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Editorial

The Botulinum Toxin and Spasticity: Exploring New Horizons

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Special Issue Introduction

This Special Issue aims to provide an updated overview of the current state and future perspectives of botulinum toxin treatment for spasticity.

Spasticity is a disorder that typically develops as a result of lesions in the central sensorimotor network, leading to upper motor neuron syndrome. It has a negative impact on motor performance, independence, and quality of life: botulinum toxin type A is described as one of the principal therapeutic options for focal spasticity. Its use has gradually evolved from a treatment primarily aimed at reducing hypertonia toward more complex approaches incorporating functional goals and improved quality of life [1].

"The Botulinum Toxin and Spasticity: Exploring New Horizons" is the title of this Special Issue of *Toxins*, because botulinum toxin, for many years, has been the gold standard therapy for spasticity, and the Issue focuses on new horizons in terms of different conditions or effects caused by using this effective drug.

Bibliometric analysis is an increasingly utilized approach in medical research for quantifying and characterizing scientific outputs. It offers a systematic method to evaluate the impact, trends, and network of research on a given topic. Using tools such as Cite Space, bibliometric studies can visualize the development and trajectory of a research area, including by identifying key papers, authors, and institutions that have contributed significantly to the field.

Facciorusso et al. have used this method to map the evolution of BoNT-A research in the context of spasticity by elucidating key trends, major contributors, and emerging themes (Contribution 1). This analysis aimed to provide a broad view of the global research landscape on this topic, highlighting the central role of BoNT-A in managing spasticity and guiding future research directions.

The bibliometric analysis conducted on research examining the application of BoNT-A to spasticity from 2000 to 2022 reveals a compelling picture of scientific advancement and collaboration. The annual trend of publications displays a significant growth trajectory, with a noteworthy increase in research output starting in 2007 and peaking in 2020, which may reflect the heightened recognition of BoNT-A's potential in spasticity treatment following pivotal studies.

The contribution discusses many aspects of BoNT-A treatment, including dose, injection techniques, additional treatments to BoNT-A, products, and indication, describing the authors and the journals that are leaders for each specific topic.

The most highly represented countries were the United States, the United Kingdom, and Italy. Assistance Publique–Hôpitaux de Paris was the institution contributing the largest

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number of publications, while *Toxins* was the journal publishing the greatest number of relevant articles.

The authors highlight a gradual shift toward more individualized spasticity management. Important future directions include early intervention after stroke, combining botulinum toxin with multimodal rehabilitation strategies, and improving diagnostic and monitoring tools, including advanced imaging techniques and wearable technologies.

The analysis also highlights the growing importance of guided injection techniques to improve treatment precision [2]. This tool can also be used for patients with dysphagia due to cricopharyngeus muscle spasticity that have been treated with BoNT-A injection.

Another study published in this Special Issue was performed on cadaveric models: the aim was to determine whether an ultrasound-guided injection delivered through accessible lateral regions of the muscle can also reach the posterolateral areas, which contain particularly high densities of nerve endings (Contribution 2). The investigation showed that macroscopically identifiable nerve endings were concentrated predominantly in the posterolateral region of the cricopharyngeus muscle.

The study demonstrates that, in most trials, an ultrasound-guided approach can reach the cricopharyngeal regions with the highest density of nerve endings, but it did not assess actual upper exophageal sphincter relaxation, improvement in swallowing, safety of oral feeding, or respiratory outcomes, or the clinical efficacy of botulinum toxin for cricopharyngeal dysphagia.

Moreover, ultrasound guidance may make it possible to reach the most densely innervated regions of the cricopharyngeus, but anatomical feasibility is not equivalent to demonstrated clinical efficacy.

To date, for spasticity treatment, a correct patient's evaluation is needed: nerve block represents a useful tool to distinguish spasticity from tendon retraction and to consider the specific muscles to be injected.

In their study, Filippetti et al. have considered the possibility of using diagnostic nerve block before the first botulinum toxin treatment in order to choose which muscles to inject and the initial doses administered (Contribution 3).

Data from 99 adults with upper and/or lower-limb spasticity who received their first BoNT-A treatment were analyzed retrospectively. Patients were assessed both clinically and using a diagnostic nerve block, and using clinical examination alone.

The initial toxin doses administered to individual muscles, total doses, and number of injected muscles were compared.

The authors reported that the mean dose administered to the flexor digitorum profundus and soleus muscles was higher in the group also assessed using diagnostic nerve block.

This result does not mean that the outcome measures for these patients are better then those for patients submitted to evaluation alone or that diagnostic nerve block systematically leads to higher toxin doses: differences were observed only in specific muscles and spastic patterns.

These findings suggest that diagnostic nerve block may help to individualize the first BoNT-A injection session, mainly by influencing muscle selection and dose distribution, but their benefits for clinical outcomes have yet to be demonstrated; the authors suggest that incorporating diagnostic nerve block into the initial assessment may promote a more individualized distribution of BoNT-A.

What is sure in the management of BoNT-A treatment, is the role of adjunctive therapy in increasing the effect of BoNT-A [3].

Stretching muscles has been showed to be a cheap, easy option out of the several kinds of adjunctive treatments [4].

In this Special Issue Hwang et al. evaluated whether a structured stretching exercise program combined with botulinum toxin injections can improve outcomes in the treatment of post-stroke upper-limb spasticity (Contribution 4).

The authors compared the effect on MAS reduction of two different protocols of stretching muscle applied on 43 subjects with a history of stroke and upper-limb spasticity of at least grade 2 at MAS treated with BoNT-A injection: one group (experimental group) was submitted to a structured hospital-based stretching program for 20 min sessions, five days per week, for six months.

The control group included patients assigned to independently perform stretching exercises at home. Changes in spasticity were assessed using the MAS at the elbow, wrist, and fingers after three months and at six months.

The structured stretching group experienced greater improvements than the group performing stretching independently at home.

This study demonstrates that, under the experimental conditions used, a structured hospital-based program produced better outcomes than independently performed home exercises combined with the same pharmacological treatment.

Another interesting tool for adjunctive treatment is robotic hand orthosis.

Ranzani et al.'s study explores a potential technological approach to supporting rehabilitation exercises after BoNT-A injections using RELab tenoexo, a robotic hand orthosis connected to a smartphone application and designed to assist users in performing exercises (Contribution 5).

The authors therefore consider whether the temporary reduction in hypertonia after injections could facilitate repetitive rehabilitation training using robotic devices.

The protocol comprised two sessions: in the first session, participants received BoNT-A injections and were introduced to the device. In the second session, approximately four to six weeks later, an unsupervised rehabilitation session was simulated using the robotic orthosis. Functional (Box and Block Test, Action Research Arm Test), and muscle tone (Modified Ashworth Scale) assessments were conducted to assess impairment, along with usability evaluations. The authors hypothesized that robotic assistance may allow patients with residual weakness and spasticity to perform exercises that would be difficult without support.

However, patients with central nervous system lesions may also have pre-existing muscle weakness alongside spasticity, which contributes to motor and functional difficulties.

A systematic review by Gill et al. considered whether BoNT-A treatment affects muscle strength and its effect on injected muscles, antagonist muscles, and overall limb strength, taking into account different intervals after treatment (Contribution 6).

In 74% of the results analyzed, no change in agonist muscle strength was observed after injection.

The findings do not allow definitive conclusions about whether, to what extent, or for how long BoNT-A alters muscle strength.

Reduction in spasticity does not mean changes in muscle strength: in fact, muscle tone reduction may facilitate movement, but this does not necessarily imply an increased capacity to generate force. Similarly, the pharmacological effect on the injected muscle cannot automatically be interpreted as a functional deterioration of the entire limb.

The authors emphasize the need to distinguish agonist from antagonist muscles accurately and to use sufficiently sensitive measures to detect genuine changes.

The authors conclude that the effect of BoNT-A on muscle strength remains uncertain, particularly over the long term.

The possibility to observe adverse effects of BoNT-A therapy has been shown by Keles et al. (Contribution 7): the authors note that, in addition to reducing active muscle force,

BoNT-A may alter mechanical muscle properties, including increased passive force and increased extracellular matrix stiffness.

These phenomena may be associated with changes in muscle structure, connective tissue, and the fascial component.

An experimental preclinical animal study examined C3 transferase, a substance capable of interfering with certain cellular mechanisms involved in the contractility of myofibroblasts and fascial tissue. The authors hypothesized that combining BoNT-A with C3 transferase may preserve the reduction in active force while preventing some undesirable changes in muscle mechanics.

After several experiments in male Wistar rats, they interpret their findings as indicating that combining BoNT-A with C3 transferase may mitigate the adverse effects of BoNT-A on muscular mechanical properties in an animal model. The authors consider the combination of BoNT-A and C3 transferase as a potential way to reduce active force without significantly altering passive forces compared with controls.

BoNT-A is the gold standard treatment for focal spasticity, even if different approaches are employed in several countries and by several practitioners regarding its frequency of use, dilution, timing of treatment, therapeutic goals, and instrumental or clinical evaluation.

One obstacle to standardizing these issues is the difficulty of analyzing the large amounts of clinical information in electronic health records, particularly when information is recorded as narrative text rather than in structured fields. The paper published in this Special Issue by Antón et al. aimed to describe the demographic and clinical characteristics, as well as the treatment patterns, of patients with post-stroke spasticity in a real-world setting in Spain using natural language processing and machine learning techniques focusing on the use of BoNT-A to identify potential areas for improvement and to optimize this kind of treatment (Contribution 8). Electronic health records from patients with spasticity evaluated in five hospitals were reviewed retrospectively: information was extracted using EHRead® technology, which combines natural language processing and machine learning. Data analyzed included demographic characteristics, stroke features, comorbidities, use of BoNT-A, treatment timing, and associated therapeutic interventions. The results of this study showed that only 25.5% of patients with post-stroke spasticity received BoNT-A treatment at least once. The median interval between stroke and the first documentation of spasticity was 205 days, whereas the median interval between stroke and the first BoNT-A administration was 364 days. Among non-pharmacological interventions, rehabilitation was the most frequently documented treatment, reported in 95.5% of cases. The primary goal of BoNT-A treatment was pain control. Among the study cohort, rehabilitation was the most common non-pharmacological treatment.

Although the eight publications in this Special Issue differ in their objectives and experimental designs, several recurring themes emerge: the possibility of safely using BoNT-A for different clinical conditions, but the need to be sure of the correct injection site, to provide an adjunctive treatment to increase its pharmacological effect and to consider clinical information about the patients with spasticity after stroke to identify a correct treatment at the correct timing.

Conflicts of Interest: The author declares no conflicts of interest.

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