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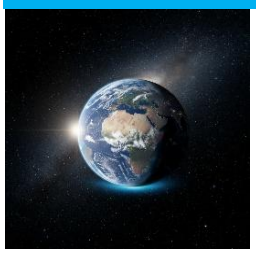

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

BAJKO, Julia, CISZEWSKI, Artur, BŁAŻEWICZ, Juliusz, BULLMANN, Agnieszka Irena, CHMIELEWSKI, Michał, PISKOR, Michał, KAPUSTA, Kinga, PAZIO, Klaudia, STRZALIŃSKA, Dominika and KOWALCZUK, Maciej. Botulinum Toxin Type A in the Treatment of Post-Stroke Spasticity - A Review of Current Evidence. Quality in Sport. 2026;54:70227. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70227

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 l.p. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 25.03.2026. Revised: 05.04.2026. Accepted: 10.04.2026. Published: 16.04.2026.

Botulinum Toxin Type A in the Treatment of Post-Stroke Spasticity – A Review of Current Evidence

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Abstract

Background: Post-stroke spasticity (PSS) affects up to 42% of stroke survivors and significantly impairs rehabilitation. Botulinum toxin type A (BoNT-A) is a first-line pharmacological treatment that reduces muscle overactivity by inhibiting acetylcholine release at the neuromuscular junction.

Aim: To summarize the current evidence on BoNT-A therapy for PSS, with emphasis on mechanisms of action, optimal administration timing, injection guidance, dosing, safety, and functional outcomes, to inform individualized neurorehabilitation.

Material and Methods: A literature search of PubMed was conducted to identify relevant studies on the efficacy and safety of BoNT-A in adult patients with PSS (2013–2026). Records were screened by title, abstract, and full text against predefined inclusion criteria.

Results: BoNT-A effectively reduces PSS with Grade A evidence, with the greatest benefit when administered early (3–12 weeks post-stroke). Imaging- or electrophysiology-guided injections improve precision. Therapeutic effects are temporary (approximately 12 weeks), requiring repeated administration. Adverse events are mild and uncommon, supporting a favorable safety profile.

Conclusions: BoNT-A is a safe and effective treatment for PSS, particularly when initiated early and guided by imaging or electrophysiological techniques. Its impact on functional recovery remains variable, highlighting the need for individualized treatment strategies integrated with comprehensive rehabilitation programs.

Keywords: botulinum toxin, post-stroke spasticity, spasticity treatment, neurorehabilitation, neuromuscular junction

Contents:

1. Introduction

Botulinum toxin (BoNT) is a dichain, potent neuromodulatory protein produced by the gram-positive anaerobic bacterium Clostridium botulinum and related species. Initial clinical deployment targeted strabismus, where its remarkable efficacy and tolerability established proof-of-concept for broader neuromuscular applications—subsequently extending to blepharospasm, cervical dystonia, and spasticity of varied etiology. Formal regulatory recognition followed with FDA approval in 1989, and the ensuing decades have generated an extensive evidence base delineating its mechanisms, optimal dosing strategies, and clinical outcomes, consolidating BoNT-A as a cornerstone of modern neurorehabilitation. Among the seven serologically distinct toxin variants (A through G), type A occupies a dominant clinical position by virtue of its superior potency, prolonged duration of biological activity, low immunogenic liability in contemporary formulations, and the extensive body of clinical evidence underpinning its efficacy and safety [1,2,3].

The toxin exerts its therapeutic action by cleaving the SNAP-25 protein, providing selective inhibition of acetylcholine exocytosis at the neuromuscular junction, thereby reducing pathological muscle overactivity [3]. This mechanism is particularly relevant to post-stroke spasticity, for which BoNT-A is internationally recognised as a primary treatment, strongly supported by randomised controlled trials and consensus guidelines. [16,22].

Post-stroke spasticity (PSS) represents one of the most consequential neurological complications following cerebrovascular injury, affecting over 40% of stroke survivors [6,17]. PSS is a positive feature of upper motor neuron syndrome (UMNS) and constitutes only one dimension of post-stroke motor impairment; it coexists with weakness and disordered motor control, collectively impairing activities of

daily living and rehabilitation engagement. Its pathophysiology is multifactorial, reflecting a complex interplay of neural and non-neural mechanisms—including biomechanical alterations and connective tissue remodelling—with the neural component typically manifesting earlier in the post-stroke course [7,21]. Clinically, PSS encompasses velocity-dependent hypertonia, involuntary spasms, clonus, spastic dystonia, and co-contraction, distributed across presentations ranging from focal (single-joint) to generalised (multi-limb, potentially involving the jaw and trunk) patterns [6].

Notwithstanding its well-established anti-spastic efficacy, several clinically significant questions remain incompletely resolved: the differential impact of early versus delayed intervention, the potential complementarity of therapies targeting neural versus non-neural pathophysiological components, and the extent to which tone reduction translates into gains in activity and participation [7]. This review provides a comprehensive, evidence-based synthesis of BoNT-A therapy for PSS, addressing mechanisms of action, clinical applications, dosing strategies, injection timing, immunological non-response, safety, and functional outcomes, with the goal of informing individualised neurorehabilitation practice.

2. Materials and Methods

A systematic literature search of the PubMed database was conducted to identify peer-reviewed studies pertaining to the efficacy and safety of BoNT-A in adult patients with PSS, encompassing publications from 2013 to 2026. Search terms included 'botulinum toxin', 'post-stroke spasticity', 'spasticity treatment', and 'spasticity treatment guidelines'. Records underwent sequential screening by title, abstract, and full text against predefined inclusion criteria: adult participants (≥18 years of age), BoNT-A as the primary intervention or active comparator, and reporting of clinically relevant outcomes related to spasticity severity or functional status. Disagreements in study selection were resolved through discussion and consensus among the reviewing authors.

3. Literature Review

3.1 Molecular Pharmacology and Mechanism of Action

BoNT-A exerts its biological effects via selective proteolytic cleavage of SNAP-25, a constituent of the SNARE complex integral to synaptic vesicle fusion. This action inhibits acetylcholine exocytosis at the neuromuscular junction, producing reversible chemodenervation and consequent attenuation of pathological muscle overactivity. The reversibility of this mechanism—attributable to axonal sprouting and reinnervation—underlies both the therapeutic benefit and the time-limited nature of its effect; clinical efficacy typically diminishes after approximately 12 weeks, requiring periodic re-administration to sustain therapeutic gains [12,16,20].

Beyond peripheral neuromuscular effects, emerging electrophysiological evidence suggests that BoNT-A may exert broader central neurophysiological influences. Several investigations have documented improvements in abnormal somatosensory evoked potentials following injection, implicating a role in attenuating maladaptive cortical plasticity. Possible modulation of short-interval intracortical inhibition (SICI) has also been described, though these findings remain preliminary and contested. The hypothesis that peripheral chemodenervation triggers secondary cortical reorganisation carries substantial implications for neurorehabilitation, particularly in the context of activity-dependent plasticity, yet the evidence base remains insufficient to draw definitive conclusions [12].

3.2 Optimal Timing of BoNT-A Administration

Considerable clinical and investigative evidence supports early intervention in PSS to preempt complications including pain, contracture formation, and functional deterioration, and to facilitate timely engagement with rehabilitation. Accumulating evidence suggests that earlier BoNT-A administration may further enhance outcomes through modulation of cortical excitability, thereby mitigating maladaptive neuroplasticity and impeding contracture development [4,7]. Clinical experience corroborates this position: injections targeting the flexor musculature of the fingers and wrists within 4 to 6 weeks of stroke onset are associated with the most consistent and pronounced clinical responses [4].

A secondary analysis of a comparative cohort study found that patients in an early-treatment group (median onset-to-treatment interval: 0.5 years) achieved significantly greater improvement in Goal Attainment Scaling (GAS) scores at 12 weeks compared with those in a late-treatment cohort (median interval: 5.4 years), despite equivalent reductions in muscle tone as quantified by the Modified Ashworth Scale [15,23,24]. This dissociation between tone reduction and patient-centred functional goal attainment suggests that early BoNT-A administration may more effectively harness neuroplastic processes and support rehabilitation-oriented outcomes, even when its anti-spastic effect is tonometrically comparable across temporal cohorts.

A systematic review of early-intervention trials, employing either electromyography or the Modified Ashworth Scale as primary outcome instruments, confirmed consistent spasticity reduction over 3 to 6 months; three studies documented sustained effects at 6 months, whereas two did not confirm efficacy at 5 to 6 months. Outcomes associated with early treatment (< 3 months post-stroke) appeared broadly comparable to those achieved in the chronic phase (> 6 months) [7]. Collectively, these findings suggest that while spasticity reduction is attainable irrespective of treatment timing, early intervention may uniquely promote neuroplasticity and reduce long-term spasticity-related morbidity. Further prospective investigation is required to delineate the optimal therapeutic window with greater precision [15].

3.3 Injection Guidance and Dosing

Meta-analytic evidence supports the use of imaging or electrophysiological guidance for BoNT-A injections in limb spasticity, with guided techniques demonstrating superior targeting accuracy and improved clinical outcomes relative to anatomical landmark-based approaches [4,6]. The two principal modalities—ultrasound (US) and electrical stimulation (ES)—differ in their equipment requirements and procedural characteristics; selection is informed by institutional resources, practitioner expertise, patient tolerance, and comfort considerations, all of which may influence adherence and therapeutic effect [4,6].

The evidence underpinning optimal dosing strategies remains limited. Few rigorous dose-ranging studies have been conducted to guide muscle-specific dose selection, and current clinical practice is largely governed by product labelling, clinician experience, toxin formulation availability, and expert consensus. This dependence on experiential rather than empirically derived dosing represents a significant evidence gap, and systematic dose-finding investigations are warranted to reduce heterogeneity in clinical outcomes and standardise therapeutic protocols [6].

3.4 Comprehensive Spasticity Management

BoNT-A is the preferred first-line pharmacological treatment for focal and multifocal PSS, commanding strong support from randomised controlled trial evidence and international clinical guidelines [22]. Its optimal deployment, however, occurs within a structured, tiered therapeutic framework that integrates pharmacological and non-pharmacological modalities across distinct therapeutic layers (Table 1).

Table 1. Multi-layer framework for comprehensive post-stroke spasticity management.

Layer	Category	Modalities
Layer 1	Anti-spastic pharmacotherapy	Botulinum toxin type A; oral antispastics (baclofen, tizanidine, dantrolene, benzodiazepines); intrathecal baclofen; surgical interventions
Layer 2	Adjuvant pharmacotherapy	Analgesics; anxiolytics; antidepressants
Layer 3	Non-pharmacological adjuvant therapy	Physiotherapy; prolonged passive stretching; high-frequency TENS; dry needling; whole-body vibration therapy (WBV)

Among oral antispastic agents, baclofen, tizanidine, dantrolene, and benzodiazepines demonstrate only marginal to moderate efficacy in PSS and are associated with clinically significant, dose-dependent adverse effects—principally sedation and cognitive impairment. The available randomised controlled trial evidence is constrained by small sample sizes and lack of functional outcome measures. Benzodiazepines are specifically discouraged in the management of PSS unless concurrent indications exist, such as seizure disorders, anxiety, or insomnia, due to their substantial adverse effect burden. Baclofen reduces spasticity and spasms in a dose-dependent manner, operating via GABAergic mechanisms; tizanidine attenuates spasticity and clonus through inhibition of facilitatory ceruleospinal pathways and suppression of excitatory neurotransmitter release from spinal interneurons; dantrolene, uniquely, acts peripherally on skeletal muscle by inhibiting calcium release from the sarcoplasmic reticulum during excitation-contraction coupling. Overall, systemic antispastic agents carry a significant risk of adverse effects and provide insufficient evidence for efficacy in PSS [6].

Intrathecal baclofen (ITB) is FDA-approved for the treatment of severe, generalised spasticity refractory to oral pharmacotherapy. The SISTERS trial—a multicentre, open-label randomised controlled trial—demonstrated that ITB produced statistically significant reductions in spastic hypertonia and lower-limb muscle tone compared with conventional medical management over 6 months in patients with Ashworth Scale scores ≥3 in at least two affected lower-extremity muscle groups [4,17]. In selected cases, and following exhaustive evaluation within a multiprofessional team, surgical interventions may be considered for chronic spastic movement disorders once all reversible therapeutic options have been exhausted [6].

Among non-pharmacological adjuncts, passive static and dynamic stretching are recommended as a complementary intervention but are not efficacious as standalone approaches. Prolonged stretching programmes produce superior outcomes compared with brief, repetitive sessions, though evidence for improvements in range of motion remains inconclusive [19]. Neuromuscular electrostimulation applied for 3 to 5 days following BoNT-A therapy may enhance treatment effects in targeted musculature [6]. Casting and adhesive taping can potentiate the effects of BoNT-A on limb spasticity, with serial casting producing superior outcomes in spasticity severity, range of motion, and gait [18].

High-frequency transcutaneous electrical nerve stimulation (TENS), when used adjunctively, attenuates lower-extremity spasticity in chronic stroke survivors, likely through modulation of stretch reflex excitability, enhanced presynaptic inhibition, and reciprocal inhibition. Radial extracorporeal shockwave therapy (rESWT) has demonstrated the capacity to reduce PSS, with effects persisting for up to 12 weeks, mediated through nitric oxide production, attenuation of acetylcholine availability at the neuromuscular junction, and reduced motor neuron excitability. Non-invasive brain stimulation techniques—specifically low-frequency repetitive transcranial magnetic stimulation (rTMS) targeting

the contralesional hemisphere and anodal transcranial direct current stimulation (tDCS) applied to the affected cortex—have demonstrated efficacy in reducing upper-extremity PSS. Whole-body vibration (WBV) is supported by moderate-quality evidence as an adjunctive modality, with the most pronounced effects observed in individuals under 60 years of age when applied at frequencies below 20 Hz for sessions of 10 minutes. Dry needling may provide short-term adjunctive benefit for lower-extremity PSS (assessed at 1-week follow-up), but this effect is not sustained at 4 weeks [4].

3.5 Primary and Secondary Non-Response

Treatment failure with BoNT-A may manifest as either primary non-response (PNR) or secondary non-response (SNR). PNR is defined as the absence of meaningful clinical improvement following initial and subsequent injection cycles, conventionally operationalised as <25% benefit despite two to three administrations with dose escalation. True pharmacological PNR is uncommon in clinical practice; apparent primary resistance is more often attributable to non-immunological, modifiable factors, including subtherapeutic dosing, incorrect muscle targeting, suboptimal injection technique, pre-existing contractures, or toxin degradation during handling and storage [9].

SNR occurs when patients who initially benefit from BoNT-A therapy subsequently experience attenuation or loss of clinical response following repeated treatment cycles. Although the development of neutralising antibodies (NAbs) constitutes a recognised immunological mechanism, it accounts for only approximately half of SNR cases; in the remainder, diminished response is more plausibly attributable to inadequate dosing, inappropriate muscle selection, disease progression, or fixed contractures refractory to chemodenervation. Discrepancies between patient and clinician perceptions of treatment benefit may also contribute to SNR classification [9].

BoNT-A preparations contain foreign proteins capable of eliciting antibody formation. Two antibody subtypes are recognised: neutralising antibodies, which directly inhibit toxin biological activity, and non-neutralising antibodies, which bind to the toxin or associated proteins without impairing clinical efficacy. Immunogenicity is potentiated by high cumulative or single doses, high injection frequency, and abbreviated inter-treatment intervals—particularly booster injections administered within 1 to 3 weeks of treatment. Accordingly, clinical guidelines universally recommend minimum inter-injection intervals of 12 weeks [9,11].

Meta-analytic estimates place NAb prevalence at approximately 0.5% for incobotulinumtoxinA, 1.5% for onabotulinumtoxinA, and 1.7% for abobotulinumtoxinA. In PSS specifically, NAb formation with onabotulinumtoxinA has been documented in 0.3 to 0.5% of patients, with no antibodies detected in small-scale trials of abobotulinumtoxinA or incobotulinumtoxinA [9,11]. Risk mitigation strategies include the use of the lowest effective dose, avoidance of unnecessary booster injections, and maintenance of adequate inter-treatment intervals. Genetic polymorphisms influencing immune response pathways and toxin-binding sites have been proposed as additional contributors to

immunogenicity, although mutations directly impairing BoNT binding or cleavage appear exceedingly rare. In confirmed immunological SNR, transition to lower-protein formulations—notably incobotulinumtoxinA—has been proposed as a rational management strategy [9,11].

3.6 Safety Profile and Tolerability

BoNT-A demonstrates an excellent safety and tolerability profile across therapeutic applications, substantiated by clinical trial data, retrospective analyses, and meta-analyses. Adverse events are generally infrequent, mild in severity, and self-limiting. The principles of optimal patient selection, adherence to injection site protocols, and appropriate dosing are the primary determinants of risk minimisation [13].

Injection-site reactions—including transient pain, erythema, and localised oedema—constitute the most commonly encountered adverse effects. Ecchymosis is reported with greater frequency than frank haematoma formation, both of which are typically self-resolving. Transient hypotonia in adjacent, non-target musculature may occur, particularly at elevated doses or with suboptimal technique, attributable to toxin diffusion beyond the intended site of action [14].

Long-term safety data are reassuring. In a retrospective analysis of extended onabotulinumtoxinA use for PSS, 74 of 88 patients who continued beyond eight treatment cycles maintained therapy without late discontinuation attributable to insufficient efficacy or adverse events; treatment-related discontinuation occurred in only two patients across the entire cohort. Transient worsening of gait parameters and sensory disturbance were documented as mild, self-resolving events in a subset of patients. Notably, lower initial BoNT-A doses were associated with higher treatment completion rates, suggesting that conservative initial dose selection may be appropriate for patients with milder spasticity [16].

Serious adverse events, though uncommon, require clinical awareness. These include dysphagia following cervical injections (rarely after limb injections), large haematomas requiring surgical evacuation, and—at very high doses or in patients with pre-existing neuromuscular conditions—generalised weakness or respiratory compromise. Rare hypersensitivity reactions, including urticaria and anaphylaxis, have been reported. Very rare complications documented in the literature include necrotising fasciitis, brachial plexopathy, Guillain-Barré syndrome, and aspiration pneumonia. BoNT-A is contraindicated in patients with myasthenia gravis, and chemodenervation injections should be withheld in this population. Patients receiving anticoagulation therapy require appropriate monitoring; concomitant use of non-steroidal anti-inflammatory drugs and other antiplatelet agents may increase injection-site haemorrhagic risk [4,13,14,18].

Patients who functionally exploit residual spasticity—for instance, to stabilise a paretic limb during object handling or weight-bearing—should receive pre-treatment counselling regarding the potential for temporary impairment of such compensatory strategies following tone reduction.

3.7 Functional Outcomes and the Central Role of Rehabilitation Integration

The ASPIRE (Adult Spasticity International Registry) prospective registry reported that 85% of patients and 93% of treating clinicians expressed satisfaction or high satisfaction that BoNT-A injections provided meaningful spasticity relief; 91% of patients and 98% of physicians indicated intention to continue therapy [18]. Notwithstanding consistent attenuation of pathological muscle tone, translation of this benefit into measurable gains in activities of daily living and broader participation remains inconsistent—a discrepancy of fundamental clinical significance.

This finding reinforces that BoNT-A alone is insufficient to restore motor function. Its therapeutic value is most fully realised when embedded within structured, goal-oriented rehabilitation programmes tailored to individual patient needs. Early administration, particularly when combined with targeted neurorehabilitation, appears to augment motor recovery and enhance functional outcomes [4,15]. Adjunctive therapies—including extracorporeal shockwave therapy, which has demonstrated superiority to electrical stimulation for combined spasticity and pain outcomes post-injection, and casting or taping which potentiate BoNT-A effects on limb spasticity—further expand the therapeutic toolkit available to clinicians [18].

Evidence also suggests that BoNT-A may confer broader neurophysiological benefits beyond peripheral chemodenervation. Several studies have documented improvements in abnormal somatosensory evoked potentials (SEPs) following injection, raising the possibility of indirect modulation of cortical somatosensory processing. However, the literature remains insufficiently robust to draw definitive conclusions regarding central effects, and unresolved controversies—including BoNT-A-associated changes in short-interval intracortical inhibition (SICI)—warrant prospective investigation [12].

4. Conclusions

Botulinum toxin type A is unequivocally established as the first-line pharmacological intervention for post-stroke spasticity, supported by Grade A evidence for tone reduction and endorsed by international consensus guidelines. Its optimal therapeutic value is realised through early administration—ideally within 3 to 12 weeks of stroke onset—under imaging or electrophysiological guidance, and in conjunction with individualised, goal-oriented neurorehabilitation programmes. Therapeutic effects are transient (approximately 12 weeks), necessitating periodic re-administration, yet the long-term safety record is favourable across extended treatment courses.

The persistent disparity between reliable tone reduction and variable functional recovery underscores the insufficiency of chemodenervation as a standalone strategy; BoNT-A must be contextualised within a comprehensive, multidisciplinary treatment framework responsive to patient-centred goals. Significant

evidence gaps remain, particularly with regard to muscle-specific dosing algorithms, the precise delineation of optimal intervention windows, and the neuroplasticity implications of repeated chemodenervation. Future research priorities should include rigorous dose-ranging studies, adequately powered randomised controlled trials incorporating validated functional endpoints, and longitudinal investigation of central neurophysiological effects, to optimise and standardise the management of this prevalent and disabling condition.

Disclosure

Author's contribution

Conceptualization: [JBa], [AC]

Methodology: [JB], [MC], [KK]

Check: [KP], [MP], [MK]

Investigation: [JBa], [DS], [AB]

Data curation: [KK], [MP], [JB], [MC]

Writing - rough preparation: [DS], [MK], [KP]

Writing - review and editing: [AB], [MK]

Visualization: [JBa], [AC], [JB]

Project administration: [AC], [MP], [MC]

Funding Statement

The article did not receive any funding.

Institutional Review Board Statement

Not Applicable.

Informed Consent Statement

Not Applicable.

Data Availability

Statement Not Applicable.

Acknowledgements

This research has not received any administrative or technical support.

Conflict Of Interest

The authors declare no conflict of interest.

All authors have read and agreed with the published version of the manuscript.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.

In preparing this work, authors used ChatGPT (OpenAI) and Claude to assist in drafting and language editing of the text and streamline the organization of some sections. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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