

Comments to authors

Reviewer #1

**A very nice review on a clinically relevant topic that is increasingly being incorporated in our practices. It is critical to understand the pathophysiologic mechanism of botox to easily identify potential complications of the treatment and to maximize its clinical potential as we are still very much exploring how to maximize the utility of this drug in our clinical practice. A few comments on the paper**

**a. in the section covering the urodynamic changes seen with injection, there is a lot of data mentioned. As this is a review tailored for a non-urologic population, the data should be simplified to include only data relevant to the upper tract deterioration and decrease in detrusor pressure, which is the focus of the paper. Rather than incontinence data etc. which are important to mention but not critical for the goal of preserving the upper tract.**

Answer: This paragraph has been rewritten and corrected with deletion of most clinical information not relevant for the context of this review. Manuscript has been modified accordingly.

**b. In the section of the pathophysiology. Please elucidate on the Hoffman reflex**

Answer: We thank the reviewer for this comment. A definition of the principle of the Hoffmans'reflex has been added and the manuscript has been modified accordingly.

**c. in the section on VUR and botox, it is important to note that in pediatric populations it indicated the utility of urodynamics prior to VUR repair. As primary VUR may reflect a dysfunctional voider or unrecognized neurologically induced high pressure voiding rather than an anatomical defect.**

Answer: We thank the reviewer for this important comment. A statement about this has been included at the end of the paragraph.

**d. lastly although it is mentioned in the introduction, it should be mentioned that when DO is associated with DSD, botox can be used in some cases at the sphincter as opposed to intravesical injections. Perhaps a comment can be made indicating that when DSD is present with neurogenic DO, upper tract preservation may be better preserved by reducing outlet obstruction rather than detrusor hypereflexia**

Answer: We thank the reviewer for this comment. A specific statement has been added in the introduction, mentioning the fact that the paper is focused on NDO but that DSD management in itself is mandatory.

Reviewer #2

**The authors are invited to address the following points:**

**1. In the proof of concept study Schurch et al had injected 300 U of Botox, not 200 IU. Please correct**

Answer: We thank the reviewer for this important comment. Manuscript has been corrected.

**2. Also, Schurch et al did not compare 200 to 300U Botox, as their study was not designed to detect differences between the 2 doses. This needs to be clarified.**

Answer: We thank the reviewer for this comment. In this paper (REF [7]) Schurch et al have done a 3-arm study with 200UI, 300UI and placebo, with intergroup comparison (on

incontinence episodes). It is detailed in their material and methods. We added that the study was not powerful enough to conclude on secondary outcomes such as urodynamic parameters, and clarified this in the manuscript by introducing an additional comment to this paper.

**3. The authors spend a good size text in the Bladder effect section pinpointing some studies from the earlier literature on Botox and NDO, but there are already several systematic reviews discussing this comprehensively and producing accumulative data which the authors could have used instead. Please include collective data from systematic reviews**

Answer: The goal of the present study was to produce a comprehensive overview of the available data on pathomechanisms related to protection of the urinary tract. During such a process, original data have to be presented, not a review of reviews. As bladder effects are an important part of this benefits of the upper tract, we decided that giving the crude information to the reader, without basing our manuscript of previous reviews, was more profitable. We leave the decision to the associate editor to determine whether all other systematic reviews have to be covered.

**4. Discussion of UTI pathophysiology is confusing. The authors have not taken a robust route on whether Botox actually decreases or increases UTIs. As a result they produce hypotheses on both induction of UTIs by Botox and decrease of UTIs by Botox in the same paragraph! Please revise appropriately. Further, they have not discussed the apparent discrepancies between level of evidence 3 studies which show a decrease of UTIs and the level of evidence 1 studies which show no change in SCI patients and a definitive increase in MS patients. Please discuss**

Answer: We thank the reviewer for this important comments. We understand that it may not appear very clear, but the statements made about pathomechanisms reflect the actual scientific hypotheses that are postulated. About the clinical data, the "disparancies" pointed out by the reviewer are clearly explained by the fact that in level 1 studies, no adequate definition of UTIs have been applied, and authentic UTIs are confounded with colonization. We thus entirely re-structured and re-wrote the paragraph to make is easier to understand for the reader. The manuscript has been modified accordingly.

**5. Despite improvements seen in VUR after BTX-A injections, results also suggest a surprising decrease in GFR. The discussion proposed by the authors is not satisfactory, particularly since Botox has been found to reduce all risk factors for renal impairment in SCI patients. Could other factors, such as retrograde transport of the toxin to the kidney have such a contradictory effect? Please discuss if appropriate**

Answer: The decrease in GFR has been showed in only one study by Kuo et al. As we state immediately after, the same authors have completed another study with more patient a few years after and did not confirm their results. The overall result is that long term effects of Botox injections are protective for the kidney.

**6. Conclusions are not justified by the evidence the authors have produced in the manuscript! Please revise accurately**

Answer: The data about symptoms and quality of life have been removed from this section as they are not reviewed in the manuscript.

**7. Extensive editing is needed as a lot of typos can be identified throughout the manuscript**

Answer: This has been done.

**8. The title of the manuscript could be revised to something less ambitious. par example, CAN BOTULINUM TOXIN IN NEUROGENIC DETRUSOR OVERACTIVITY REDUCE UPPER URINARY TRACT DAMAGE?**

Answer: With all due respect to the reviewer, the authors decide to stick to the original title "**HOW BOTULINUM TOXIN IN NEUROGENIC DETRUSOR OVERACTIVITY CAN REDUCE UPPER URINARY TRACT DAMAGE?**" which was the title proposed by the editorial board at the time of invitation. The proposed modification is so minor that it does not changed anything to us. Furthermore, the heart of the paper is focused on pathophysiology so the title seems both appealing and not misleading.