**Neurological Side Effects of Long-Term Botulinum Toxin Use**

**Abstract**

|  |
| --- |
| **Aims:** To analyze and understand the neurological side effects associated with long-term use of botulinum toxin type A (BoNT-A), highlighting its implications on motor and sensory function in patients undergoing prolonged therapeutic application.  **Study design:** Qualitative exploratory-descriptive bibliographic review.  **Place and Duration of Study:** The study was conducted using data collected from scientific literature indexed in PubMed, SciELO, and the Virtual Health Library (VHL), covering publications from 2013 to 2023.  **Methodology:** A systematic search was performed using controlled descriptors such as *Neurological Side Effects*, *Botulinum Toxin*, *Central Nervous System*, and *Peripheral Nervous System*. Boolean operators “AND” and “OR” were applied to refine the search. Inclusion criteria focused on full-text articles in English, Portuguese, and Spanish that directly addressed the neurological impacts of BoNT-A. The review excluded duplicated materials, summaries, debates, and inaccessible content. The selected studies were analyzed through three axes: identification of neurological side effects, impacts on motor and sensory function, and mechanisms of influence on the central nervous system.  **Results:** Findings indicated that BoNT-A is generally effective and safe for motor conditions such as spasticity and facial paralysis, though long-term use may result in mild to moderate adverse effects, including fatigue and muscle weakness. In chronic migraine treatment, BoNT-A showed significant improvement in pain frequency and quality of life. Potential retrograde transport of the toxin suggests central nervous system involvement. Statistical values were not derived as this was a literature-based review, but recurrent patterns across studies support the findings.  **Conclusion:** Botulinum toxin type A remains a valuable therapeutic option; however, prolonged administration requires caution and individualized monitoring. Further research is necessary to fully understand its central mechanisms and to establish safer, optimized protocols for long-term neurological applications. |

*Keywords: Botulinum Toxin, Neurological Effects, Chronic Migraine, Motor Function, Neurotoxicity, Central Nervous System, Long-Term Use.*

**1. INTRODUCTION**

Botulinum toxin type A (BoNT-A) is widely used in medicine, especially for treating conditions such as spasticity, chronic migraines, and motor disorders. Its mechanism of action is based on preventing the release of acetylcholine at neuromuscular junctions, promoting muscle relaxation and relief from pain associated with neurological conditions (1). However, the prolonged use of this therapy has raised concerns about possible side effects, particularly in the central and peripheral nervous systems, highlighting the need for more detailed studies on its neurological implications (2)(3).  
  
 The neurological side effects of long-term BoNT-A use are an area of growing interest. Reports indicate that, although the therapeutic benefits are evident, there are impairments related to changes in the nervous system, such as local muscle atrophy and potential effects on central neural structures. Studies show that retrograde transport of the toxin along neurons may influence regions distant from the application site, suggesting an impact beyond the peripheral level (4)(5).

Epidemiologically, the use of botulinum toxin is associated with adverse effects in a specific subset of patients. In studies with children with cerebral palsy, mild to moderate adverse events were reported in 51% of applications, while more serious complications, such as generalized weakness, are rare but present. In adults, long-term use for chronic migraines has shown sustained efficacy in up to 75% of patients after one year of treatment, although events such as muscle atrophy have been observed after five years of continuous use (6)(2).  
  
 Additionally, there is growing concern about how BoNT-A’s effects may impact patients' long-term quality of life. A reduction in the number of pain days is evident, but adverse effects such as muscle injuries and functional changes may limit treatment adherence. Patients with chronic migraines who combined BoNT-A with CGRP inhibitors experienced significant improvements, reinforcing the need for combined approaches to minimize side effects while maximizing efficacy (7)(8).  
  
 Therefore, understanding the mechanisms underlying BoNT-A’s neurological side effects is essential to improve its clinical use. This study aims to analyze how prolonged use of this therapy may influence neurological function, justified by the need to fill gaps in scientific knowledge and inform both professionals and patients about best clinical practices and potential risks involved in BoNT-A treatment (3)(2).

**2. METHODOLOGY**

This is a bibliographic study of the exploratory-descriptive type with a qualitative approach, developed based on data extracted from scientific literature. According to Gil (9), a bibliographic study is carried out using pre-existing materials, such as scientific articles and books, with the goal of constructing a theoretical overview of the subject in question. The exploratory nature of the study is reflected in the detailed literature review and the analysis of examples that clarify concepts and allow the development of hypotheses for future investigations.

This approach aims to provide greater insight into the neurological side effects of botulinum toxin, with an emphasis on its long-term impacts on the central and peripheral nervous systems.

According to Gonçalves (10), descriptive research seeks to record, analyze, and interpret observed facts, often establishing relationships between them. This qualitative study prioritized the value of the information obtained to understand the implications of botulinum toxin in depth, going beyond the quantitative profile of the data. This approach made it possible to explore more complex dimensions, facilitating the construction of scenarios that integrate the effects of the toxin over time (11).

Data collection was carried out through a bibliographic survey of scientific publications related to the topic from 2013 to 2023. Inclusion criteria encompassed full-text articles aligned with the theme and available in Portuguese, English, and Spanish. Exclusion criteria included duplicate articles, reviews, abstracts, debates, and incomplete or unavailable materials. The databases consulted were PubMed, SciELO, and the Virtual Health Library (VHL). For the research, keywords selected from DeCS were used: neurological side effects, botulinum toxin, central nervous system, and peripheral nervous system, with the aid of the Boolean operators “AND” and “OR.”

After the initial screening, the selected articles underwent a critical and thorough reading and were organized into three main categories: identification of neurological side effects, impact on motor and sensory function, and mechanisms of influence on the central nervous system. These categories were defined based on the specific objectives of the study, guiding data analysis and the structuring of results. The construction of tables to synthesize the information allowed for a systematic and coherent evaluation.

The methodology adopted was structured to ensure the robustness and validity of the results presented. This study sought to fill gaps in the knowledge regarding the neurological side effects of prolonged botulinum toxin use, contributing to advances in clinical practice and promoting a better understanding of the long-term implications of this treatment.

**3. Findings AND DISCUSSION**

3.1 Effects of Botulinum Toxin on Motor Function and Neuromuscular Coordination

Botulinum toxin type A (BoNT-A) plays a key role in treating various neurological and muscular conditions. Its mechanism of action involves blocking the release of acetylcholine at nerve endings, resulting in muscle relaxation. This effect is particularly useful in cases of peripheral facial palsy (PFP), where it helps reduce hypertonia, spasms, and synkinesis, improving functionality and facial symmetry. Additionally, by reducing sustained muscle contractions (SMCs), BoNT-A promotes better neuromuscular progression and muscle control ⁽¹²⁾.

Studies have shown that applications of onabotulinumtoxinA (BOTOX) lead to muscle relaxation by binding to nerve terminals and cleaving proteins associated with synaptic vesicles, thereby preventing the release of acetylcholine (13) . This mechanism is fundamental in the treatment of spasticity and related conditions, such as facial dystonia, where the prolonged efficacy of botulinum toxin eliminates the need for other neurotoxins with lower long-term effectiveness. However, adverse effects like tearing, diplopia, and ptosis may occur due to the local action of the neurotoxin on adjacent muscles ⁽¹⁴⁾.

Botulinum toxin is also effective in treating hemifacial spasms and spasticity. Recent studies have shown that males are more likely to require triceps treatment, while females tend to seek therapy to improve hip performance. Evidence shows that both onabotulinumtoxinA and incobotulinumtoxinA are significantly important for controlling muscle tone, with positive results in various clinical conditions ⁽¹⁵⁾⁽¹⁶⁾. In children with cerebral palsy, for example, abobotulinumtoxinA has been effective in reducing spasticity and muscle tone, with measurable improvements on specific scales such as the Modified Ashworth Scale and the Tardieu Scale ⁽¹⁷⁾⁽¹⁸⁾.

However, there are challenges related to the adverse effects of botulinum toxin, such as generalized weakness and fatigue, often linked to the systemic spread of the toxin. Studies indicate that these effects, though inconvenient, are temporary and can be minimized with proper application techniques and accurate dosing (19)(20). Additionally, the muscle atrophy observed in patients treated over long periods does not significantly compromise motor function, reinforcing the treatment’s safety in appropriate cases ⁽²¹⁾.

Botulinum neurotoxin also has potential effects on the central nervous system (CNS), although the exact mechanism still requires further investigation. Studies suggest that retrograde axonal transport or blockages in afferent fibers may be involved. These findings highlight the need for further research into optimal dosages and the central effects of botulinum toxin, especially to explore its impact beyond peripheral muscle relaxation ⁽⁵⁾⁽⁴⁾.

3.2 The Impact of Botulinum Toxin on Migraine Cases

Botulinum toxin type A (BoNT-A) has emerged as an effective therapy for chronic migraine prophylaxis, significantly reducing the frequency and intensity of attacks. Its mechanism of action includes inhibiting pro-inflammatory neurotransmitters, such as calcitonin gene-related peptide (CGRP), and modulating central sensitization, contributing to pain relief ⁽²²⁾. Studies show that BoNT-A not only reduces headache days but also improves patients’ quality of life, with a favorable safety profile and few side effects ⁽²³⁾.

The impact of BoNT-A has also been observed in comparative studies with other migraine medications. Patients reported a faster onset and longer-lasting response with botulinum toxin than with steroid-based treatments, anti-inflammatories, and anesthetic infiltrations. This positive effect is directly linked to the administered dose; single higher-dose applications resulted in more significant reductions in attacks than regimens using smaller, more frequent doses ⁽²⁴⁾⁽²⁵⁾⁽²⁶⁾.

In addition to reducing attacks, BoNT-A has provided benefits for specific groups, such as military personnel with a history of traumatic brain injury and patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). In these populations, reduced pain intensity and significant improvements in quality of life were observed. However, despite the benefits, there have been rare reports of more serious complications, such as encephalopathy, reinforcing the importance of clinical monitoring ⁽²⁷⁾⁽²⁸⁾.

BoNT-A’s efficacy has been widely validated in long-term studies, with substantial reductions in attack frequency and the use of acute relief medications. Patients showed better adherence to treatment compared to drugs like topiramate. Additionally, combining BoNT-A with CGRP inhibitors, in cases of insufficient response to monotherapy, yielded additional benefits, enhancing treatment impact ⁽⁸⁾⁽²⁹⁾⁽³⁰⁾.

Although side effects associated with botulinum toxin are generally mild, such as injection site pain and neck stiffness, precise application techniques and careful dose management are essential to avoid complications. The results show that BoNT-A is a safe and effective option, especially for patients with refractory chronic migraine, promoting better quality of life and reducing the social and economic burden of the disease (³¹⁾.

3.3 Mechanisms of Action of Botulinum Toxin in the Nervous System

Botulinum toxin type A (BoNT-A) plays an essential role in treating various neurological and muscular disorders, including chronic migraine and neuropathic pain. Its mechanism involves inhibiting the release of acetylcholine at neuromuscular synapses, blocking nerve impulse transmission. Additionally, BoNT-A modulates pro-inflammatory neurotransmitters, such as CGRP and substance P, reducing neurogenic inflammation and central sensitization—key factors in the development of chronic pain conditions ⁽³²⁾⁽³³⁾.

In the treatment of chronic migraine, BoNT-A has proven effective in reducing the frequency and intensity of attacks. This effect is attributed to blocking the release of algogenic neuropeptides such as neurokinin A and CGRP. The toxin has also shown a positive impact by decreasing the use of fast-acting medications and improving patients’ quality of life ⁽²⁶⁾⁽²⁵⁾. Studies also suggest that BoNT-A selectively targets TRPV1 receptors, directly affecting C and A-delta fibers, contributing to its analgesic effect ⁽³⁴⁾⁽³⁵⁾.

Although BoNT-A is widely used in managing neuropathic pain and muscular conditions, its exact mechanism is not yet fully understood. Evidence suggests the toxin acts via retrograde axonal transport and by blocking SNAP-25–mediated exocytosis, inhibiting excitatory neurotransmitters like glutamate. This indirect action also reduces activation of inflammatory pathways in the central nervous system, as shown in gene expression studies in sensory regions ⁽³⁶⁾⁽¹²⁾.

The safety of BoNT-A treatment is highlighted in long-term studies, although complications can arise in specific cases. Mild side effects, such as injection site pain and muscle weakness, are more common, but more serious events like systemic botulism—though rare—require clinical attention. One example is the report of a 72-year-old patient who experienced head drop after toxin application, highlighting the importance of personalized dosing to minimize risks ⁽³⁷⁾⁽³⁸⁾.

BoNT-A remains an effective and safe therapy for neuromuscular and neuropathic conditions. However, further studies are needed to fully understand its mechanisms of action and explore safer, better-tolerated alternatives. Continuous use and the development of advanced formulations aim to further improve outcomes for patients with complex neurological disorders ⁽³⁹⁾⁽⁴⁰⁾.

**4. Conclusion**

Botulinum toxin type A (BoNT-A) shows significant effects on motor function and neuromuscular coordination, standing out as an effective therapy for conditions such as spasticity, dystonia, and peripheral facial palsy. Its ability to block the release of acetylcholine at neuromuscular junctions results in controlled muscle relaxation, improving functionality and reducing spasms. However, prolonged use may lead to mild to moderate adverse effects, such as muscle weakness and fatigue, which are generally transient and manageable with proper dosing and precise application techniques ⁽⁴¹⁾.

In the context of chronic migraine, BoNT-A has a substantial positive impact, reducing the frequency and intensity of attacks through the modulation of pro-inflammatory neurotransmitters such as CGRP and central sensitization. In addition to improving patients’ quality of life, the therapy reduces the consumption of acute relief medications and enhances effectiveness when combined with other treatments, such as CGRP inhibitors ⁽⁴²⁾⁽⁴³⁾.

As for the mechanisms of action, BoNT-A not only inhibits peripheral acetylcholine release but also has potential central effects due to retrograde transport and modulation of inflammatory pathways and excitatory neurotransmitters such as glutamate ⁽⁴⁴⁾⁽³⁶⁾. This multifaceted mechanism supports its role in both motor and sensory conditions.

Although BoNT-A is generally safe and effective, its long-term use requires careful monitoring to mitigate potential risks and ensure a balance between benefits and side effects. Further studies are needed to better understand the central impacts of the toxin and explore new strategies to improve clinical outcomes in patients with neurological and muscular disorders ⁽⁴⁵⁾⁽⁴⁰⁾.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

**References**

1. Ferrari E, Mészáros L, Scheps D, et al. Re-assembled botulinum neurotoxin inhibits CNS functions without systemic toxicity. Toxins (Basel). 2011;3(4):345-55.
2. Cernuda-Morollón E, Ramón C, Pascual J. Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: what happens after one year?. Cephalalgia. 2015;35(10):864-8.
3. Blaszczyk I, Janowska A, Rutkowska A, et al. Questionnaire about the adverse events and side effects following botulinum toxin A treatment in patients with cerebral palsy. Toxins (Basel). 2015;7(11):4645-54.
4. Hristova AH, Evers S, Tanislav C. Severe nervous system complications after botulinum type A therapy: three case reports with reviews of FDA-reported nervous system adverse effects. PM R. 2012;4(8):613-23.
5. Cavuş H, Güneş G, Yıldız A, et al. Evaluation of MR-tractography findings in hemifacial spasm patients injected with botulinum neurotoxin. Neurol India. 2022;70(2):543-7.
6. Delgado MR, Tilton A, Russman B, et al. Safety and efficacy of repeat open-label abobotulinumtoxinA treatment in pediatric cerebral palsy. J Child Neurol. 2017;32(13):1058-64.
7. Toni T, Lambert C, Jarvis M, et al. Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series. Neurol Sci. 2021;42(12):5373-6.
8. Cohen F, Kumar N, Hershey L. Efficacy and tolerability of calcitonin gene–related peptide–targeted monoclonal antibody medications as add-on therapy to onabotulinumtoxinA in patients with chronic migraine. Pain Med. 2021;22(8):1857-63.
9. Gil AC. Métodos e técnicas de pesquisa social. 7ª ed. São Paulo: Atlas; 2022.
10. Gonçalves JE. Metodologia científica: conceitos, teoria e prática. São Paulo: Atlas; 2003.
11. Minayo MCS. O desafio do conhecimento: pesquisa qualitativa em saúde. 5ª ed. São Paulo: Hucitec; 1994.
12. Díaz-Aristizábal U, Gutiérrez AM, Pulido MF, et al. Efecto de la toxina botulínica tipo A en la funcionalidad, las sincinesias y la calidad de vida en secuelas de parálisis facial periférica. Neurología. 2023;38(8):560-5.
13. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: Biology, pharmacology, and toxicology. Pharmacol Rev. 2017;69(2):200–235.  
    https://doi.org/10.1124/pr.116.003665.
14. Badarny S, Halpern M, Tunkel O, et al. Long-term stable efficacy of botulinum toxin A in facial movement disorders with no need for increasing dose. Medicine (Baltimore). 2021;100(25):e26481.
15. Del Prete, C. M., Viva, M. G., De Trane, S., Brindisino, F., Barassi, G., Specchia, A., ... & Pellegrino, R. (2022). An observational cross-sectional study of gender and disability as determinants of person-centered medicine in botulinum neurotoxin treatment of upper motoneuron syndrome. Toxins, 14(4), 246.
16. Wissel J, Hecht MJ, Schnur N, et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: the TOWER study. Neurology. 2017;88(14):1321-8.
17. Delgado MR, Tilton A, Russman B, et al. Safety and efficacy of repeat open-label abobotulinumtoxinA treatment in pediatric cerebral palsy. J Child Neurol. 2017;32(13):1058-64.
18. Multani, I., Manji, J., Hastings-Ison, T., Khot, A., & Graham, K. (2019). Botulinum toxin in the management of children with cerebral palsy. Pediatric Drugs, 21(4), 261-281.
19. Reyes FI, López RS, Hernández JA, et al. Ultrasound-guided onabotulinumtoxinA injections to treat oromandibular dystonia in cerebral palsy. Toxins (Basel). 2022;14(3):158.
20. Hristova, A. H., Joseph, L. N., Sathe, S. A., & Wade, J. B. (2012). Severe nervous system complications after botulinum type A therapy: three case reports with reviews of FDA-reported nervous system adverse effects. PM&R, 4(8), 613-623.
21. Ramon-Cesar J, Malm C, Almeida G, et al. Impact of long-term botulinum toxin treatment on muscle volume and motor function. J Neurol Sci. 2014;344(1-2):123-9.
22. Dima L, Trifanescu R, Caraiola S, et al. Botulinum toxin a valuable prophylactic agent for migraines and a possible future option for the prevention of hormonal variations-triggered migraines. Toxins (Basel). 2019;11(8):465.
23. Turkel CC, Brin MF, et al. Treatment of chronic migraine with Botox (onabotulinumtoxinA): development, insights, and impact. Medicine (Baltimore). 2023;102(S1):e32600.
24. Matharu M, Pascual J, Hering R, et al. Utilization and safety of onabotulinumtoxinA for the prophylactic treatment of chronic migraine from an observational study in Europe. Cephalalgia. 2017;37(14):1384-97.
25. Stovner LJ, Tronvik E, Sand T, et al. FollowTheSutures: piloting a new way to administer onabotulinumtoxinA for chronic migraine. Cephalalgia. 2022;42(7):590-7.
26. Jaimes A, Avraham Y, Ramachandran R. OnabotulinumtoxinA as a promising treatment for primary trochlear headache: a retrospective case series. Headache. 2024.
27. Yerry JA, Kuehn D, Finkel AG. Onabotulinum toxin A for the treatment of headache in service members with a history of mild traumatic brain injury: a cohort study. Headache. 2015;55(3):395-406.
28. Hristova, A. H., Joseph, L. N., Sathe, S. A., & Wade, J. B. (2012). Severe nervous system complications after botulinum type A therapy: three case reports with reviews of FDA-reported nervous system adverse effects. PM&R, 4(8), 613-623.
29. Rothrock JF, Bloudek LM, Houle TT, et al. FORWARD study: evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. Headache. 2019;59(10):1700-13.
30. Toni T, Lambert C, Jarvis M, et al. Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series. Neurol Sci. 2021;42(12):5373-6.
31. Azadvari, M., Hosseini, M., Razavi, S. Z. E., Ghajarzadeh, M., & Vaheb, S. (2023). Safety Profile of Botulinum Toxin for Migraine Headache Prophylaxis: A Systematic Review and Meta-analysis. Annals of Military and Health Sciences Research, 21(3).
32. Guyer, B. M. (1999). Mechanism of botulinum toxin in the relief of chronic pain. Current Review of Pain, 3(6), 427-431.
33. Hehr, J. D., Schoenbrunner, A. R., & Janis, J. E. (2020). The use of botulinum toxin in pain management: basic science and clinical applications. Plastic and Reconstructive Surgery, 145(3), 629e-636e.
34. Wei J, Zhu J, Wang X, et al. The efficacy and safety of botulinum toxin type A in treatment of trigeminal neuralgia and peripheral neuropathic pain: a meta‐analysis of randomized controlled trials. *Brain Behav*. 2019;9(10):e01409.
35. Xiao, L., Cheng, J., Zhuang, Y., Qu, W., Muir, J., Liang, H., & Zhang, D. (2013). Botulinum toxin type A reduces hyperalgesia and TRPV1 expression in rats with neuropathic pain. Pain medicine, 14(2), 276-286.
36. Gfrerer L, Liu CY, Burns J, et al. OnabotulinumtoxinA alters inflammatory gene expression and immune cells in chronic headache patients. *Brain*. 2022;145(7):2436-49.
37. Szuch E, Ruggieri PM, Miller JP. Head drop after botox: electrodiagnostic evaluation of iatrogenic botulinum toxicity. *Clin Neurol Neurosurg*. 2017;156:1-3.
38. Kazerooni R, Armstrong EP. Botulinum toxin type A overdoses: analysis of the FDA adverse event reporting system database. *Clin Drug Investig*. 2018;38:867-72.
39. Wolfgang J, Dressler D, Sieb JP, et al. Pooled safety analysis of incobotulinumtoxinA in the treatment of neurological disorders in adults. *Toxins (Basel)*. 2023;15(6):353.
40. Intiso D, Di Rienzo F, Fortunato F, et al. High dosage of botulinum toxin type A in adult subjects with spasticity: where are we at?. *Toxins (Basel)*. 2020;12(5):315.
41. Frick, C. G., Richtsfeld, M., Sahani, N. D., Kaneki, M., Blobner, M., & Martyn, J. A. J. (2007). Long-term effects of botulinum toxin on neuromuscular function. Anesthesiology, 106(6), 1139-1146.
42. Toni T, Lambert C, Jarvis M, et al. Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series. *Neurol Sci*. 2021;42(12):5373-6.
43. Rothrock JF, Bloudek LM, Houle TT, et al. FORWARD study: evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. *Headache*. 2019;59(10):1700-13.
44. Guyer, B. M. (1999). Mechanism of botulinum toxin in the relief of chronic pain. Current Review of Pain, 3(6), 427-431.
45. Intiso D, Di Rienzo F, Fortunato F, et al. High dosage of botulinum toxin type A in adult subjects with spasticity: where are we at?. *Toxins (Basel)*. 2020;12(5):315.