

Research Round Up- Prescribing Uses of Botulinum Toxin

Introduction

Last month the research round up provided you with an overview of articles which reported on some issues, barriers, and challenges in prescribing practice. This month we will be reviewing articles looking at the many and varied uses of botulinum toxin. The three articles reviewed look at the more commonly known area of prescribing for glabellar lines in aesthetic practice but also the round up will consider the use in overactive bladder conditions and in the management of hyperhidrosis. New areas for uses of Botox continue to emerge and this review is not exhaustive in the conditions presented.

BoNT/A in the Urinary Bladder—More to the Story than Silencing of Cholinergic Nerves

Ibrahim, H., Maignel, J., Hornby, F., Daly, D., & Beard, M. (2022). BoNT/A in the Urinary Bladder- More to the Story than Silencing of Cholinergic Nerves. *Toxins*, 14(1), 53.

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This article published in January 2022 in the Journal *Toxins*, sought to review the current evidence on Botulinum neurotoxin (BoNT/A) with regard to its effect on bladder sensation and the potential mechanism by which it may have these effects. BoNT/A is one of a family of Botulinum toxins with this subtype having known benefit in the treatment and management of many medical conditions including cervical dystonia, strabismus and migraine. It exerts its primary effect on cholinergic neurones and prevents the exocytotic release of the neurotransmitter acetylcholine at neuromuscular junctions. This however is not a complete answer as to how this may have effects on the overactive urinary bladder. The article gives a very good overview of botulinum toxins and bladder physiology before moving on to review published work and the different effects of BoNT/A and how these may play a part in management of bladder conditions. The authors discuss the fact that clinical and non-clinical observations of BoNT/A are not easily reconciled with its principal action, that of the blockade of acetylcholine release. Other mechanisms investigated include the following.

Direct action of BoNT/A on sensory nerve innervation of the bladder which have been seen to be affected by the drug use and have influenced stretch responses in bladder filling. This direct action on nerves is also seen as effective in other conditions such as migraine pain.

Changes in neuropeptide release by the action of BoNT/A on sensory nerves. It is known that nerve growth factor (NGF) which is a neuropeptide is implicated in idiopathic detrusor overactivity where it is seen in high levels and reducing this with the use of BoNT/A is a plausible option.

Changes in urothelial function via sensory nerve effect is also postulated and a suggestion that BoNT/A acts directly on these cells in the bladder to inhibit release of ATP in response to stretching.

The authors also discuss the need for further research in many other areas of postulated action but do conclude that BoNT/A is effective in treating lower urinary tract disorders, even if the exact mechanism of action is yet to be elucidated.

Long-term Efficacy and Safety of Liquid AbobotulinumtoxinA Formulation for Moderate-to-Severe Glabellar Lines: A Phase III, Double-Blind, Randomized, Placebo-Controlled and Open-Label Study

Kestemont P, Hilton S, Andriopoulos B, Prygova I, Thompson C, Volteau M, Ascher B. Long-term Efficacy and Safety of Liquid Abobotulinumtoxin-A Formulation for Moderate-to-Severe Glabellar Lines: A Phase III, Double-Blind, Randomized, Placebo-Controlled and Open-Label Study. *Aesthet Surg J.* 2022 Feb 15;42(3):301-313. doi: 10.1093/asj/sjab329. PMID: 34472596; PMCID: PMC8844979.

This study, published in the *Journal of Aesthetic Surgery* in February 2022 aimed to assess the long-term efficacy and safety of Abobotulinumtoxin-A (aboBoNT-A) solution for the treatment of moderate to severe glabellar lines in a clinical trial format. The study was multicentred and multinational across 24 sites in France, Germany, and the UK. It was a double blind, placebo controlled, phase three randomised controlled trial with the primary outcome measure being the appearance of glabellar lines at maximum frown on day 29 of the treatment period. The aim was to ascertain if aboBoNT-A was superior to placebo. Patients were 18 to 65 years old, BoNT-naïve, and dissatisfied/ very dissatisfied with moderate/severe glabellar lines at maximum frown. The randomisation was on a 2:1 basis and so the numbers in the study were 120 receiving aboBoNT-A and 60 who received placebo. All patients were monitored throughout for improvement and for adverse effects. The authors claim that their study is the first to demonstrate the long-term efficacy and safety (over 5 treatment cycles) of aboBoNT-A solution for marked improvement of moderate to severe glabellar lines. Results showed that there was a significant improvement in patient satisfaction and in clinician observation of glabellar line appearance in the treatment group as compared to the control group (81.6% vs 0.8%, 68.1% vs 2.3%, and 83.1% vs 5.7%, respectively: all $P < 0.0001$). No new or unexpected adverse events were observed.

These results support the long-term efficacy and safety of aboBoNT-A solution, and its superiority over placebo, for treatment of glabellar lines in adults and suggest it may provide benefits to injectors and patients due to its convenience for use and allowance of precise and controlled dosing with every injection.

A Practical Approach to the Diagnosis and Treatment of Palmar Hyperhidrosis

Solish, M. J., Savinova, I., & Weinberg, M. J. (2022). A Practical Approach to the Diagnosis and Treatment of Palmar Hyperhidrosis. *Plastic and reconstructive surgery. Global open*, 10(3), e4172. <https://doi.org/10.1097/GOX.0000000000004172><https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901220/>

This article published in March 2022 in the *Journal of Plastic and Reconstructive Surgery (global open)* sought to give an overview of current literature specific to the diagnosis and treatment of palmar hyperhidrosis. There is a very good overview of the condition of palmar hyperhidrosis itself and its epidemiological background with classifications explained and pathophysiology well attended to. Diagnostic criteria is outlined and surgical and non-surgical treatments explained in appropriate detail. Hyperhidrosis, whose main symptom is excess sweating which is independent of the body's normal heat loss mechanisms affects up to 4.8% of the population of the USA and has an even representation between male and female. Palmar hyperhidrosis is present in around 40% of hyperhidrosis patients and can have a detrimental effect on quality of life leading to many sufferers

seeking treatment for this condition. Studies outlining treatments are reviewed and discussed. While several studies summarize treatment options for hyperhidrosis in general, few outline the therapeutic options available specifically for PH. With regard to the use of Botulinum neurotoxin (BoNT/A), currently 4 types of the drug formulation are available to prescribe in the USA. It is described as a second line therapy and given as a local palmar injection. Its mechanism of action on cholinergic neurones and preventing the release of the neurotransmitter acetylcholine is thought to account for its effectiveness in reduction of sweating. The authors acknowledge that currently in the USA BoNTA is not currently approved for palmar hyperhidrosis, and therefore is considered to be off label, although it is still widely utilized and supported by positive outcomes.

The article concludes that a practical approach is needed to manage this condition with a range of treatments. They provide a suggested treatment ladder and outline emerging therapeutic approaches. The suggestion is that after diagnosis and classification, nonsurgical treatments (i.e., topical antiperspirants, iontophoresis, botulinum toxin A injection, and topical/oral anticholinergics) should be utilized in a stepwise manner. They do however suggest that in patients with severe palmar hyperhidrosis who do not respond to nonsurgical treatments, surgical intervention may be warranted, generally in the form of sympathetic denervation.

Conclusion

What is clear is that prescribing botulinum toxin is not only the preserve of aesthetic practitioners for cosmetic purposes but that it has many and varied uses in what may be considered more clinically important areas of prescribing practice by some. As more uses for botulinum toxin emerge, more research is needed into the effectiveness of such treatments and the mechanism of action of this toxin as a drug, for example the use in migraine prevention to ensure cost and clinically effective management.