 Department of Neurological, Biomedical and Movement Sciences, Neuromotor and Cognitive Rehabilitation Research Center, University of Verona, Verona, Italy

3 Department of Physical Medicine and Rehabilitation, "OORR Hospital", Università di Foggia, Foggia, Italy

4 Neuropsychology and Neurorehabilitation Service, Department of Clinical Neuroscience, Lausanne University Hospital (CHUV), Lausanne, Switzerland

5 Department of Medical and Surgical Specialties and Dentistry, University of Campania "Luigi Vanvitelli", Naples, Italy

1 Introduction

Post-stroke spasticity (PSS) occurs in approximately 30% of stroke survivors; it has a negative impact on activities of daily living (ADLs) and involves a significant burden on the caregivers of these patients [1–3]. Spasticity can vary from a subtle neurological sign to a high increase in tone, causing joint immobility, and its management requires a balanced approach.

Botulinum toxin type A (BoNT-A) is an effective, safe, and reversible treatment for focal spasticity in stroke survivors [4], and it has been approved by the US Food and Drug Administration (FDA) and European regulatory agencies for this indication. However, at the present time, there is no consensus on the maximum dose of BoNT-A in terms of safety and clinical interchangeability among the three commercially approved products: onabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA, USA), abobotulinumtoxinA (Dysport®, Ipsen, Paris, France), and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany).

In fact, currently approved doses indicate a maximum dose of 400 units (U) for onabotulinumtoxinA and incobotulinumtoxinA and 1500 U for abobotulinumtoxinA [5], whereas current guidelines suggest doses of up to 600 U of onabotulinumtoxinA or up to 1500 U of abobotulinumtoxinA per session [6].

A recent survey suggested the necessity to reconsider the maximum dose administered per single treatment of BoNT-A in order to improve clinical outcomes of treated patients [7]. In fact, the use of high doses of BoNT-A is a common practice in the management of patients with PSS [8], although the most important adverse effect of BoNT-A might be systemic diffusion of the toxin, which is potentially related to its dose [9].

Therefore, in light of these considerations, the aim of this narrative review was to investigate the safety profile of high doses of BoNT-A in the rehabilitation treatment of PSS, focusing on both clinical and instrumental assessment of systemic effects of BoNT-A.

2 Literature Search

For this review, we considered clinical reports published from December 1989 to February 2018 that provided a description of higher doses of BoNT-A (at least 600 U of onabotulinumtoxinA and incobotulinumtoxinA and 1800 U of abobotulinumtoxinA per injection visit) for treatment of PSS and which also considered the safety profile of the treatment. Searches were conducted in the Cochrane Central Register of Controlled Trials, Scopus, Web of Science, and PubMed databases using the terms "Botulinum Toxin" and "high doses" combined with "spasticity", "stroke", and "adverse effects". Search filters were applied in order to include English language and human studies only. Subsequently, we carefully reviewed the references of selected studies in order to identify other potentially relevant studies.

At the end of the screening process, we obtained the 13 studies included in this review (see Table 1 for further details).

3 Botulinum Toxin Type A (BoNT-A) and Post-Stroke Spasticity (PSS)

PSS is velocity-dependent increased muscle tone with exaggerated tendon jerks subsequent to stroke, resulting from hyperexcitability of the stretch reflex [10]. Its prevalence ranges from 4% to 27% in the early time course (1–4 weeks post-stroke), 19–26.7% in the post-acute phase (1–3 months post-stroke), and 17–42.6% in the chronic phase (> 3 months post-stroke) [2]. In the upper limbs, the most frequently observed pattern is internal rotation and adduction of the shoulder combined with flexion of elbow, wrist, and fingers; the combination of adduction and extension of the knee with equinovarus foot is a typical manifestation in the lower limbs [11, 12].

BoNT-A is an enzyme acting in the cytosol of nerve endings that cleaves synaptosomal-associated protein (SNAP)-25, resulting in blocked acetylcholine release at neuromuscular junctions [13, 14].

Intramuscular injections of BoNT-A are currently considered the gold standard for treatment of PSS [4, 8, 15] and have been shown to be effective in reducing spastic hypertonia, with reversibility and a low prevalence of complications [16, 17]. Therefore, BoNT-A, which reduces disability in patients affected by PSS, might improve patients' participation in ADLs and health-related quality of life (HRQoL) [18–20].

To date, three preparations of BoNT-A are approved by the FDA: onabotulinumtoxinA and abobotulinumtoxinA are composed of active neurotoxin (150 kD) and non-toxic accessory proteins (NAPs), whereas incobotulinumtoxinA contains only the 150 kD neurotoxin [21].

It should be noted that the potency of BoNT-A depends on the quantity of active neurotoxin required to achieve the median lethal dose (LD_{50}) [22, 23]. However, due to the lack of LD_{50} bioassay harmonization, units of BoNT formulations are not easy to compare. Considering these aspects, physicians must consider that different preparations might show different therapeutic profiles.

Table 1 Studies included in the review focusing on the effects of high doses of botulinum toxin type A (abobotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA) in post-stroke spasticity treatment

Study (year)	Patients	BoNT-A (dose)	Muscle injected	Injection guide	Outcome measures	Clinical results/adverse events
Hesse et al. (1995) [51]	6 chronic stroke survivors; lower-limb spasticity	AbobotulinumtoxinA (2000 U)	GAM, GAL, SOL, TP	EMG	AS, MRC, cycle parameters	Bladder paresis (1 patient)
Mancini et al. (2005) [52]	45 chronic stroke survivors with spastic foot, randomized in three groups ($n = 15$)	OnabotulinumtoxinA (Group I: mean dose 167 U; Group II: mean dose 320 U; Group III: mean dose 540 U)	Selected individually (GAM, GAL, SOL, TA, TP, FDL, FDB, FHL, EHL)	EMG	MAS, MRC, gait assessment, Achilles tendon clonus, VAS for gait function and pain, adverse event scale	All groups showed significant scale score improvements after treatment. Groups II and III showed a greater and more prolonged response than Group I. Group III showed the highest rate of adverse effects 4 weeks post-treatment (prolonged weakness of the treated limb, flu-like syndrome and edema of the injected leg)
Varghese-Kroll and Elovic (2009) [53]	1 stroke survivor	OnabotulinumtoxinA 500, 600, 700, 800, 700 U	PM, SS, B, BR, PT, FSD, FPD, L, GAM, SOL, PT, TA, FDL	Not indicated	MAS, MRC	800 U: fatigue and contralateral weakness; 500, 600, and 700 U: well-tolerated
Thomas and Simpson (2012) [54]	1 stroke survivor, right hemiparesis	OnabotulinumtoxinA 700 U	TB, FSD, FPD, L, FBP, FLP, OP, GAM, GAL, SOL, PT, EHL	EMG, ES	MAS, MRC, RNS	Contralateral upper-extremity weakness (no adverse events at previous injection visit)
	1 stroke survivor, left hemiparesis	OnabotulinumtoxinA 700 U	D, TB, T, FUC, FLP, L, GAM, SOL, FDB	EMG, ES	MAS, MRC, RNS	Contralateral upper-extremity weakness (observed also in previous treatment with 700 U and subsequent session with 600 U)
Santamato et al. (2013) [56]	25 stroke survivors	IncobotulinumtoxinA up to 840 U	PM, BB, BR, PT, FSD, FPD, FUC, FRC, FLP, ABP, RF, ADD, BF, GAM, GAL, SOL, TP, TA, FDL, FHL, EHL	US	MAS, MRC, VAS, FAT, GOS, BS	2 patients had local adverse effects (hematoma); 1 subject reported muscle weakness and reduction of active motility of the injected arm
Intiso et al. (2014) [57]	14 stroke survivors	IncobotulinumtoxinA up to 840 U	PM, BB, BR, PT, FSD, FPD, FUC, FRC, FLP, RF, ADDLBM, BF, GAM, GAL, SOL, PT, TA, FDL, FHL	US	MAS, MRC, VAS, FAT, GOS, BI	2 patients had local adverse effects (hematoma); 1 subject reported muscle weakness and reduction of active motility of the injected arm

Table 1 (continued)

Study (year)	Patients	BoNT-A (dose)	Muscle injected	Injection guide	Outcome measures	Clinical results/adverse events
Dressler et al. (2015) [18]	54 spastic patients	IncobotulinumtoxinA up to 1200 U	Not reported	Clinical identification; US; EMG	Systemic toxicity questionnaire	No adverse events
Baricich et al. (2015) [8]	26 stroke survivors	OnabotulinumtoxinA 676.9 ± 86.3 U	PM, BB, B, BR, FUC, FRC, FSD, FPD, FLP, FBP, ADP, RF, BF, ADD, GAM, GAL, SOL, TP, TA, FHL, FDL, FDB, EHL	US	MAS, DAS, GAE	No adverse events
Invernizzi et al. (2015) [75]	11 stroke survivors	IncobotulinumtoxinA 677 ± 69.3 U	PM, B, BB, BR, FDP, FSD, FUC, FRC, FPL, ADP, L, RF, ST, SM, GAL, GAM, SOL, TA, TP, FDL, FHL, EHL, FDB	Not indicated	FAC, BI, MI, HRV	No reported adverse events; no variations in HRV parameters
Santamato et al. (2017) [59]	20 stroke survivors	IncobotulinumtoxinA up to 840 U	SS, PM, BB, B, BR, PT, FUC, FRC, FSD, FPD, FPL, FBP, GAM, GAL, SOL, ADD, RF, BF, TP, TA, FDL, FHL, EHL	US	AS, DAS, GATR	No reported systemic effects
Wissel et al. (2017) [58]	155 stroke survivors	IncobotulinumtoxinA 400, 600, and 800 U	Not indicated	Not indicated	REPAS, GAE, adverse events	No serious treatment-related adverse events; dose escalation did not lead to an increased incidence of treatment-related adverse events
Baricich et al. (2017) [76]	10 stroke survivors	IncobotulinumtoxinA/onabotulinumtoxinA 665 ± 81.82 U	Not indicated	Not indicated	MI, BI, FAC, HRV	No reported adverse events; no variations in HRV parameters

ABP abductor pollicis brevis, *ADD* adductors, *ADP* adductor pollicis brevis, *AS* Ashworth Scale, *B* brachialis, *BB* biceps brachii, *BF* biceps femori, *BI* Barthel Index, BoNT-A Botulinum Toxin Type A, *BR* brachioradialis, *BS* Barthel Scale, *D* deltoid, *DAS* Disability Assessment Scale, *EHL* extensor hallucis longus, *EMG* electromyography, *ES* electrical stimulation, *FAC* Functional Ambulation Categories, *FAT* Frenchay Arm Test, *FBP* flexor brevis pollicis, *FDB* flexor digitorum brevis, *FDL* flexor digitorum longus, *FHL* flexor hallucis longus, *FLP* flexor longus pollicis, *FPD* flexor profundus digitorum, *FRC* flexor radialis carpi, *FSD* flexor superficialis digitorum, *FUC* flexor ulnaris carpi, *GAE* global assessment of efficacy, *GAL* gastrocnemius lateralis, *GAM* gastrocnemius medialis, *GATR* Global Assessment of Treatment Response, *GOS* Glasgow Outcome Scale, *HRV* heart rate variability, *L* lumbricals, *MAS* Modified Ashworth Scale, *MI* Motricity Index, *MRC* Medical Research Council, *OP* opponens pollicis, *PM* pectoralis major, *PT* pronator teres, *REPAS* Resistance to Passive Movement Scale, *RF* rectus femoris, *RNS* repetitive nerve stimulation, *SM* semimembranosus, *SOL* soleus, *SS* subscapularis, *ST* semitendonosus, *T* trapezius, *TA* tibialis anterior, *TB* triceps brachii, *TP* tibialis posterior, *US* ultrasound, *VAS* visual analog scale

3.1 Dose Equivalence

Each BoNT-A formulation contains different amounts of active 150 kD neurotoxin/NAPs, showing a different LD_{50}: for this reason, it is mandatory to identify a conversion factor for different preparations [24, 25]; however, it must be pointed out that there are no validated conversion ratios, and regulatory authorities' labels clearly state that units of each BoNT-A product are specific and not interchangeable.

IncobotulinumtoxinA showed a similar clinical efficacy and adverse event profile as onabotulinumtoxinA with a clinical conversion ratio of 1:1 or 1:1.2 [26–32]. On the other hand, the conversion ratio between onabotulinumtoxinA (or incobotulinumtoxinA) and abobotulinumtoxinA is still under discussion, and ranges from 1:1 [33] to as high as 1:11 [34]. However, a conversion ratio for onabotulinumtoxinA/abobotulinumtoxinA of 1:3 or lower has been observed both in preclinical and clinical settings, suggesting that it is appropriate for treating spasticity [35–39]. Moreover, a higher conversion ratio could lead to an abobotulinumtoxinA overdosing or, conversely, underdosing when switching from abobotulinumtoxinA to onabotulinumtoxinA [40–43].

3.2 BoNT-A and Systemic Diffusion

After administration, BoNT-A remains mainly localized at the injection site, and it is of note that this aspect is probably related to its safety profile [44]. However, spread to contiguous areas could increase the risk of adverse effects and, even if uncommon, distant spread can also occur; this phenomenon might cause unintended neuromuscular blockade away from the local injection site with clinical symptoms such as generalized weakness [45] and flu-like syndrome [46]. With regard to this issue, no clear differences were reported among the various BoNT-A preparations [32]. In addition, several factors other than the pharmaceutical preparation could affect the local and distal spread of BoNT-A, such as dose, dilution, injection technique, target site, location of injection within the muscle belly, depth of injection, level of muscle hyperactivity, and post-injection rehabilitation treatment [8, 47–49].

4 BoNT-A Doses, Spread, and Adverse Events in PSS Treatment

As reported earlier, BoNT-A injection is the gold standard therapy for focal PSS, showing a low prevalence of complications and reversibility [17].

In recent years, use of doses higher than those currently approved (maximum dose of 400 U for onabotulinumtoxinA and incobotulinumtoxinA and 1500 U for abobotulinumtoxinA [5]) has been reported for treatment of patients affected by severe, multilevel PSS [50]. On the other hand, many clinicians hypothesized that higher doses of BoNT-A may cause generalized, adverse effects [51–55]. In particular, Lange et al. hypothesized a possible relationship between the BoNT-A dose and systemic effects, although this was not observed in their study [9].

In light of these considerations, the assessment of patients treated with high doses of BoNT-A should include a systematic evaluation of the presence of undesired, adverse events; moreover, in association with clinical assessment, a non-invasive, instrumental evaluation should also be considered in order to detect subclinical diffusion of BoNT-A.

4.1 Clinical Assessment

In 1995, Hesse et al. [51] published one of the first studies focused on high doses of BoNT-A. All patients in the group treated with 2000 U of abobotulinumtoxinA ($n=5$) completed the study; 4 weeks after injection they reported a reduction in muscle tone and improved gait velocity, stride length, stance, and swing symmetry. In a randomized, double-blind, dose-ranging study, Mancini and colleagues [52] treated 45 patients with three different doses of onabotulinumtoxinA. All groups showed significant improvements after treatment: Group II (mean BoNT-A total dose: 322 U) and Group III (mean dose: 540 U) showed a greater and more prolonged response than Group I (mean dose: 167 U).

In 2009, Varghese-Kroll and Elovic [53] reported the first known case of repeated, contralateral weakness and fatigue after high-dose BoNT-A injection. A 53-year-old woman developed contralateral weakness and fatigue, without autonomic symptoms, 2 weeks after receiving an injection of 800 U of onabotulinumtoxinA for management of PSS, and she reported resolution 4 weeks later. Interestingly, three previous injections of onabotulinumtoxinA 700, 500, and 600 U, spaced 3 months apart, were well-tolerated.

In 2012, Thomas and Simpson [54] also described contralateral weakness following repetitive onabotulinumtoxinA administrations in two patients affected by PSS. In the first case report, a 43-year-old woman treated for more than 1 year with 575–700 U of onabotulinumtoxinA into the upper and lower limb muscles without adverse effects developed contralateral weakness after a re-injection of a total dose of 700 U. In the second case report, a 21-year-old woman with post-stroke spasticity and dystonia reported weakness of her non-treated right arm starting within days after the last injection of a new BoNT-A treatment with a total dose of 700 U of onabotulinumtoxinA; interestingly, during previous injection visits she did not report any adverse effects with doses ranging from 550 to 700 U into the proximal upper limb muscles. However, she described the same symptoms after the injection of 600 U, whereas no adverse effects were described with 500 U of onabotulinumtoxinA administrated

in upper limb distal muscles. The authors hypothesized the development of contralateral limb weakness as a consequence of the diffusion of BoNT-A through tissue planes from proximal upper extremity muscles, across the midline, to contralateral muscles. They also posited that the risk of systemic effects is related to the total injection dose and injection frequency of BoNT-A.

In recent years, the effects of higher BoNT-A doses in PSS have been widely investigated [4, 6, 7]. In an interesting report on a recent survey conducted by Bensmail et al. [55], it was estimated that 24.6% of the patients in their study could benefit from higher doses than those permitted by current directives in the countries studied.

As a consequence of these considerations, several recent papers have focused on this issue in order to clarify the possible clinical implications of higher doses of BoNT-A.

In a prospective, non-randomized, open-label study, Santamato and colleagues [56] described the safety and efficacy of higher doses (ranging from 750 to 840 U) of incobotulinumtoxinA in 25 subjects with upper- and lower-limb PSS. Patients were treated in several muscles of the upper and lower limbs under ultrasound guidance, reporting a substantial improvement in functional disability, spasticity-related pain, and muscle tone after 30 days of follow-up.

Intiso and colleagues [57] reported the effectiveness of high doses of incobotulinumtoxinA (up to 840 U) in 14 hemiparetic patients with spasticity of the upper and lower limbs due to brain injury or cerebral palsy. The authors observed a significant reduction in muscle tone and pain, even if global function was unchanged. Adverse events were reported in three subjects: two patients showed local hematoma at the injection site, and one subject showed weakness and reduction of active motility in the injected arm for 2 weeks.

Recently, Dressler et al. [18] demonstrated that high doses of incobotulinumtoxinA (minimum 400 U and maximum 1200 U) injected into 54 patients suffering from spasticity of several etiologies, including stroke, did not cause any generalized effects that could be related to BoNT administration.

In a retrospective analysis, Baricich et al. [8] evaluated the efficacy and safety of high doses of onabotulinumtoxinA (from 600 to 800 U) in 26 patients affected by upper- and/or lower-limb PSS; they were assessed before treatment and at 30 and 90 days after treatment. The authors observed a significant muscle tone reduction and functional improvement, with no adverse events reported.

In 2017, Wissel and colleagues [58] evaluated the safety and efficacy of increasing doses (400 U up to 800 U) of incobotulinumtoxinA for patients with limb spasticity. They received three consecutive injection cycles with 400, 600, and 800 U of incobotulinumtoxinA, each followed by observation at 12–16 weeks. The authors concluded that escalating incobotulinumtoxinA doses (400 U up to 800 U) increased treatment efficacy but did not compromise safety or tolerability.

However, the available evidence mainly referred to a single set of injections evaluating the efficacy and safety of BoNT-A. Interestingly, in a recent prospective, non-randomized, open-label study, Santamato et al. [59] analyzed the long-term safety of repeated higher doses (up to 840 U) of incobotulinumtoxinA in 20 stroke survivors affected by post-stroke upper- and lower-limb spasticity. In a 2-year follow-up, a total of eight sets of BoNT-A injection appeared to be safe, with no general adverse effects reported.

4.2 Instrumental Assessment

As previously stated, various studies have investigated the remote effects of systemic spread of BoNT-A, using several methods [44–60].

In 1993, Garner et al. [61] analyzed eight patients treated with BoNT-A for focal dystonias in the head/neck region with repeated single-fiber electromyography (EMG) in the extensor digitorum brevis muscle, detecting an increase of jitter and blocking in six of those patients. In addition, quantitative EMG was proposed in order to detect the remote effects of BoNT. Erdal and colleagues [62] analyzed 27 patients affected by cervical dystonia after repeated, unilateral BoNT-A injections in the sternocleidomastoid muscle. By measuring quantitative EMG at rest and at maximal contraction, the authors demonstrated no cumulative effect provoked by repeated BoNT injections.

Interestingly, since a frequent target of BoNT-A during botulism is the autonomic nervous system, several researchers have investigated autonomic function in patients with cervical dystonia receiving BoNT-A, showing controversial evidence about the development of signs of subclinical diffusion [63].

In particular, heart rate variability (HRV), a simple and non-invasive electrocardiographic (ECG)-derived measure, can provide detailed information about the control exerted by the autonomic nervous system on cardiovascular activities [64–68]. HRV has been categorized into high frequency (HF), equivalent to the respiratory sinus arrhythmia, low frequency (LF), jointly contributed by both vagal and sympathetic, and very low frequency (VLF) power ranges according to its frequency [69].

In the previously published literature, there are few works investigating HRV modifications after BoNT-A injection; these studies have contrasting results, and all of them describe HRV modification in patients affected by cervical dystonia [70–74]. However, it must be pointed out that in cervical dystonia the BoNT-A doses are largely inferior to those utilized in spasticity.

In recent years, the possible effect of high doses of BoNT-A on the autonomic nervous system has also been deeply investigated in PSS patients.

In a case-control study, Invernizzi et al. [75] evaluated the changes in autonomic heart drive induced by high doses (higher than 600 U) of incobotulinumtoxinA injection in patients affected by PSS. Each patient underwent an ECG recording before injection and 10 days after treatment, and none of the variables considered showed statistically significant changes.

More recently, in order to confirm these results, Baricich et al. [76] evaluated the changes in HRV induced by high doses (> 600 U) of incobotulinumtoxinA or onabotulinumtoxinA, recruiting patients affected by PSS in a single-blind, randomized controlled crossover study [76]. In the initial part of the study, patients in the first group were injected with incobotulinumtoxinA while patients in the second group were injected with onabotulinumtoxinA; after 6 months, a crossover intervention was performed. All patients were blinded to BoNT-A type, and an ECG registration was performed in the 24 h before and 10 days after the treatment injection, both in the first and in the second part of the study. HRV analysis showed no significant changes after each BoNT-A injection in either group at any evaluation time.

5 Discussion

Current evidence in the published literature suggests that higher doses of BoNT-A are effective in reducing spasticity of the upper and lower limbs after stroke, with only rare occurrences of mild adverse effects. However, even if systemic BoNT-A toxicity is a rare event, this is still the most vigorous concern against application of increased BoNT-A doses.

In addition, as previously affirmed, cumulative data suggest that high doses (> 600 U) of incobotulinumtoxinA and onabotulinumtoxinA do not influence the cardiovascular activity of the autonomic nervous system in chronic hemiplegic spastic stroke survivors. Furthermore, it must be pointed out that generalized weakness can also occur with recommended doses of BoNT-A [51, 77].

A possible explanation is that local and systemic diffusion of BoNT could depend on several factors such as injection technique, volume, dilution, needle size, hematogenous transport, and other physical factors [78]. Current guidelines regarding dosing of BoNT-A in adults recommend a maximum of 1 mL per site, except in specific situations [79]. It has been hypothesized that higher BoNT-A doses or volumes might saturate local cholinergic nerve terminals, allowing unbound BoNT-A to spread to the bloodstream or to the structures adjacent to the target muscles [54].

On the other hand, it should be pointed out that, despite the observed reduction of muscle tone, there is limited evidence that treating patients with higher BoNT-A doses in the upper and lower limbs is related to a significant functional improvement, although this might be related to several other possibilities.

First of all, it is well-known that in severe spasticity, a meaningful improvement in active performance might be difficult to obtain even with BoNT-A treatment. Conversely, high doses should be considered in several neurological conditions in order to obtain a reduction of muscle tone with significant improvement in hygiene, gait, and balance [80, 81].

In addition, it should be pointed out that the impact of spasticity treatment on well-being and life satisfaction may not be clearly detected by quantitative score results, and may only be demonstrated by patient-reported outcome measures [82–86]. In fact, it should be considered that PSS also has an afferent, sensory component, which might be related to some differences in the sensations described by patients [85, 87].

In a recent study, for example, Turner-Stokes and colleagues [88] reported a significant effect on goal attainment for the real-life management of upper-limb spasticity following stroke in both patients treated with currently approved doses and those treated with high doses of BoNT-A (e.g., abobotulinumtoxinA dose range 40–1900 U; incobotulinumtoxinA dose range 100–600 U). Interestingly, this study confirmed the feasibility of using the Goal Attainment Scale in order to capture person-centered outcomes relating to passive and active functions and pain.

Finally, another critical issue that should be investigated is the possible impact of higher doses on inter-injection intervals: in fact, if demonstrated, a reduction in the number of sessions per year for each patient could have a possible beneficial impact on health and social costs.

Future studies focusing on the clinical effect of higher doses of BoNT-A should consider these critical aspects.

6 Conclusions

Current evidence suggests that the use of doses of BoNT-A higher than those reported in product labels might be considered a safe therapeutic option to reduce multifocal or generalized PSS in selected patients.

However, it must be pointed out that clinicians have to carefully define the clinical goal before starting BoNT-A treatment. Further evidence is mandatory to confirm our findings and the potential role of higher doses of BoNT-A in order to improve the functional outcome of patients affected by PSS should be noted.

Acknowledgements The authors wish to thank Lucrezia Moggio, MD for manuscript revision.

Compliance with Ethical Standards

Funding No funding was received to prepare this review.

Conflict of interest Dr. Baricich received consulting fees and speaking honoraria from Allergan, Ipsen, and Merz. Dr. Picelli received consulting fees from Allergan and Ipsen and speaking honoraria from Allergan. Dr. Santamato received consulting fees from Allergan, Ipsen, and Merz. Prof. Smania received consulting fees from Allergan and Ipsen and speaking honoraria from Allergan.

References

1. Lundström E, Smits A, Borg J, Terént A. Four-fold increase in direct costs of stroke survivors with spasticity compared with stroke survivors without spasticity: the first year after the event. Stroke. 2010;41(2):319–24.
2. Wissel J, Manack A, Brainin M. Toward an epidemiology of post stroke spasticity. Neurology. 2013;80(3 Suppl 2):S13–9.
3. Denno MS, Gillard PJ, Graham GD, DiBonaventura MD, Goren A, Varon SF, et al. Anxiety and depression associated with caregiver burden in caregivers of stroke survivors with spasticity. Arch Phys Med Rehabil. 2013;94(9):1731–6.
4. Santamato A, Micello MF, Ranieri M, Valeno G, Albano A, Baricich A, et al. Employment of higher doses of botulinum toxin type A to reduce spasticity after stroke. J Neurol Sci. 2015;350(1–2):1–6.
5. Santamato A, Panza F. Benefits and risks of non-approved injection regimens for botulinum toxins in spasticity. Drugs. 2017;77(13):1413–22.
6. Wissel J, Ward AB, Erztgaard P, Bensmail D, Hecht MJ, Lejeune TM, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. J Rehabil Med. 2009;41(1):13–25.
7. Picelli A, Baricich A, Cisari C, Paolucci S, Smania N, Sandrini G. The Italian real-life post-stroke spasticity survey: unmet needs in the management of spasticity with botulinum toxin type A. Funct Neurol. 2017;32(2):89–96.
8. Baricich A, Grana E, Carda S, Santamato A, Cisari C, Invernizzi M. High doses of onabotulinumtoxinA in post-stroke spasticity: a retrospective analysis. J Neural Transm (Vienna). 2015;122(9):1283–7.
9. Lange DJ, Brin MF, Warner CL, Fahn S, Lovelace RE. Distant effects of local injection of botulinum toxin. Muscle Nerve. 1987;10(6):552–5 (**Erratum in: Muscle Nerve. 1988;11(5):520**).
10. Pandyan AD, Gregoric M, Barnes MP, Wood D, Van Wijck F, Burridge J, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disabil Rehabil. 2005;27(1–2):2–6.
11. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: physiology, assessment and treatment. Brain Inj. 2013;27(10):1093–105.
12. Esquenazi A, Alfaro A, Ayyoub Z, Charles D, Dashtipour K, Graham GD, et al. OnabotulinumtoxinA for lower limb spasticity: guidance from a Delphi Panel approach. PM R. 2017;9(10):960–8.
13. Simpson LL. Identification of the major steps in botulinum toxin action. Annu Rev Pharmacol Toxicol. 2004;44:167–93.
14. Humeau Y, Doussau F, Grant NJ, Poulain B. How botulinum and tetanus neurotoxins block neurotransmitter release. Biochimie. 2000;82:427–46.
15. Franceschini M, Iocco M, Molteni F, Santamato A, Smania N, Italian Spasticity Study Group. Management of stroke patients submitted to botulinum toxin type A therapy: a Delphi survey of an Italian expert panel of specialist injectors. Eur J Phys Rehabil Med. 2014;50(5):525–33.
16. Baker JA, Pereira G. The efficacy of botulinum toxin A for spasticity and pain in adults: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. Clin Rehabil. 2013;27(12):1084–96.
17. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818–26.
18. Dressler D, Adib Saberi F, Kollewe K, Schrader C. Safety aspects of incobotulinumtoxinA high-dose therapy. J Neural Transm. 2015;122(2):327–33.
19. Hefter H, Benecke R, Erbguth F, Jost W, Reichel G, Wissel J. An open-label cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). BMJ Open. 2013. https://doi.org/10.1136/bmjopen-2012-001853.
20. Rychlik R, Kreimendahl F, Schnur N, Lambert-Baumann J, Dressler D. Quality of life and costs of spasticity treatment in German stroke patients. Health Econ Rev. 2016;6(1):27.
21. Aoki KR, Guyer B. Botulinum toxin type A and other botulinum toxin serotypes: a comparative review of biochemical and pharmacological actions. Eur J Neurol. 2001;8(Suppl. 5):21–9.
22. Sesardic D, Leung T, Gaines-Das R. Role for standards in assays of botulinum toxins: International collaborative study of three preparations of botulinum type A toxin. Biologicals. 2003;3:265–76.
23. McLellan K, Das RE, Ekong TA, Sesardic D. Therapeutic botulinum type A toxin: factors affecting potency. Toxicon. 1996;34:975–85.
24. Chen JJ, Dashtipour K. Abo-, Inco-, Ona-, and Rima-Botulinum toxins in clinical therapy: a primer. Pharmacotherapy. 2013;33:304–18.
25. Frevert J. Pharmaceutical, biological, and clinical properties of botulinum neurotoxin type A products. Drugs R D. 2015;15(1):1–9.
26. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology. 2005;64:1949–51.
27. Roggenkamper P, Jost WH, Bihari K, Comes G, Grafe S, NT 201 Blepharospasm Study Team. Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm. 2006;113:303–12.
28. Jost WH, Kohl A, Brinkmann S, Comes G. Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (BOTOX) in healthy volunteers. J Neural Transm. 2005;112:905–13.
29. Park J, Lee MS, Harrison AR. Profile of Xeomin (incobotulinumtoxinA) for the treatment of blepharospasm. Clin Ophtalmol. 2011;5:725–32.
30. Zoons E, Dijkgraaf MGW, Dijk JM, van Schaik IN, Tijssen MA. Botulinum toxin as treatment for focal dystonia: a systematic review of the pharmaco-therapeutic and pharmaco-economic value. J Neurol. 2012;259:2519–26.
31. Dressler D, Benecke R. Pharmacology of therapeutic botulinum toxin preparations. Disabil Rehabil. 2007;29:1761–8.
32. Dressler D, Mander G, Fink K. Measuring the potency labelling of onabotulinumtoxinA (Botox®) and incobotulinumtoxinA (Xeomin®) in an LD50 assay. J Neural Transm. 2012;119:13–5.

33. Wohlfarth K, Goschel H, Frevert J, Dengler R, Bigalke H. Botulinum A toxins: units versus units. Arch Pharmacol. 1997;355:335–40.
34. Marchetti A, Magar R, Findley L, Larsen JP, Pirtosek Z, Ruzicka E, et al. Retrospective evaluation of the dose of Dysport and BOTOX in the management of cervical dystonia and blepharospasm: the REAL DOSE study. Mov Disord. 2005;20:937–44.
35. Marion MH, Sheehy M, Sangla S, Soulayrol S. Dose standardisation of botulinum toxin. J Neurol Neurosurg Psychiatry. 1995;59:102–3.
36. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. Toxins (Basel). 2016;8(3):65.
37. Odergren T, Hjaltason H, Kaakkola S, Solders G, Hanko J, Fehling C, et al. A double-blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. J Neurol Neurosurg Psychiatry. 1998;64:6–12.
38. Shin JH, Jeon C, Woo KI, Kim YD. Clinical comparability of Dysport and Botox in essential blepharospasm. J Korean Ophthalmol Soc. 2009;50:331–5.
39. Kollewe K, Mohammadi B, Köhler S, Pickenbrock H, Dengler R, Dressler D. Blepharospasm: long-term treatment with either Botox®, Xeomin® or Dysport®. J Neural Transm. 2015;122(3):427–31.
40. Sampaio C, Ferreira JJ, Simões F, Rosas MJ, Magalhães M, Correia AP, et al. Dysport: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox, assuming a ratio of 4:1. Mov Disord. 1997;12(6):1013–8.
41. Nussgens Z. Comparison of two botulinum toxin preparations in the treatment of essential blepharospasm. Arch Clin Exp Ophthalmol. 1997;235(4):197–9.
42. Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: a doubleblind, randomised, crossover study in cervical dystonia. J Neurol Neurosurg Psychiatry. 2002;72(4):459–62.
43. Bentivoglio AR, Ialongo T, Bove F, de Nigris F, Fasano A. Retrospective evaluation of the dose equivalence of Botox and Dysport in the management of blepharospasm and hemifacial spasm: a novel paradigm for a never ending story. Neurol Sci. 2012;33:261–7.
44. Ramirez-Castaneda J, Jankovic J, Comella C, Dashtipour K, Fernandez HH, Mari Z. Diffusion, spread, and migration of botulinum toxin. Mov Disord. 2013;28(13):1775–83.
45. Bhatia KP, Münchau A, Thompson PD, Houser M, Chauhan VS, Hutchinson M, et al. Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. J Neurol Neurosurg Psychiatry. 1999;67(1):90–3.
46. Baizabal-Carvallo JF, Jankovic J, Pappert E. Flu-like symptoms following botulinum toxin therapy. Toxicon. 2011;58(1):1–7.
47. Roche N, Schnitzler A, Genet FF, Durand MC, Bensmail D. Undesirable distant effects following botulinum toxin type A injection. Clin Neuropharmacol. 2008;31(5):272280.
48. Pickett A. Dysport: pharmacological properties and factors that influence toxin action. Toxicon. 2009;54(5):683–9.
49. Brodsky MA, Swope DM, Grimes D. Diffusion of botulinum toxins. Tremor Other Hyperkinet Mov (N Y). 2012. https://doi.org/10.7916/D88W3C1M
50. Aoki KR. Review of a proposed mechanism for the antinociceptive action of Abotulinum toxin type A. NeuroToxicology. 2005;26:785–93.
51. Hesse S, Jahnke MT, Luecke D, Mauritz KH. Short-term electrical stimulation enhances the effectiveness of Botulinum toxin in the treatment of lower limb spasticity in hemiparetic patients. Neurosci Lett. 1995;201(1):37–40.
52. Mancini F, Sandrini G, Moglia A, Nappi G, Pacchetti C. A randomised, double-blind, dose-ranging study to evaluate efficacy and safety of three doses of botulinum toxin type A (Botox) for the treatment of spastic foot. Neurol Sci. 2005;26(1):26–31.
53. Varghese-Kroll E, Elovic EP. Contralateral weakness and fatigue after high-dose botulinum toxin injection for management of post-stroke spasticity. Am J Phys Med Rehabil. 2009;88(6):495–9.
54. Thomas AM, Simpson DM. Contralateral weakness following botulinum toxin for poststroke spasticity. Muscle Nerve. 2012;46(3):443–8.
55. Bensmail D, Hanschmann A, Wissel J. Satisfaction with botulinum toxin treatment in post-stroke spasticity: results from two cross-sectional surveys (patients and physicians). J Med Econ. 2014;17(9):618–25.
56. Santamato A, Panza F, Ranieri M, Frisardi V, Micello MF, Filoni S, et al. Efficacy and safety of higher doses of botulinum toxin type A NT 201 free from complexing proteins in the upper and lower limb spasticity after stroke. J Neural Transm. 2013;120(3):469–76.
57. Intiso D, Simone V, Di Rienzo F, Iarossi A, Pazienza L, Santamato A, et al. High doses of a new botulinum toxin type A (NT-201) in adult patients with severe spasticity following brain injury and cerebral palsy. NeuroRehabilitation. 2014;34:515–22.
58. Wissel J, Bensmail D, Ferreira JJ, Molteni F, Satkunam L, Moraleda S, et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: the TOWER study. Neurology. 2017;88(14):1321–8.
59. Santamato A, Panza F, Intiso D, Baricich A, Picelli A, Smania N, et al. Long-term safety of repeated high doses of incobotulinumtoxinA injections for the treatment of upper and lower limb spasticity after stroke. J Neurol Sci. 2017;378:182–6.
60. Sanders DB. Clinical impact of single-fiber electromyography. Muscle Nerve Suppl. 2002;11:S15–20.
61. Garner CG, Straube A, Witt TN, Gasser T, Oertel WH. Time course of distant effects of local injections of botulinum toxin. Mov Disord. 1993;8(1):33–7.
62. Erdal J, Ostergaard L, Fuglsang-Frederiksen A, et al. Long-term botulinum toxin treatment of cervical dystonia-EMG changes in injected and noninjected muscles. Clin Neurophysiol. 1999;110(9):1650–4.
63. Vita G, Girlanda P, Puglisi RM, Marabello L, Messina C. Cardiovascular reflex testing and single-fiber electromyography in botulism. A longitudinal study. Arch Neurol. 1987;44(2):202–6.
64. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981;213:220–2.
65. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol. 1985;248(1 Pt 2):H151–3.
66. Kleiger RE, Bigger JT, Bosner MS, Chung MK, Cook JR, Rolnitzky LM, et al. Stability over time of variables measuring heart rate variability in normal subjects. Am J Cardiol. 1991;68(6):626–30.
67. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(11):2850–5.
68. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043–65.
69. Wichterle D, Simek J, La Rovere MT, Schwartz PJ, Camm AJ, Malik M. Prevalent low-frequency oscillation of heart rate: novel predictor of mortality after myocardial infarction. Circulation. 2004;110(10):1183–90.

70. Girlanda P, Vita G, Nicolosi C, Milone S, Messina C. Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system. J Neurol Neurosurg Psychiatry. 1992;55:844–5.
71. Borodic G, Johnson E, Goodnough M, Schantz E. Botulinum toxin therapy, immunologic resistance, and problems with available materials. Neurology. 1996;46:26–9.
72. Nebe A, Schelosky L, Wissel J, Ebersbach G, Scholz U, Poewe W. No effects on heart-rate variability and cardiovascular reflex tests after botulinum toxin treatment of cervical dystonia. Mov Disord. 1996;11:337–9.
73. Meichsner M, Reichel G. Effect of botulinum toxin A and B on vegetative cardiac innervation. Fortschr Neurol Psychiatr. 2005;73:409–14.
74. Tiple D, Strano S, Colosimo C, Fabbrini G, Calcagnini G, Prencipe M, et al. Autonomic cardiovascular function and baroreflex sensitivity in patients with cervical dystonia receiving treatment with botulinum toxin type A. J Neurol. 2008;255:843–7.
75. Invernizzi M, Carda S, Molinari C, Stagno D, Cisari C, Baricich A. Heart rate variability (HRV) modifications in adult hemiplegic patients after botulinum toxin type A (NT-201) injection. Eur J Phys Rehabil Med. 2015;51(4):353–9.
76. Baricich A, Grana E, Carda S, Santamato A, Molinari C, Cisari C, et al. Heart rate variability modifications induced by high doses of incobotulinumtoxinA and onabotulinumtoxinA in hemiplegic chronic stroke patients: a single blind randomized controlled, crossover pilot study. Toxicon. 2017;138:145–50.
77. Bakheit AM, Ward CD, McLellan DL. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases. J Neurol Neurosurg Psychiatry. 1997;62(2):198.
78. Henzel MK, Munin MC, Niyonkuru C, Skidmore ER, Weber DJ, Zafonte RD. Comparison of surface and ultrasound localization to identify forearm flexor muscles for botulinum toxin injections. PM R. 2010;2(7):642–6.
79. Mayer NH, Simpson DM. Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset muscle overactivity in patients with an upper motoneuron lesion. In: Mayer NH, Simpson DM, editors. Spasticity: etiology, evaluation, management and the role of botulinum toxin. 3rd ed. New York: We Move; 2005.
80. Ward AB, Wissel J, Borg J, Ertzgaard P, Herrmann C, Kulkarni J, et al. Functional goal achievement in post-stroke spasticity patients: the BOTOX® Economic Spasticity Trial (BEST). J Rehabil Med. 2014;46(6):504–13.
81. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. J Neurol Neurosurg Psychiatry. 2000;69(2):217–21.
82. Zorowitz RD, Wein TH, Dunning K, Deltombe T, Olver JH, Davé SJ, et al. A screening tool to identify spasticity in need of treatment. Am J Phys Med Rehabil. 2017;96(5):315–20.
83. Leach E, Cornwell P, Fleming J, Haines T. Patient centered goal-setting in a subacute rehabilitation setting. Disabil Rehabil. 2010;32(2):159–72.
84. Sunnerhagen KS, Francisco GE. Enhancing patient–provider communication for long-term post-stroke spasticity management. Acta Neurol Scand. 2013;128:305–10.
85. Baricich A, Picelli A, Molteni F, Guanziroli E, Santamato A. Post-stroke spasticity as a condition: a new perspective on patient evaluation. Funct Neurol. 2016;31(3):179–80.
86. Baricich A, Cosenza L, Sandrini G, Paolucci S, Morone G, Santamato A, et al. Development of a patient-centered questionnaire for post-stroke spasticity assessment: a reliability study. Funct Neurol. 2018;33(2):113–5.
87. Walsh LD, Moseley GL, Taylor JL, Gandevia SC. Proprioceptive signals contribute to the sense of body ownership. J Physiol. 2011;589(Pt 12):3009–21.
88. Turner-Stokes L, Ashford S, Jacinto J, Maisonobe P, Balcaitiene J, Fheodoroff K. Impact of integrated upper limb spasticity management including botulinum toxin A on patient-centred goal attainment: rationale and protocol for an international prospective, longitudinal cohort study (ULIS-III). BMJ Open. 2016;6(6):e011157.