World Journal of Urology
https://doi.org/10.1007/s00345-018-2456-7

ORIGINAL ARTICLE

Modifications to Botulinum toxin A delivery in the management of detrusor overactivity recalcitrant to initial injections: a review

A. Doherty[1] · D. B. Hennessey[1] · J. R. Onggo[2] · W. Ranasinghe[2] · J. Gani[2,3]

Received: 25 July 2018 / Accepted: 16 August 2018

Abstract

Purpose One quarter of patients will not respond to initial intra-detrusor Botulinum toxin A (BTX) injections for detrusor overactivity. Alternative treatment options include long-term catheterization, sacral neuromodulation, urinary diversion or bladder augmentation. Some of these procedures are invasive. This review explores modifications to BTX delivery that can improve outcome.

Methods A search of Medline, Embase and Cochrane Library to December 2017 was performed according to Preferred Reporting Items for Systematic Review and Metaanalysis (PRISMA) guidelines. Search criteria included, dose escalation, increasing injection site number, trigone injection, switching preparation and alternative methods of BTX delivery.

Results Several modifications to BTX delivery may improve response. There is moderate evidence that increasing the dose from 100 U to 200 U results in statistically better symptom control. Trigone-including injections were associated with significantly improved patient-reported symptom scores, as well as superior results in urodynamic outcomes without risking urinary retention and vesico-ureteric reflux. Switching from onabotulinum (OTA) or abobotulinum (ATA) or vice versa may also improve response in over 50% of patients as shown in limited studies. Increasing the number of injection sites is not beneficial. Indeed, decreasing the number of injections to as low as three sites does not result in decreased clinical outcomes. Injection-free delivery is associated with lower efficacy compared to conventional intradetrusor injections.

Conclusion Before contemplating alternative treatments, practitioners can try to improve on BTX delivery. Firstly, the dose can be increased to 200 U; the trigone included in the injection sites and switching brands may also be helpful.

Keywords Bladder botox® · Intradetrusor botox® · Number of injection sites · Number of injections · BTX brand · Treatment failure

Introduction

Refractory detrusor overactivity (DO) can cause considerable morbidity; in the case of neurogenic detrusor overactivity (NDO), it can put the upper tracts at risk. When conservative treatments such as intra-detrusor Botulinum toxin A (BTX) and sacral neuromodulation (SNM) have failed, the last recourse for treatment is to surgically increase functional bladder capacity and decrease maximal detrusor pressure [1]. In select patients, augmentation cystoplasty is a suitable procedure for recalcitrant DO. However, augmentation cystoplasty can be considered major surgery and is not for everyone. Patients who undergo the procedure must be prepared to perform lifelong intermittent catheterization and be aware of problems such as bladder stones, metabolic and nutritional abnormalities, renal insufficiency and malignancy [2]. In addition to this, one in three patients having the procedure will have a complication [3].

Instead of augmentation cystoplasty or SNM when initial BTX has failed, various modifications to BTX administration have been reported to improve efficacy and outcome. To date, no review exists regarding BTX modifications to improve treatment outcome. Therefore, this review aims to summarise current data regarding the impact of these

✉ A. Doherty
a-doherty@hotmail.co.uk

[1] Department of Urology, Craigavon Area Hospital, Portadown, UK

[2] Department of Urology, Austin Health, Melbourne, Australia

[3] Department of Urology, Western Health, University of Melbourne, Melbourne, Australia

Published online: 23 August 2018

modifications in patients with recalcitrant DO to initial BTX treatments to aid urologists in treating these patients.

Methods

Systematic review

A review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. This included pre-publication of our intended analysis on PROSPERO, registration number is: CRD42018090399. Criteria for considering studies for this review were: Studies published in English in a peer-reviewed journal. Only human patients of all ages with recalcitrant DO of any type and at least one intervention of any sort. The primary outcome is patient outcome with intervention(s). The following electronic databases were explored; Cochrane Central Register of Controlled Trials (CENTRAL) (1946–30 December 2017), EMBASE (1974–30 December 2017) and MEDLINE (1946–30 December 2017). Separate searches were carried out for each sub-topic of the review. Searches utilised the Boolean operators as follows; (OR items #1–#2) AND (OR items #3–#8), searching for terms within abstracts of English language studies, with items of 1. Bladder Botox®, OR 2. Intradetrusor Botox®, AND 3. Dose, 4. Number of injection sites, 5. Number of injections, 6. Technique, 7. BTX brand, and 8. Treatment failure.

Data collection and analysis

Eligible studies measured the compliance of patients with recalcitrant DO to modifications to intra-detrusor BTX and SNM. Two independent authors screened the titles and abstracts of identified studies and selected those that met the pre-defined inclusion criteria. Identified studies were screened by title and abstract, followed by a full-text review. Articles were then progressed to data extraction, including review of references. Uncertainty was resolved with discussion. A flow-chart was planned to illustrate sequential screening of identified titles and is shown in Fig. 1.

Data extraction and synthesis

Two authors extracted data onto a pre-designed extraction form. Data were recorded regarding:

Author, year of publication, journal, language, country, study design and methodology, population, follow-up duration, compliance rates and other outcomes. The risk of bias was assessed with the Newcastle–Ottawa Scale, in accordance with the Cochrane Handbook [4]. Data extraction was performed twice, to confirm accuracy. The final list of included articles was determined by compliance with the inclusion criteria and with the consensus of all authors.

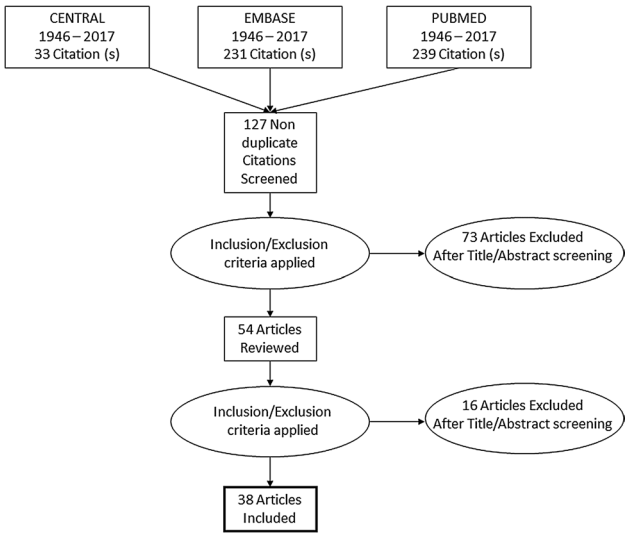

Fig. 1 PRISMA flow diagram of citations reviewed in the course of a systematic review of treatment options for when initial intradetrusor Botox® fails. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Intra-detrusor Botulinum toxin A injections

Why does treatment fail?

Currently, there is no consensus decision as to what signifies the failure of bladder BTX treatment. Peyronnet et al. Studies examining [5] surveyed 21 experts in neuro-urology in France, who suggested that BTX failure in neurogenic detrusor overactivity should be defined both by clinical parameters (e.g., persistence of urinary incontinence) and urodynamic outcomes (e.g., persistence of a maximum detrusor pressure > 40 cm H_2O).

Limited studies have been carried out to try to predict which patients are more likely to fail treatment. Makovey et al. [6] suggested that patients with idiopathic detrusor overactivity were more likely to fail on BTX if they had not seen any improvement with anticholinergic medications, as opposed to patients who could not tolerate anticholinergics due to their side effects. Data from the RELAX study examined by Owen et al. [7] suggested that among female patients with refractory detrusor overactivity, 23.8% had no change in urgency episodes at 6 weeks, and 23% self-reported their symptoms to be no better or worse. In this group, smoking status and increased number of leakage episodes at baseline were associated with a higher risk of failure.

Similar rates of treatment failure were quoted among NDO patients by Leitner et al. [8] who pointed out that over 10 years, 40% of the patients studied discontinued

treatment with BTX. Around half of these (21%) stopped due to lack of clinical effect. Joussain et al. [9] also examined long-term outcomes in NDO patients and found that predictive factors for treatment failure included the presence of pre-treatment of urinary incontinence, higher maximum detrusor pressure, a higher number of febrile urinary tract infections (UTIs) and decreased bladder compliance. Additionally, Lacout et al. [10] suggested that longer duration of symptoms before commencing BTX for NDO was predictive of primary failure.

New data are emerging on the role of antibody production in BTX treatment failure. Neutralising antibodies directed against Botulinum Toxin proteins can lead to loss of clinical effect. However, in the past, this has been more commonly associated with patients receiving frequent high doses of onabotulinum toxin A for the treatment of cervical dystonia [11]. A more recent meta-analysis by Naumann et al. [12] analysed 2240 patients receiving onabotulinum toxin A for various indications including non-urological ones. Only 0.49% of patients who were not antibody positive at the start of treatment converted into antibody positive during treatment. In the 22 patients with overactive bladder (OAB) who had BTX, none produced antibodies. Additionally, the effects of antibody positivity on treatment efficacy were considered clinically negligible.

Although the failure of BTX for OAB is still relatively poorly understood, it can be concluded that it is likely multi-factorial. Patients with more severe disease before treatment commencement seem to have a higher likelihood of treatment failure, and while this should not necessarily deter the clinician from using BTX, this would be an essential counselling point for these patients.

Approaches when initial treatment fails

Current guidelines recommend the use of BTX when symptoms of overactive bladder (OAB) are refractory to therapy with conservative or lifestyle measures, and oral medications [13]. Unfortunately, a subset of patients fail to achieve adequate improvement in their symptoms with standard administration of intra-detrusor BTX injections [14]. The purpose of this review was to examine how a better outcome could be achieved for a patient who initially had a poor result with BTX, to avoid them progressing to more invasive surgical options. In particular, the following approaches were assessed: dose escalation, injection site variation, injection number variation and differences in outcome due to changing brand. Additional to this, novel data regarding BTX tolerance and injection-free delivery were examined.

Dose escalation

The recommended initial starting treatment dose of Onabotulinum Toxin A for idiopathic DO is 100 units (U) [13, 15, 16]. A number of dose-ranging studies have been performed, which compare low/standard doses of Botox® (50 U/100 U) of onabotulinum toxin A to higher doses (150 U/200 U/300 U) [14, 17–25]. Several general conclusions can be drawn from the data. Compared to placebo, onabotulinum toxin A injections result in a statistically significant improvement in symptoms [17, 21–24]. 150 U and 200 U doses resulted in statistically better symptom control compared to lower doses [14, 21, 22]. Dmochowski et al. suggested further benefit from a dose of 150 U, however minimal additional benefit beyond this [22] and Cohen et al. suggested a non-significant trend that patients with idiopathic DO and incontinence tended to be drier when given a higher dose of 150 U as opposed to 100 U [14].

Higher doses tended to be more durable and lasted longer than lower doses too. Kuo et al. [25] reported a shorter duration of action with 100 U, compared with 150 U and 200 U, however, no difference in urodynamic parameters and a reduced risk of urinary retention. The highest dose of onabotulinum toxin A (300 U) was not statistically superior to 200 U. It was associated with a higher incidence of urinary retention and urinary tract infection (UTI) among the group treated with the higher dose of 200 U [17, 22].

Little evidence exists regarding alteration of an already established dose of intra-detrusor Botox® to a lower dose. A study by Malki et al. [26] reported retrospective data on 44 patients (both neurogenic and idiopathic DO) who had been receiving a dose of 300 U Onabotulinum toxin A but were switched to 200 U to comply with new guidelines. Although the majority of patients continued to note similar symptomatic improvement with the lower dose, a subset of patients did report subjective worsening of their symptoms – 18% of the idiopathic DO group. Of the neurogenic detrusor overactivity (NDO) group, 25% of patients reverted to the higher dose of 300 U with good effect.

In reality, there is a lack of high-quality evidence examining the effects of up-titrating the dose of intra-detrusor Botox®. But several studies suggest that some patients may respond to a higher dose of 200–300 U. However, this comes with an increased risk of adverse effects such as UTI and urinary retention. Data on randomised control trials reporting on dose escalation of Botox® are summarised in Table 1.

Injection site variation

Conventional wisdom regarding the administration of bladder BTX has been to avoid the bladder base and trigone, in an attempt to avoid vesico-ureteric reflux (VUR) [13]. However, the evidence base for this is limited, and it has

Table 1 Studies examining BTX dose escalation

	Study type	Pathology	Agent	Dose(s)	*N*	Results
Rovner et al. [17]	Multicentre, double-blind RCT	NDO	OTA	Placebo/200 U/300 U	691	A significant difference between OTA and placebo. No difference between doses
Ginsberg et al. [18]	Multicentre, double-blind RCT	NDO	OTA	Placebo/200 U/300 U	416	Significant difference with OTA, no improvement with 300. Higher risk of ISC/large PVR
Cruz et al. [19]	Multicentre, double-blind RCT	NDO	OTA	Placebo/200 U/300 U	275	Significant difference between OTA and placebo. No difference between doses
Grise et al. [20]	Multicentre, double-blind RCT	NDO	ATA	500 U/750 U	78	No significant difference between 500 and 750 U
Apostolidis et al. [21]	Double-blind, RCT, parallel group study	NDO	OTA	Placebo/50 U/100 U/200 U	73	Significant improvement with 200 U compared to lower doses
Dmochowski et al. [22]	Multicentre, double-blind RCT	IDO	OTA	Placebo/50 U/100 U/150 U/200 U/300 U	313	OTA better than placebo, no improvement with doses over 150 U
Schurch et al. [23]	Double-blind, RCT, parallel group study	NDO	OTA	Placebo/200 U/300 U	59	No significant difference between 200 U and 300 U
Sussman et al. [24]	Multicentre, double-blind RCT	NDO	OTA	Placebo/200 U/300 U	275	No significant difference between 200/300
Cohen et al. [14]	Randomised, prospective study	IDO	OTA	100 U/150 U	44	No statistical difference though patients who were wet tended to be drier with 150
Kuo, et al. [25]	Randomised, prospective, single-blind study	IDO and NDO	OTA	100 U/150 U/200 U	75	Significantly shorter duration of action with 100 U, however also fewer side effects

N number, *RCT* randomised control trial, *IDO* idiopathic detrusor overactivity, *NDO* neurogenic detrusor overactivity, *U* units, *OTA* onabotulinum toxin A, *ATA* abobotulinum toxin A

more recently been suggested that inclusion of the trigone may lead to improved efficacy without an increase in complications [27]. It has been identified that the suburothelial afferent nerve plexus is particularly dense in the bladder base and trigone; therefore, it would follow that injection of BTX to these regions would lead to higher efficacy [28].

A comprehensive systematic review on this topic was recently undertaken by Jo et al. [27]. Overall, 334 patients were included in five trials. Trigone-including injections were associated with significantly improved patient-reported symptom scores, as well as superior results in urodynamic outcomes (detrusor pressure, volume at first desire to void) compared to the trigone-sparing approach. The five studies analysed did not report rates of VUR post-procedure. However, the adverse effects that were reported (urinary tract infection, haematuria, general weakness, and high post-void residual) did not vary between the groups. Furthermore, Jo et al. also examined suburothelial Vs intradetrusor injection and found that there was no difference in outcome between these techniques [16].

Emerging data suggest that injection technique for bladder BTX should include the base and trigone, and that to do so does not increase the risk of VUR. For a patient with suboptimal outcomes using the conventional trigone-sparing approach, a switch to trigone-including could lead to better results.

Injection site number variation

Although techniques vary, the standard method of administration of 100 U of onabotulinum toxin A is to dilute to 10 ml and deliver in 0.5 ml aliquots to 20 sites around the bladder wall [13]. As this procedure is now increasingly performed under local anaesthetic, there has been some interest in decreasing the number of injections to improve tolerability under local anaesthetic.

Mehnert et al. performed a small study of six patients, who received an injection of onabotulinum toxin A, partly diluted with a contrast agent, in either 10 or 30 injections [29]. Shortly after Botox® administration, the patients underwent MRI scanning. The MRI results showed similar amounts of contrast agent found within the detrusor muscle and a comparable percentage cover of detrusor volume between the two injection techniques.

Three more recent studies examining different numbers of injection sites are summarised below. Although overall patient numbers are low, results between these studies are consistent. The most extensive study performed by Liao et al, who examined 67 patients with either idiopathic DO or NDO, randomised to receive 100 U of onabotulinum toxin A in 10, 20 or 40 injections [30]. No significant difference was found regarding patient-reported or urodynamic outcomes between the three groups. However, they did not demonstrate any benefit for reduced injection sites regarding patient tolerability or adverse effects. Similarly, Karsenty et al. noted no difference between 30 and 10 injection sites [31]. Most recently, Avallone et al. reported the efficacy of one Vs. three injection sites in a less-is-more study and found similar efficacy and side effect profile compared to published data for the standard 20 injection site technique [32].

Thus, the number of injection sites may be safely reduced and appears to give similar results compared to standard regimes. Although this may be advantageous regarding reduction in operating time and patient comfort, it is unlikely that altering this variable will improve outcomes for patients with a suboptimal response to BTX treatment. Data on trials reporting on number of injection sites of BTX are summarised in Table 2.

Brand variation

In the United Kingdom, the only licensed preparation for treatment of idiopathic DO and NDO is onabotulinum toxin A (Botox®, *Allergan*). Abobotulinum toxin A (Dysport® *Ipsen Biopharmaceuticals Inc.*) is also used but is used off-license. A small but potentially useful body of data exists regarding switching patients who have previously failed on one of these brands on to the other.

A paper by Peyronnet et al. [33] retrospectively analysed the charts of 58 patients for whom initial intra-detrusor injection (either onabotulinum (OTA) or abobotulinum (ATA) treatment) was unsuccessful. Failure was defined broadly as the persistence of urinary urgency, incontinence or urodynamic detrusor overactivity. Half of these patients had a second treatment with the same brand, while the other half received treatment with the other agent. The success rate in the group that switched toxins was 51.7%, significantly higher than the 24.1% of patients who had success with a second injection of the same agent. Treatment outcomes were the same regardless of the direction of the change (abobotulinum to onabotulinum or vice versa).

Two similar studies have subsequently been published, one again by Peyronnet et al. [34] examining the switch from ATA to OTA, and Bottet et al. [35] studying the switch from onabotulinum to abobotulinum. Although these studies were small (26 and 57 patients, respectively), non-randomised and without controls, they demonstrated consistent results. In both trials, just over 50% of patients saw improvement in clinical or urodynamic outcomes after the switch to the second agent. Crucially, while the work by Peyronnet and his team focussed on patients with primary treatment failure, the work by Bottet et al. included patients with secondary treatment failure, and success rates after a switch to ATA were shown to be similar between these two groups. Bottet et al. also found lower rates of success after switching agents with patients whose bladder compliance was recorded as < 20 ml/cm H2O, possibly suggesting that for this subset of patients, earlier consideration of surgical options may be appropriate. The work of both of these groups focussed solely on neurogenic detrusor overactivity and no data were found pertaining to switching agent in patients with idiopathic DO. For either primary or secondary treatment failure, there is evidence that switching to a different agent may be of benefit. However, all trial data come from patients with NDO.

Table 2 Trials reporting on Injection site number

	Study Type	Pathology	Number of sites	*N*	Results
Mehnert et al. [29]	Experimental prospective	NDO	10 vs. 30	6	On MRI, comparable cover of detrusor volume
Avallone et al. [32]	Prospective, non-randomised cohort study	NDO and IDO	1–3	45	Similar results for efficacy and side effect profile compared to published data for the standard technique
Karsenty et al. [31]	Prospective, randomised, single-blind study	NDO	10 vs 30	30	Similar rates of efficacy and complications between the two groups
Liao et al. [30]	Randomised, single-blind, parallel, actively controlled trial	NDO and IDO	10 vs 20 vs. 40	67	Similar rates of efficacy and complications between all groups

N number, *vs* versus, *IDO* idiopathic detrusor overactivity, *NDO* neurogenic detrusor overactivity

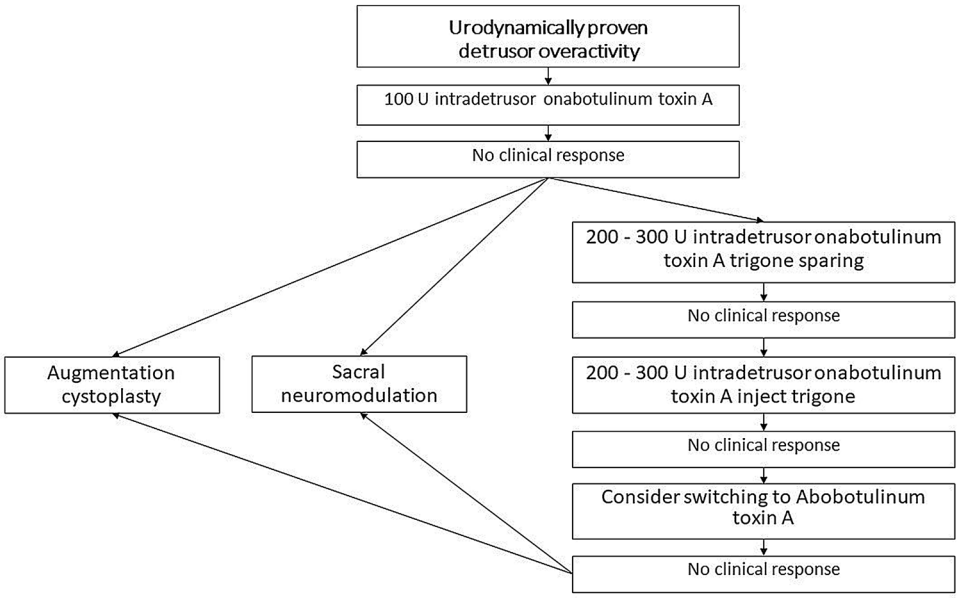

Fig. 2 Suggested treatment algorithm for recalcitrant DO. *U* units

For a certain subset of patients (e.g. those with poor bladder compliance) there may be a lower likelihood of success.

Figure 2 shows a treatment algorithm for the management of patients who have refractory DO to initial 100 U BTX injections. When a patient fails initial treatment, subsequent treatment options include increasing BTX dose, involving the trigone in BTX injections and switching brands. Should the patient remain refractory to BTX still, SNM and augmentation cystoplasty are treatment options that could be considered at any stage.

Injection-free delivery

A drawback of bladder BTX treatment is the mode of delivery. The procedure is often performed under local anaesthesia and is well tolerated, but is still unacceptable to some patients. Additionally, maintaining position for cystoscopy may be challenging for patients with underlying neurological disorders. Recent interest has turned to the possibility of injection-free delivery. Not only would this improve acceptability and ease of delivery, but also theoretically should lower the risk of urinary retention, as penetration should be limited to the sensory nerves in the urothelium and not to the deeper detrusor.

Kuo et al. and Chuang et al. have performed small-scale placebo-controlled studies of liposome-encapsulated onabotulinum toxin A on patients with proven idiopathic overactive bladder [36, 37]. In both studies, the formulation used contained 200 U onabotulinum toxin A with 80 g sphingomyelin liposomes. This formulation was instilled into the bladder with a 6Fr catheter and left in situ for 1 h. Both studies demonstrate a short-term reduction in urinary frequency episodes compared to placebo; results regarding urinary urgency were inconclusive, and there is no significant improvement of urge urinary incontinence episodes. There were significant exclusion criteria including patients with neurological disorders, previous radiotherapy and a PVR > 150 ml. Importantly, there were no episodes of urinary retention demonstrated in either study. Additional studies showed similar results [38].

Liposome-encapsulated delivery probably has lower efficacy compared to conventional intradetrusor injections. However, it may be appropriate in some patients, for example, those at high risk of urinary retention, patients who cannot tolerate traditional treatment, and those who find it difficult to maintain position for cystoscopy. Work in this area is in its early stages, and more data are needed, particularly with regards to neurogenic patients, and long-term efficacy.

Conclusion

If a patient with DO fails their initial treatment of 100 U intradetrusor BTX, various modifications to BTX delivery exist that can be utilised prior to considering invasive options. There is evidence that increasing the injected dose from 100 to 150–200 U can be beneficial. If the initial treatment spared the trigone, injecting the trigone on subsequent treatments may also help. Additionally, switching the brand from onabotulinum to abobotulinum may also be valuable. Increasing the number of injection sites does not increase clinical response and liposome-encapsulated delivery is an emerging option but evidence for its efficacy is lacking.

Acknowledgements None.

Author's contribution AD data collection or management, data analysis, manuscript writing/editing. DBH data collection or management, Manuscript writing/editing. JRO manuscript writing/editing. WR manuscript writing/editing. JG protocol/project development.

Compliance with ethical standards

Conflicts of Interest No potential conflict of interest relevant to this article was reported.

Ethical statement No ethical issues as this is a systematic review.

References

1. Chapple CR, Bryan NP (1998) Surgery for detrusor overactivity. World J Urol 16(4):268–273
2. Gurung PM et al (2012) Long-term outcomes of augmentation ileocystoplasty in patients with spinal cord injury: a minimum of 10 years of follow-up. BJU Int 109(8):1236–1242
3. Schlomer BJ, Saperston K, Baskin L (2013) National trends in augmentation cystoplasty in the 2000s and factors associated with patient outcomes. J Urol 190(4):1352–1357
4. Stang A (2010) Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
5. Peyronnet B et al (2015) Definition of botulinum toxin failure in neurogenic detrusor overactivity: preliminary results of the DETOX survey. Prog Urol 25(17):1219–1224
6. Makovey I et al (2011) Botulinum toxin outcomes for idiopathic overactive bladder stratified by indication: lack of anticholinergic efficacy versus intolerability. Neurourol Urodyn 30(8):1538–1540
7. Owen RK et al (2017) Patient factors associated with onabotulinum toxin A treatment outcome in women with detrusor overactivity. Neurourol Urodyn 36(2):426–431
8. Leitner L et al (2016) More than 15 years of experience with intradetrusor onabotulinumtoxinA injections for treating refractory neurogenic detrusor overactivity: lessons to be learned. Eur Urol 70(3):522–528
9. Joussain C et al (2018) Long-term outcomes and risks factors for failure of intradetrusor onabotulinumtoxinA injections for the treatment of refractory neurogenic detrusor overactivity. Neurourol Urodyn 37(2):799–806
10. Lacout M et al (2015) Seniority of neurobladder and effectiveness of a first intradetrusor injection of botulinum toxin. Prog Urol 25(11):642–648
11. Jankovic J, Schwartz K (1995) Response and immunoresistance to botulinum toxin injections. Neurology 45(9):1743–1746
12. Naumann M, Jankovic J (2004) Safety of botulinum toxin type A: a systematic review and meta-analysis. Curr Med Res Opin 20(7):981–990
13. Lucas MG et al (2013) EAU guidelines on surgical treatment of urinary incontinence. Actas Urol Esp 37(8):459–472
14. Cohen BL et al (2009) Predictors of response to intradetrusor botulinum toxin-A injections in patients with idiopathic overactive bladder. Adv Urol p. 328–364
15. Duthie JB (2011) Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev (12):p. CD005493
16. Denys P et al (2012) Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. Eur Urol 61(3):520–529
17. Rovner E et al (2013) OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourol Urodyn 32(8):1109–1115
18. Ginsberg D et al (2012) Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol 187(6):2131–2139
19. Cruz F et al (2011) Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol 60(4):742–750
20. Grise P et al (2010) Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. Eur Urol 58(5):759–766
21. Apostolidis A et al (2013) An exploratory, placebo-controlled, dose-response study of the efficacy and safety of onabotulinumtoxinA in spinal cord injury patients with urinary incontinence due to neurogenic detrusor overactivity. World J Urol 31(6):1469–1474
22. Dmochowski R et al (2010) Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol 184(6):2416–2422
23. Schurch B et al (2007) Botulinum toxin A improves the quality of life of patients with neurogenic urinary incontinence. Eur Urol 52(3):850–858
24. Sussman D et al (2013) Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurourol Urodyn 32(3):242–249
25. Kuo HC (2006) Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? Urology 68(5):993–997 **discussion 997-8**
26. Malki M et al (2014) What is the feasibility of switching to 200IU OnabotulinumtoxinA in patients with detrusor overactivity who have previously received 300IU? Cent Eur J Urol 67(1):35–40
27. Jo JK et al (2018) The effect of onabotulinumtoxinA according to site of injection in patients with overactive bladder: a systematic review and meta-analysis. World J Urol 36(2):305–317
28. Andersson KE (2002) Bladder activation: afferent mechanisms. Urology 59(5 Suppl 1):43–50
29. Mehnert U et al (2009) A morphological evaluation of botulinum neurotoxin A injections into the detrusor muscle using magnetic resonance imaging. World J Urol 27(3):397–403
30. Liao CH, Chen SF, Kuo HC (2016) Different number of intravesical onabotulinumtoxinA injections for patients with refractory detrusor overactivity do not affect treatment outcome: a prospective randomized comparative study. Neurourol Urodyn 35(6):717–723
31. Karsenty G, Carsenac A, Boy S, Reitz A, Bardot P, Tournebise H, Bladou F, Serment G, Schurch B (2007) 890 Botulinum toxin-A (BTA) in the treatment of neurogenic detrusor overactivity incontinence (NDOI)-A prospective randomized study to compare 30 Vs. 10 injection sites. Eur Urol Suppl 6(2):245
32. Avallone MA et al (2017) Less is more-A pilot study evaluating one to three intradetrusor sites for injection of OnabotulinumtoxinA for neurogenic and idiopathic detrusor overactivity. Neurourol Urodyn 36(4):1104–1107
33. Peyronnet B et al (2015) Failure of botulinum toxin injection for neurogenic detrusor overactivity: switch of toxin versus second injection of the same toxin. Int J Urol 22(12):1160–1165

34. Peyronnet B et al (2016) Preliminary results of botulinum toxin A switch after first detrusor injection failure as a treatment of neurogenic detrusor overactivity. Neurourol Urodyn 35(2):267–270
35. Bottet F et al (2018) Switch to Abobotulinum toxin A may be useful in the treatment of neurogenic detrusor overactivity when intradetrusor injections of Onabotulinum toxin A failed. Neurourol Urodyn 37(1):291–297
36. Kuo HC et al (2014) Pilot study of liposome-encapsulated onabotulinumtoxinA for patients with overactive bladder: a single-center study. Eur Urol 65(6):1117–1124
37. Chuang YC et al (2014) Bladder instillation of liposome encapsulated onabotulinumtoxinA improves overactive bladder symptoms: a prospective, multicenter, double-blind, randomized trial. J Urol 192(6):1743–1749
38. Chuang YC, Kuo HC (2017) A Prospective, Multicenter, Double-Blind, Randomized Trial of Bladder Instillation of Liposome Formulation OnabotulinumtoxinA for Interstitial Cystitis/Bladder Pain Syndrome. J Urol 198(2):376–382