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Medium- to long-term outcomes of botulinum toxin A for idiopathic overactive bladder

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Abstract: Botulinum toxin A (BoNT-A) has become an important therapeutic tool in the management of refractory overactive bladder (OAB). Over the last decade, there have been growing numbers of patients receiving repeat injections and these outcomes have begun to be reported in large, high-quality cohorts. This article reviews the current evidence for the medium- to long-term use of BoNT-A in adults with idiopathic detrusor overactivity (IDO) receiving repeat injections. We find that medium-term outcomes are encouraging but long-term outcomes are not as extensively reported. There is high-quality evidence that efficacy following the first injection persists across multiple treatment cycles. There are no additional safety concerns from repeat injections up to six treatment cycles. However, there is a need for further data to confirm the efficacy and safety of BoNT-A beyond the follow-up period in the current literature.

Keywords: botulinum toxin, overactive bladder, detrusor overactivity, botox, onabotulinumtoxinA, Dysport, abobotulinumtoxinA

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Introduction

Botulinum toxin A (BoNT-A) injections have become a well established therapy in the management of refractory overactive bladder (OAB). There are increasing numbers of patients receiving repeat injections on a regular basis. OnabotulinumtoxinA (BOTOX; Allergan, Inc., Irvine, USA) has been approved for the treatment of refractory OAB. It has been shown to be effective and well tolerated in phase III multicentre randomized, double-blind, placebo-controlled trials utilizing a 100 U dose [Chapple *et al.* 2013; Nitti *et al.* 2013].

This review discusses the current literature on BoNT-A as a medium- to long-term treatment for idiopathic OAB. This review covers the efficacy, quality of life, injection intervals, immunological aspects and longer term safety reported across the published literature in this group treated with BoNT-A.

Methods

A search of the PubMed database was performed using the MeSH terms 'Botulinum A toxin' or 'overactive bladder' and keywords 'botulinum neurotoxin', 'idiopathic detrusor overactivity'. The inclusion criteria were papers reporting the medium- to long-term outcomes in adults with idiopathic OAB. These studies generally reported follow up in terms of number of treatment cycles. Therefore medium-term outcomes were defined as more than one treatment cycle and long-term outcomes as more than five treatment cycles. The term 'refractory OAB' includes patients who had an inadequate response or were unable to tolerate first-line medical and behavioural treatments. No language exclusions were applied. The bibliographies of the papers were examined for additional studies meeting the inclusion criteria. Overall 12 published papers were identified and underwent full review.

Efficacy

Levels of evidence

There have been two phase III placebo-controlled trials which have provided level 1 evidence for the short-term efficacy of a single injection of onabotulinumtoxinA 100 U in OAB [Chapple *et al.*

2013; Nitti *et al.* 2013]. The only longitudinal randomized controlled trial [Gousse *et al.* 2011] was a dose-ranging study comparing six injections of onabotulinumtoxinA 100 U and 150 U administered at 24-week intervals up to 3 years. Sixty patients were randomized but there was a significant dropout rate with only nine patients (15%) completing the study. This demonstrates the challenge of investigating medium- to long-term outcomes in a randomized controlled trial setting.

The remaining published studies comprised level 2 or 3 evidence divided into prospective longitudinal studies and retrospective case series (Table 1). The standard follow up across these studies is on average around 3 years, although the maximum for an individual patient is up to 7 years [Veeratterapillay *et al.* 2014]. The number of repeat injections ranges from 2 to 10 [Dowson *et al.* 2012], with the majority of studies providing data on approximately three to four repeat injections (Table 2). Given that patients have been receiving repeat BoNT-A injections for over a decade, longer-term data are still required to fully evaluate the outcomes of BoNT-A injections beyond 3–4 years.

The largest cohort is from the phase III extension study in which patients from the pivotal randomized controlled trials (RCTs) were invited to participate in a 3.5-year follow-up period [Nitti *et al.* 2016]. The other studies are smaller cohorts and they have significant variability in methodology, follow up and outcome measures. Some studies report efficacy data for a set duration of follow up [Granese *et al.* 2012; Kuschel *et al.* 2008; Mohee *et al.* 2013], others compare efficacy across the first and subsequent injections [Dowson *et al.* 2012; Game *et al.* 2011; Gousse *et al.* 2011; Khan *et al.* 2009; Sahai *et al.* 2010] and others select patients who have undergone a set number of injections but do not comment on the size of the original cohort [Abeywickrama *et al.* 2014]. All these methods bias the outcome data and skew it towards a positive effect as patients discontinuing treatment are not included in the efficacy outcome measures.

A range of efficacy outcomes have been used, including urodynamic parameters, voiding diaries and quality of life scores. There are limited studies which evaluate the effect of repeat injections on urodynamic parameters [Granese *et al.* 2012; Sahai *et al.* 2010]. The majority of studies use quality of life scores as the primary outcome measure [Game *et al.* 2011; Gousse *et al.* 2011; Khan *et al.* 2009] and some combine these with voiding diaries to provide objective data on symptoms [Dowson *et al.* 2012; Nitti *et al.* 2016; Sahai *et al.* 2010; Veeratterapillay *et al.* 2014]. A few studies do not report any specific efficacy outcomes but it is inferred from discontinuation rates across treatment cycles [Frohme *et al.* 2010; Irwin *et al.* 2013; Kuschel *et al.* 2008; Mohee *et al.* 2013; Veeratterapillay *et al.* 2014].

Urodynamic outcomes

There are two studies which assess changes in urodynamic parameters after repeat injections. Sahai and colleagues showed a significant improvement in maximum cystometric capacity (MCC), a decrease in maximum detrusor pressure and no reduction in bladder compliance (BC) across three injections Sahai *et al.* [2010]. This was confirmed by Granese and colleagues who found a persistent improvement in MCC and BC after the second treatment cycle and an average duration of urodynamic efficacy of 9 months [Granese *et al.* 2012].

Voiding diaries

Voiding diaries following repeat injections have been analysed by four studies [Abeywickrama *et al.* 2014; Dowson *et al.* 2012; Nitti *et al.* 2016; Sahai *et al.* 2010]. These studies have demonstrated an improvement in frequency, urgency, and urgency incontinence (UI) compared with baseline. The phase III extension study showed an absolute reduction of UI episodes of around three per day which was sustained across six treatment cycles [Nitti *et al.* 2016]. This was combined with a consistent increase in volume voided, a reduction in urgency episodes and a decrease in frequency episodes. Abeywickrama and colleagues reported an improvement in nocturia which was constant across three injections [Abeywickrama *et al.* 2014].

Quality of life and patient satisfaction scores

The early studies evaluated quality of life using the Urinary Distress Inventory 6 (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) [Dowson *et al.* 2012; Game *et al.* 2011; Sahai *et al.* 2010]. Dowson and colleagues and Game and colleagues have shown a consistent improvement in both scores following up to five injections [Dowson *et al.* 2012; Game *et al.* 2011].

Table 1. Summary of studies.

Study	Design	Level of evidence*	Patients	Preparation and dose	Duration of follow up	Maximum injections	Injection interval	Outcome measures
Kuschel *et al.* [2008]	Prospective longitudinal study	2	26	BOTOX 100 U	2 years[$†]	3 injections	14 months[$] (range 5–26)	Discontinuation rates after 2 years of follow up
Khan *et al.* [2009]	Prospective longitudinal study	2	81	BOTOX 200 U	2.8 years[$] (range 0.3–5.7)	6 injections	14 months[†] (IQR 11–17)	Quality of life scores (UDI-6 and IIQ-7) after first and subsequent injections
Sahai *et al.* [2010]	Prospective longitudinal study	2	34	BOTOX 100–300 U	Up to 4 years	4 injections	14 months[†]	After first and subsequent injections: Urodynamics for maximum of 3 cycles Voiding diaries Quality of life scores (UDI-6 and IIQ-7)
Frohme *et al.* [2010] (in German)	Prospective case series	3	40	Dysport 500 U	9 months[†] (range 1–45)	4 injections	6 months[$] (range 2–10)	Voiding diaries after first and subsequent injections
Game *et al.* [2011]	Retrospective case series	3	42	BOTOX 200 U	2.3 years[$]	5 injections	17.1 months[$]	Quality of life scores (UDI-6, IIQ-7 and EQ-5D) after first and subsequent injections
Gousse *et al.* [2011]	Randomized controlled trial	1	60	BOTOX 100–150 U	3 years[$†]	6 injections	2 months[$†] (set by protocol)	Quality of life (UDI-6) and Global Impression (VAS) scores after first and subsequent injections
Dowson *et al.* [2012]	Prospective longitudinal study	2	100	BOTOX 100–300 U	NR	10 injections	10.7 months[$]	After first and subsequent injections: Voiding diaries Quality of life scores (UDI-6 and IIQ-7)
Granese *et al.* [2012]	Prospective cohort study	2	68	BOTOX 100 U	1.1 years[$]	2 injections	12 months[$]	After first and second injection: Urodynamics parameters Voiding diaries
Irwin *et al.* [2013]	Prospective case series	3	73	Dysport 250 U	NR	>4 injections	26.7 months[$]	Duration of effect and reinjection interval
Mohee *et al.* [2013]	Retrospective case series	3	104	BOTOX 100–200 U	⩾3 years	4 injections	8 months[$]	Discontinuation rates in patients with > 3 years of follow up
Abeywickrama *et al.* [2014]	Prospective case series	3	33	Dysport 500–750 U	Up to 7 years	>3 injections	17.2 months[$]	After first and subsequent 3 injections Voiding diaries Quality of life scores (ICIQ-SF)
Veeratterapillay *et al.* [2014]	Retrospective case series	3	96	BOTOX 200 U	3.2 years[†‡]	8 injections‡	14.4 months[†‡]	Discontinuation rates in patients with ⩾1 injection
Nitti *et al.* [2016]	Prospective longitudinal study	2	829	BOTOX 100 U	3.2 years[†]	6 injections	7.6 months[§]	After first and subsequent 6 injections in patients with 3.5 years of follow up: Voiding diaries Quality of Life scores (I-QOL, KHQ and TBS)

*Level of evidence was rated according to a modified Oxford system as used by the European Urology Association [Thuroff *et al.* 2011].
[$]Mean.
[†]Median.
‡Includes IDO (96 patients) and NDO (29 patients).
[§]Time to request for treatment.
EQ-5D, EuroQol five-dimensional; ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; IDO, idiopathic detrusor overactivity; IIQ-7, Incontinence Impact Questionnaire 7; I-QOL, Incontinence Quality of Life Questionnaire; IQR, interquartile range; KHQ, King's Health Questionnaire; NDO, neurogenic detrusor overactivity; NR, not reported; TBS, Treatment Benefit Scale; UDI-6, Urinary Distress Inventory 6; VAS, visual analogue scale.

Table 2. Number of repeat injections.

Study	Number of injections									
	1	2	3	4	5	6	7	8	9	10
Kuschel *et al.* [2008]	26	11	1	–	–	–	–	–	–	–
Khan *et al.* [2009]	81	24	13	6	4	1	–	–	–	–
Sahai *et al.* [2010]	34	20	9	9	–	–	–	–	–	–
Frohme *et al.* [2010] (in German)	40	15	4	1	–	–	–	–	–	–
Game *et al.* [2011]	42	42	16	12	10	–	–	–	–	–
Gousse *et al.* [2011]	60	36	23	16	12	9	–	–	–	–
Dowson *et al.* [2012]	100	53	20	13	10	5	3	1	1	1
Granese *et al.* [2012]	68	20	–	–	–	–	–	–	–	–
Veeratterapillay *et al.* [2014]*$	–	125	60	28	14	3	3	2	–	–
Nitti *et al.* [2016]	829	608	388	273	185	139	–	–	–	–

*Includes patients with idiopathic detrusor overactivity and NDO.
$All patients received repeat injections.
NDO, neurogenic detrusor overactivity; NR, not reported.

Recent studies have included global satisfaction scores and alternative questionnaires such as the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) [Abeywickrama *et al.* 2014], Incontinence Quality of Life questionnaire (I-QOL) and Treatment Benefit Scale (TBS) [Nitti *et al.* 2016]. These show that high quality of life scores and satisfaction rates, up to 90%, are consistent across treatment cycles.

Different preparations

AbobotulinumtoxinA (Dysport, Ipsen Biopharm Ltd, Slough, UK) and onabotulinumtoxinA are both type A serotypes but they are manufactured using different isolation, purification and extraction processes [Brin *et al.* 2014]. This results in different dosing units and they cannot be used interchangeably [Mangera *et al.* 2011]. The majority of published studies use onabotulinumtoxinA (BOTOX) as the only licensed preparation for refractory IDO [Dowson *et al.* 2012; Game *et al.* 2011; Gousse *et al.* 2011; Granese *et al.* 2012; Khan *et al.* 2009; Kuschel *et al.* 2008; Mohee *et al.* 2013; Nitti *et al.* 2016; Sahai *et al.* 2010; Veeratterapillay *et al.* 2014]. There are three studies which report the outcomes for abobotulinumtoxinA [Abeywickrama *et al.* 2014; Frohme *et al.* 2010; Irwin *et al.* 2013]. These are smaller cohorts with fewer repeat injections and shorter follow up. They are spread across a range of doses for abobotulinumtoxinA from 250 to 750 U. This wide range of doses makes comparisons between preparations challenging. The recommended dose conversion ratio is 3:1 (Dysport:BOTOX) [Irwin *et al.* 2013; Sampaio *et al.* 2004]; however, this ratio has been controversial, with some studies suggesting the true ratio lies between 2 and 2.5:1 [Ravindra *et al.* 2013].

The most extensive study is a prospective case series including 33 women who had more than three injections of Dysport 500 or 750 U [Abeywickrama *et al.* 2014]. This study found a significant and sustained improvement in urinary frequency and quality of life scores across three treatment cycles. Given the limited data and uncertainties around dosage of abobotulinumtoxinA, it appears that more studies are needed to confirm the long-term efficacy and safety profile of abobotulinumtoxinA.

Duration of effect

The duration of effect is an important factor for counselling patients and planning clinical services. High-volume centres have increasing numbers of patients undergoing multiple repeat injections and need to plan availability of reinjection resources. The majority of studies report the 'reinjection interval' and there is a wide range in the published data from 6 months to 26.7 months [Frohme *et al.* 2010; Irwin *et al.* 2013]. Two studies report a significant increasing interval with each injection [Abeywickrama *et al.* 2014; Irwin *et al.* 2013], two studies report a decreasing

interval [Dowson *et al.* 2012; Sahai *et al.* 2010] and two did not find any change in interval across each injection [Khan *et al.* 2009; Veeratterapillay *et al.* 2014].

The variability of results is likely because the reinjection interval is not an accurate method of evaluating duration of effect as it can be confounded by multiple local factors such as waiting lists, minimum injection intervals [Sahai *et al.* 2010; Veeratterapillay *et al.* 2014] and concomitant use of antimuscarinics to delay retreatment [Dowson *et al.* 2012; Sahai *et al.* 2010; Veeratterapillay *et al.* 2014]. A more reliable definition is used by the phase III extension study that reports the reinjection request time [Nitti *et al.* 2016]. The mean time between requests for reinjection was 7.6 months but this was equally distributed between patients requesting retreatment before 6 months, from 6 to 12 months, and beyond 12 months. The longitudinal analysis showed that this request time either increased or remained stable across the six treatment cycles [De Ridder *et al.* 2015]. A mean duration of efficacy of approximately 7–8 months is consistent with reports in neurogenic overactive bladder [Apostolidis *et al.* 2009] and in urodynamic studies showing return of detrusor contractility after BoNT-A injection [Rovner *et al.* 2011].

Adverse events

Urinary tract infection

Urinary tract infections (UTIs) are common after any endoscopic procedure but are more common following BoTN-A injection. The combined safety data from the two pivotal RCTs reported a rate of 25.5% with onabotulinumtoxinA and 9.6% with placebo. The definition of UTI was a positive urine culture with bacteriuria count of more than 10^5 colony-forming units/ml, together with leukocyturia of over five per high power field, even in the absence of symptoms [Sievert *et al.* 2014].

The long-term extension study for one to six injections reported UTI rates as 17.0%, 16.1%, 17.5%, 14.7%, 13.5% and 14.4%, respectively [Nitti *et al.* 2016]. Problems with recurrent UTIs post BoNT-A have been identified as the primary reason for cessation of treatment in 16.7% of patients undergoing repeat injection [Mohee *et al.* 2013].

Voiding dysfunction and clean intermittent self-catheterization use

The risk of clean intermittent self-catheterization (CISC) due to voiding dysfunction is particularly concerning for patients with OAB who are less likely to have prior experience with catheterization. Mohee and colleagues found that the need for CISC was the most common reason for cessation of treatment in a cohort in which two-thirds of patients had discontinued treatment at 3-year follow up [Mohee *et al.* 2013]. The rate of CISC is dose dependent. The phase III extension study has reported a CISC rate of 6.5% [Sievert *et al.* 2014] for 100 U. However, earlier studies have suggested higher rates and have had different criteria to instigate CISC [Brubaker *et al.* 2008; Sahai *et al.* 2007].

Following a repeat injection, the risk of CISC is highly dependent on whether CISC has been required in previous treatment cycles. Khan and colleagues showed that the need for CISC remained stable over multiple injections and patients who required CISC after the first injection generally needed it with repeat injections [Khan *et al.* 2009].

Other adverse events

Other side effects of botulinum toxin include haematuria, dysuria, complicated UTI and generalized muscle weakness. No study has reported worsening risk of haematuria or significant pain that persists after repeated injections. There are individual reports of patients with IDO experiencing general muscle weakness which is transient and resolves within a few weeks after the injection [Jeffery *et al.* 2007]. This rare side effect is more common in neurological patients but is seen in IDO at higher doses [Kuo *et al.* 2010]. No study has shown that this side effect occurs more frequently with repeat injections in IDO, although in patients with neurogenic overactive bladder there have been reports of cases of generalized muscle weakness which reoccurred with repeat injections [Pannek *et al.* 2009].

Histological and immunological effects

Histological effects

Although the action of single BoNT-A injections is reversible, there have been theoretical concerns that multiple injections could cause irreversible

histological changes, such as bladder fibrosis leading to reduced BC. Early animal studies suggested BoNT-A injections led to apoptosis of the bladder urothelium and other studies have shown that it causes prostate atrophy by activating apoptotic pathways in rats [Watanabe *et al.* 2010].

The results from animal experiments have not been replicated in human subjects [Kessler *et al.* 2010]. Histological analysis of bladder biopsies from patients who received up to four injections has shown no significant evidence of fibrosis, hyperplasia or dysplasia [Apostolidis *et al.* 2008]. Other histological studies have shown a reduction in bladder fibrosis [Comperat *et al.* 2006] and improved BC after up to four injections [Sahai *et al.* 2010]. Although the medium-term histological results are positive, supplementary data are needed to confirm the long-term effects of exposure to BoNT-A injections.

Immunological effects

As BoNT-A injections are formed of nonhuman proteins, they have the potential to act as antigens, leading to the formation of neutralizing antibodies [Naumann *et al.* 2013]. If produced in sufficient concentrations, these antibodies can inhibit the activity of botulinum toxin, leading to treatment resistance. The antigenicity of BoNT-A preparations depends on the amount of nonhuman protein which is presented to the immune system. The current formulations, on the market since 2001, have a reduced protein content with the aim of reducing the immunogenic potential of the toxin [Yablon *et al.* 2007].

A phase II dose-ranging randomized controlled trial in patients with OAB found antibodies in two patients (6.6%) receiving 150 U but their presence had no significant impact on efficacy [Denys *et al.* 2012]. Antibody formation has been more extensively studied in patients with neurogenic detrusor overactivity (NDO) and these studies have produced equivocal results depending on the detection method used. One study used a mouse diaphragm assay to demonstrate the formation of antibodies in 8 out of 25 patients with NDO up to three months following a repeat injection [Schulte-Baukloh *et al.* 2008]. In contrast, a prospective study of children with NDO used an enzyme-linked immunosorbent assay technique and found that while antibody titres may temporarily increase, they returned to baseline after 3 months and the presence of antibodies did not correlate with treatment failure [Kajbafzadeh *et al.* 2010]. A meta-analysis of five studies investigating antibody conversion across multiple BoNT-A indications showed that the risk of developing antibodies was 0.49% (11 out of 2240 patients) and only three patients became clinically unresponsive to treatment [Naumann *et al.* 2010].

None of the studies evaluating medium- to long-term outcomes in patients with OAB have specifically tested for the development of antibodies (Table 1). There are a few reports of nonresponse to treatment but it is important to distinguish between immunogenicity and other factors causing a poor response. There are multiple reasons for treatment failure, including improper vial storage, incorrect toxin reconstitution or poor administration techniques. Therefore, the long-term potential for antibody formation is not fully established and to reduce the potential for antibody formation it is recommended that patients on long-term treatment continue to receive the lowest effective dose at the longest dose interval.

Conclusion

The current literature shows that repeated BoNT-A injections are safe and efficacious in patients with OAB. There is high-quality evidence that efficacy following the first injection persists across multiple treatment cycles. Repeat injections do not appear to cause bladder fibrosis, antibody formation or increasing incidence of adverse events. There are no additional safety concerns from repeat injections although urinary tract infection and risk of clean intermittent self-catheterization remain an issue and high discontinuation rates outside of clinical trials require further investigation. The long-term outcomes are not as extensively reported, although medium-term results are encouraging with reasonable data up to six injections. Supplementary data from larger cohorts are required to confirm significant and sustained long-term efficacy and safety.

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Conflict of interest statement

DE-E has no conflicts of interest to declare. AS has been a trial investigator and advisor for Allergan Ltd, has received honoraria for speaking on behalf of Allergan Ltd and has received an unrestricted educational grant for research purposes.

References

Abeywickrama, L., Arunkalaivanan, A. and Quinlan, M. (2014) Repeated botulinum toxin type A (Dysport) injections for women with intractable detrusor overactivity: a prospective outcome study. *Int Urogynecol J* 25: 601–605.

Apostolidis, A., Dasgupta, P., Denys, P., Elneil, S., Fowler, C., Giannantoni, A. *et al.* (2009) Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. *Eur Urol* 55: 100–120.

Apostolidis, A., Jacques, T., Freeman, A., Kalsi, V., Popat, R., Gonzales, G. *et al.* (2008) Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. *Eur Urol* 53: 1245–1253.

Brin, M., James, C. and Maltman, J. (2014) Botulinum toxin type A products are not interchangeable: a review of the evidence. *Biologics* 8: 227–241.

Brubaker, L., Richter, H., Visco, A., Mahajan, S., Nygaard, I., Braun, T. *et al.* (2008) Refractory idiopathic urge urinary incontinence and botulinum a injection. *J Urol* 180: 217–222.

Chapple, C., Sievert, K., Macdiarmid, S., Khullar, V., Radziszewski, P., Nardo, C. *et al.* (2013) OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. *Eur Urol* 64: 249–256.

Comperat, E., Reitz, A., Delcourt, A., Capron, F., Denys, P. and Chartier-Kastler, E. (2006) Histologic features in the urinary bladder wall affected from neurogenic overactivity – a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. *Eur Urol* 50: 1058–1064.

Denys, P., Le Normand, L., Ghout, I., Costa, P., Chartier-Kastler, E., Grise, 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: 520–529.

De Ridder, D., Sussman, D., Sand, P., Sievert, K., Radomski, S., Jenkins, B. *et al.* (2015) Durable duration of effect and positive treatment response with long-term onabotulinumtoxinA treatment in patients with over-active bladder syndrome: final results of 3.5 years study. *Eur Urol* 14: 1–500.

Dowson, C., Watkins, J., Khan, M., Dasgupta, P. and Sahai, A. (2012) Repeated botulinum toxin type A injections for refractory overactive bladder: medium-term outcomes, safety profile, and discontinuation rates. *Eur Urol* 61: 834–839.

Frohme, C., Varga, Z., Olbert, P., Schrader, A., Hofmann, R. and Hegele, A. (2010) Wirkung Von Botulinumtoxin a in Der Ein- Und Mehrmaligen Behandlung Der Uberaktiven Blase [Effects of botulinum toxin type A in the single and repeated treatment of overactive bladder. A prospective analysis.]. *Urologe A* 49: 639–644 (in German).

Game, X., Khan, S., Panicker, J., Kalsi, V., Dalton, C., Elneil, S. *et al.* (2011) Comparison of the impact on health-related quality of life of repeated detrusor injections of botulinum toxin in patients with idiopathic or neurogenic detrusor overactivity. *BJU Int* 107: 1786–1792.

Gousse, A., Kanagarajah, P., Ayyathurai, R., Handa, P., Dabas, N. and Gomez, C. (2011) Repeat intradetrusor injections of onabotulinum toxin a for refractory idiopathic overactive bladder patients: a single-center experience. *Female Pelvic Med Reconstr Surg* 17: 253–257.

Granese, R., Adile, G., Gugliotta, G., Cucinella, G., Saitta, S. and Adile, B. (2012) Botox(®) for idiopathic overactive bladder: efficacy, duration and safety. Effectiveness of subsequent injection. *Arch Gynecol Obstet* 286: 923–929.

Irwin, P., Somov, P. and Ekwueme, K. (2013) Patient reported outcomes of abobotulinumtoxinA injection treatment for idiopathic detrusor overactivity: a pragmatic approach to management in secondary care. *J Clin Urol* 6: 59–63.

Jeffery, S., Fynes, M., Lee, F., Wang, K., Williams, L. and Morley, R. (2007) Efficacy and complications of intradetrusor injection with botulinum toxin A in patients with refractory idiopathic detrusor overactivity. *BJU Int* 100: 1302–1306.

Kajbafzadeh, A., Nikfarjam, L., Mahboubi, A. and Dianat, S. (2010) Antibody formation following botulinum toxin type A (Dysport) injection in children with intractable bladder hyper-reflexia. *Urology* 76: 233–237.

Kessler, T., Khan, S., Panicker, J., Elneil, S., Brandner, S., Fowler, C. *et al.* (2010) In the human urothelium and suburothelium, intradetrusor botulinum neurotoxin type A does not induce apoptosis: preliminary results. *Eur Urol* 57: 879–883.

Khan, S., Kessler, T., Apostolidis, A., Kalsi, V., Panicker, J., Roosen, A. *et al.* (2009) What a patient with refractory idiopathic detrusor overactivity should know about botulinum neurotoxin type A injection. *J Urol* 181: 1773–1778.

Kuo, H., Liao, C. and Chung, S. (2010) Adverse events of intravesical botulinum toxin a injections for idiopathic detrusor overactivity: risk factors and influence on treatment outcome. *Eur Urol* 58: 919–926.

Kuschel, S., Werner, M., Schmid, D., Faust, E. and Schuessler, B. (2008) Botulinum toxin-A for idiopathic overactivity of the vesical detrusor: a 2-year follow-up. *Int Urogynecol J Pelvic Floor Dysfunct* 19: 905–909.

Mangera, A., Andersson, K., Apostolidis, A., Chapple, C., Dasgupta, P., Giannantoni, A. *et al.* (2011) Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of BOTOX (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA). *Eur Urol* 60: 784–795.

Mohee, A., Khan, A., Harris, N. and Eardley, I. (2013) Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). *BJU Int* 111: 106–113.

Naumann, M., Boo, L., Ackerman, A. and Gallagher, C. (2013) Immunogenicity of botulinum toxins. *J Neural Transm* 120: 275–290.

Naumann, M., Carruthers, A., Carruthers, J., Aurora, S., Zafonte, R., Abu-Shakra, S. *et al.* (2010) Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX®)) across multiple indications. *Mov Disord* 25: 2211–2218.

Nitti, V., Dmochowski, R., Herschorn, S., Sand, P., Thompson, C., Nardo, C. *et al.* (2013) OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol* 189: 2186–2193.

Nitti, V., Ginsberg, D., Sievert, K., Sussman, D., Radomski, S., Sand, P. *et al.* (2016) Durable efficacy and safety of long-term onabotulinumtoxinA treatment in patients with overactive bladder syndrome: final results of a 3.5-year study. *J Urol* 196: 791–800.

Pannek, J., Göcking, K. and Bersch, U. (2009) Long-term effects of repeated intradetrusor botulinum neurotoxin A injections on detrusor function in patients with neurogenic bladder dysfunction. *BJU Int* 104: 1246–1250.

Ravindra, P., Jackson, B. and Parkinson, R. (2013) Botulinum toxin type A for the treatment of non-neurogenic overactive bladder: does using onabotulinumtoxinA (BOTOX®) or abobotulinumtoxina (Dysport®) make a difference? *BJU Int* 112: 94–99.

Rovner, E., Kennelly, M., Schulte-Baukloh, H., Zhou, J., Haag-Molkenteller, C. and Dasgupta, P. (2011) Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn* 30: 556–562.

Sahai, A., Dowson, C., Khan, M. and Dasgupta, P. (2010) Repeated injections of botulinum toxin-A for idiopathic detrusor overactivity. *Urology* 75: 552–558.

Sahai, A., Khan, M. and Dasgupta, P. (2007) Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol* 177: 2231–2236.

Sampaio, C., Costa, J. and Ferreira, J. (2004) Clinical comparability of marketed formulations of botulinum toxin. *Mov Disord* 19: S129–S136.

Schulte-Baukloh, H., Bigalke, H., Miller, K., Heine, G., Pape, D., Lehmann, J. *et al.* (2008) Botulinum neurotoxin type A in urology: antibodies as a cause of therapy failure. *Int J Urol* 15: 407–415.

Sievert, K., Chapple, C., Herschorn, S., Joshi, M., Zhou, J., Nardo, C. *et al.* (2014) OnabotulinumtoxinA 100U provides significant improvements in overactive bladder symptoms in patients with urinary incontinence regardless of the number of anticholinergic therapies used or reason for inadequate management of overactive bladder. *Int J Clin Pract* 68: 1246–1256.

Thuroff, J., Abrams, P., Andersson, K., Artibani, W., Chapple, C., Drake, M. *et al.* (2011) EAU guidelines on urinary incontinence. *Eur Urol* 59: 387–400.

Veeratterapillay, R., Harding, C., Teo, L., Vasdev, N., Abroaf, A., Dorkin, T. *et al.* (2014) Discontinuation rates and inter-injection interval for repeated intravesical botulinum toxin type A injections for detrusor overactivity. *Int J Urol* 21: 175–178.

Watanabe, T., Masago, T. and Miyagawa, I. (2010) Apoptotic action of botulinum toxin on detrusor muscle in rats. *Urol Int* 84: 341–346.

Yablon, S., Brashear, A., Gordon, M., Elovic, E., Turkel, C., Daggett, S. *et al.* (2007) Formation of neutralizing antibodies in patients receiving botulinum toxin type A for treatment of poststroke spasticity: a pooled-data analysis of three clinical trials. *Clin Ther* 29: 683–690.