National Institute for Health and Care Excellence

Final

Urinary incontinence and pelvic organ prolapse in women: management

[D] Evidence reviews for the management of overactive bladder

NICE guideline NG123

Evidence reviews

April 2019

Final

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Management of women with overactive bladder

This evidence report contains information on two evidence reviews relating to the management of women with overactive bladder (OAB).

- What is the value of urodynamic assessment before botulinum toxin type A (BoNT-A) treatment?
- What is the most effective initial dose of BoNT-A for treating OAB?

Urodynamic assessment before botulinum toxin type A treatment

Review question

What is the value of urodynamic assessment before botulinum toxin type A treatment?

Introduction

The aim of this review is to determine whether urodynamic assessment provides additional useful information to the clinical assessment of eligibility for botulinum toxin type A in women with OAB and the comparative effects of BoNT-A treatment in women with OAB with and without detrusor overactivity confirmed by urodynamic assessment. The committee agreed that only women who had proven detrusor overactivity identified by urodynamic investigation should be considered for this treatment.

This was based on biological plausibility that the pharmacological action of BoNT-A paralyses the detrusor muscle so that it is no longer contracts involuntarily and therefore is probably only effective in women in whom detrusor overactivity is the cause of OAB. Although this had not been analysed by scientific study, it was surmised that BoNT-A treatment is probably not effective for women in whom detrusor overactivity is not the cause of their symptoms.

Summary of protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of protocol (PICO table)

Population	Women with overactive bladder (OAB) who may be eligible for BoNT-A to manage their symptoms. All women with OAB who have failed to respond to: • Conservative interventions (lifestyle, behavioural or bladder retraining) and • Anticholinergic drugs or beta-3 agonist drugs. Patients with neurological diseases will be excluded.
Intervention	Botulinum toxin A following: No urodynamic assessment • Multichannel urodynamic assessment not indicating detrusor overactivity.
Comparison	Botulinum toxin A following: • Multichannel urodynamic assessment indicating detrusor overactivity.

Outcome	**Critical outcomes**:
	• Continence status (e.g. number of incontinent episodes per day in first 3 months after treatment)
	• Adverse effects of urodynamic testing
	  ○ urinary infection
	  ○ dysuria
	  ○ haematuria

	• Continence specific health-related quality of life (ICIQ, BFLUTS, I-QOL, SUIQQ, UISS, SEAPI-QMM, ISI and KHQ (all from previous guideline) and E-PAQ (new)). **Important outcomes**: • Adverse effects of surgery o Urgency o Urgency incontinence o Voiding difficulties • Adverse effects of botulinum toxin o Urinary tract infection o Requirement of self-catheterisation • Satisfaction o Patient Global Impression of Improvement (PGI-I) Change of management

BFLUTS: Bristol female urinary tract symptoms questionnaire; BoNT-A; botulinum toxin type A; E-PAQ: electronic personal health questionnaire; ICIQ: international consultation on incontinence modular questionnaire; I-QOL: incontinence quality of life questionnaire; ISI: incontinence severity score; KHQ: kings health questionnaire; OAB: overactive bladder; PGI-I: patient global impression of improvement; SEAPI-QMM: stress-related leak, emptying ability ,anatomy, protection, inhibition, quality of life, mobility and mental status incontinence classification system; SUIQQ: stress and urge incontinence and quality of life questionnaire; UISS: urinary incontinence severity score

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A – Review protocols.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

One study was identified for inclusion in this review (Jackson 2012), the study compared multichannel urodynamic assessment indicating detrusor overactivity to multichannel urodynamic assessment not indicating detrusor overactivity. This was a cohort study that examined intravesical botulinum toxin for idiopathic OAB syndrome without detrusor over-activity (DOA) on urodynamic assessment (see 'Summary of clinical studies included in the evidence review').

No clinical evidence was identified for the first comparison specified in the protocol (multichannel urodynamic assessment indicating detrusor overactivity *vs.* no urodynamic assessment)

See the literature search strategy in appendix B and the study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K – Excluded studies .

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included study.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Jackson 2012 Cohort study N=94 (75 patients with DOA; 19 patients without DOA) UK	Patients undergoing intravesical botulinum toxin injections for idiopathic OAB between 17 January 2009 and 6 November 2009 at Nottingham City Hospital	Urodynamic assessment before BoNT 200U in patients with DOA. Dilution: 20 x 1 ml Injection technique: Intra detrusor injection. Type of Anaesthesia: Local anaesthesia using flexible cystoscopy, and a non trigone-sparing approach.	Urodynamic assessment before BoNT 200U in patients without DOA. Dilution: 20 x 1 ml Injection technique: Intra detrusor injection. Type of Anaesthesia: Local anaesthesia using flexible cystoscopy, and a non trigone-sparing approach.	Response rates by urodynamic findings at 3 months. Reduction in mean voids (95% CI) per day at 3 months. Reduction in mean episodes of incontinence (95% CI) per 24 hour period at 3 months. Mean (95% CI) ICIQ-OAB) scores at 3 months. Mean (95% CI) ICIQ-UI scores at 3 months. Self-catheterisation rates at 3 months.	Study included males and females Gender - Female/N (% female) N = 78 (83%); proportion of females in each group (i.e. with or without DOA) not reported.

BoNT: botulinum toxin; CI: confidence intervals; DOA: detrusor overactivity; ICIQ-OAB: international consultation on incontinence modular questionnaire - overactive bladder; ICIQ-UI: international consultation on incontinence modular questionnaire – urinary incontinence; OAB: overactive bladder; U: units.

See also the study evidence tables in appendix D.

Quality assessment of clinical studies included in the evidence review

GRADE analysis was conducted for critical and important outcomes, including value of urodynamic assessment before BoNT-A and short-term complications. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical Evidence statements

Adverse effects of urodynamic testing (urinary infection, dysuria, haematuria)

No evidence was identified to inform this outcome.

Continence status

Mean change in incontinence episodes per 24 hours

Very low quality evidence from one cohort study (n=41) showed that there may be a clinically-important difference favouring a dose of 200 U BoNT-A over the standard licensed 100 U dose of BoNT-A on the reduction of incontinence episodes per 24 hours, at 3 months after treatment, in women with DOA compared to women without DOA (MD 0.20 [95% CI 0.04 to 0.26]), but there is uncertainty around the estimate of effect.

Quality of life

Mean change in ICIQ-OAB score

Very low quality evidence from one cohort study (n=30) showed that there may be a clinically-important difference favouring a dose of 200 U BoNT-A over the standard licensed 100 U dose of BoNT-A in mean change in ICIQ-OAB score at 3 months after treatment in women with DOA compared to women without DOA (MD -1.20 [95% CI -1.72 to -0.68]), but there is uncertainty around the estimate of effect.

Mean change in ICIQ-UI score

Very low quality evidence from one cohort study (n=30) showed that there may be a clinically-important difference favouring a dose of BoNT-A 200U over the standard licensed 100 U dose of BoNT-A in the mean change in ICIQ-UI score at 3 months after treatment in women without DOA compared to women with DOA (MD 1.30 [95% CI 0.27 to 2.33]), but there is uncertainty around the estimate of effect.

Adverse effect of stress urinary incontinence surgery (urgency, urgency incontinence, voiding difficulties

No evidence was identified to inform this outcome.

Adverse effects of botulinum toxin (urinary tract infection)

No evidence was identified to inform this outcome.

Satisfaction (PGI-I), change of management

No evidence was identified to inform this outcome.

Symptom reduction

Mean change in voids per day

Very low quality evidence from one cohort study (n=41) found no clinically-important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A on the reduction of voids per day at 3 months after treatment in women with and without DOA: MD 0.30 (95% CI to -0.85 to 1.45).

Requirement for self-catheterisation or indwelling catheterisation

Self-catheterisation rates

Very low quality evidence from one cohort study (n=94) found no clinically-important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A and 200 U BoNT-A on self-catheterisation rates at 3 months after treatment in women with and without DOA: RR 1.46 (95% CI 0.57 to 3.71).

Economic evidence statements

No economic studies were identified which were applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

For women undergoing urodynamic assessment, the committee prioritised self-reported continence status, and improvements in quality of life as critical outcomes following invasive treatment for OAB. The adverse effects of urodynamic testing including urinary tract infection are relatively common although rarely serious and were prioritised as critical by the committee. Symptom reduction (clinical improvement) and requirement for self-catheterisation or indwelling catheterisation were considered by the committee to be the most important adverse effect of treatment with Botulinum toxin. The committee considered patient satisfaction (patient related improvement) and change in management to be important.

The quality of the evidence

For women undergoing urodynamic assessment, one cohort study was available but was downgraded because the number of women included in each treatment group was not reported (i.e. total number of patients included both men and women), and data were only available for a small proportion of patients within each group. The study was considered to be of very low quality for all outcomes reported.

No evidence was identified for one critical outcome: adverse effects of urodynamic testing and four important outcomes: adverse effect of stress urinary incontinence surgery (urgency, urgency incontinence, voiding difficulties), adverse effects of botulinum toxin (urinary tract infection), satisfaction (PGI-I), change of management.

It was not possible to separate the available evidence for women with urgency incontinence (OAB wet) and women with urgency without incontinence (OAB dry).

Benefits and harms

The committee based their recommendations on the data presented and using their clinical expertise and experience.

The committee was presented with effectiveness data on the use of urodynamic assessment before BoNT-A in patient with and without DOA from one small cohort study. The committee agreed that there was no evidence available to either recommend or not recommend urodynamic testing before BoNT-A treatment. Therefore, the committee agreed to carry forward the recommendation from the 2013 guideline, to offer BoNT-A, after MDT review, to women with OAB caused by proven DOA that has not responded to conservative management (including OAB drug therapy), as they believed that it was still relevant to current clinical practice.

The committee discussed the aim of urodynamic testing in patients with OAB symptoms, to show that DOA is the underlying cause of their symptoms. The 2013 guidance recommended treatment with BoNT-A after MDT review for women with OAB caused by DOA, but treatment with percutaneous sacral nerve stimulation for patients (P-SNS) with OAB symptoms. This inconsistency in the guideline could result in patients, who might otherwise benefit from treatment with Botulinum toxin receiving P-SNS or a more invasive treatment, or being offered no further treatment, and therefore the committee agreed to extend the recommendation to women in whom detrusor overactivity has not been demonstrated, and that a decision on whether to give BoNT-A to women with OAB should be based on a more comprehensive symptom history, rather than solely DOA proven by urodynamic testing. This was based on their clinical expertise and experience and developed by consensus.

Cost effectiveness and resource use

There was no economic evidence identified to address the question of whether or not urodynamic testing was cost-effective before giving BoNT-A. The committee considered the lack of clinical and economic evidence comparing urodynamic assessment to no such assessment before BoNT-A treatment for women with OAB. The committee explained that generally urodynamic assessment should continue to be performed before treatment with BoNT-A. This would not incur significant extra resource implications since this recommendation is reinforcing standard care practice in the NHS. The 2013 guidance recommended treatment with BoNT-A for women with OAB caused by DOA but treatment with P-SNS for women with OAB symptoms. The committee noted that they were aware of studies where BoNT-A was proven to be effective without prior urodynamic testing and considering it in women with OAB symptoms in whom DOA has not been demonstrated (using urodynamic testing) and where other treatments are not acceptable may have potential cost savings to the NHS i.e. fewer women receiving P-SNS and other more invasive treatments. The committee also explained that current situation could result in women, who might otherwise benefit from treatment with BoNT-A being offered no treatment. Making sure that such women are offered appropriate treatment could have significant implications for future health and costs. For example, not being offered appropriate treatment may exacerbate symptoms associated with OAB and may require expensive specialist NHS care at a later stage.

Other factors the committee took into account

None identified.

References

Jackson 2012

Jackson,B.L., Burge,F., Bronjewski,E., Parkinson,R.J., Intravesical botulinum toxin for overactive bladder syndrome without detrusor overactivity, British Journal of Medical and Surgical Urology, 5, 169-173, 2012.

Botulinum toxin type A – treatment dose for OAB management

Review question

What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Introduction

The aim of this review is to determine the clinical and cost effectiveness of an initial dose of 100-unit botulinum toxin type A (100 U BoNT-A) compared with 200 U BoNT-A in women with overactive bladder (OAB) as new evidence has become available since the publication of the previous guideline CG171 where recommendations were made to offer a dose of 200 U of BoNT-A but to consider 100 U of BoNT-A for women who would prefer a dose with a lower chance of catheterisation and accept a reduced chance of success.

Summary of the protocol

See Table 3 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 3: Summary of protocol (PICO table)

Population	Women over 18 years of age with OAB who may be eligible for botulinum toxin type A to manage their symptoms:
	
	• All women whose OAB has failed to respond to:
	  ○ conservative interventions (lifestyle behavioural or bladder retraining) and
	  ○ anti-cholinergic drugs or beta-3 agonist drugs.
	
	Women with OAB irrespective of whether urodynamic testing was carried out before treatment.
	
	Women who are treatment naïve to botulinum toxin type A (BoNT-A).

Intervention	100-units BoNT-A
Comparison	200-units BoNT-A
Outcome	**Critical outcomes**: • Continence status (e.g. number of incontinent episodes per day in first 3 months after treatment) • Continence specific health-related quality of life (ICIQ, BFLUTS, I-QOL, SUIQQ, UISS, SEAPI-QMM, ISI and KHQ (all from previous guideline) and E-PAQ (new)) • Requirement for self-catheterisation or indwelling catheterisation **Important Outcomes:** • Symptom reduction (e.g. number of urgency and frequency episodes per day in first 3 months after treatment) • Adverse effects (e.g. urinary infection, retention) • Satisfaction (patient rated improvement)

BFLUTS: Bristol female urinary tract symptoms questionnaire; BoNT-A; Botulinum toxin type A; E-PAQ: electronic personal health questionnaire; ICIQ: International consultation on incontinence modular questionnaire; I-QOL: incontinence quality of life questionnaire; ISI: incontinence severity score; KHQ: Kings health questionnaire; OAB:

overactive bladder; PGI-I: patient global impression of improvement; SEAPI-QMM: stress-related leak, emptying ability ,anatomy, protection, inhibition, quality of life, mobility and mental status incontinence classification system; SUIQQ: stress and urge incontinence and quality of life questionnaire; UISS: urinary incontinence severity score

For full details see review protocol in appendix A. The search strategies are presented in appendix B.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A – Review protocols.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Three studies were included in the review (Abdelwahab, 2015; Brubaker, 2012; Dmochowski, 2010) (see 'Summary of the clinical studies included in this review').

Abdelwahab (2015) was a randomised controlled trial (RCT) that examined the efficacy and safety of a single intra detrusor injection of botulinum toxin-A comparing two different doses (100 U or 200 U) in patients with idiopathic overactive bladder. Brubaker (2012) was a secondary publication to Dmochowski (2010), a phase II multicentre randomised, double-blind trial. Dmochowski (2010) examined change from baseline in number of weekly urge urinary incontinence (UUI) episodes, urodynamic assessments, quality of life (QOL) measures and adverse events. Brubaker (2012) assessed patient satisfaction using the modified version of the Overactive Bladder Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ).

See the literature search strategy in appendix B and the study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K – Excluded studies.

Summary of clinical studies included in the evidence review

Table 4 provides a brief summary of the included studies

Table 4: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Abdelwahab 2015 Randomised controlled trial	Patients with idiopathic overactive bladder refractory to previous anticholinergics	BoNT-A Type: Botox Dilution: 100U/1.0ml N=40	BoNT-A Type: Botox Dilution: 200U/1.0ml N=40	Mean change urgency episodes per day at months 1, 3, 6 and 9 after treatment.	Study included males and females Gender - Female/N (%)

Study	Population	Intervention	Comparison	Outcomes	Comments
N=80 Egypt	with different types of anticholinergic agents, either as a single drug or a combination for >3 months.	Injection technique: Cystoscopic intra detrusor injection performed in 20 sites, using 30-degree lens and a rigid scope with a 6 Fr. injection needle without side holes. Injection sites determined after mapping of the bladder at the anterior, left lateral, right lateral, posterior walls and the tirgone (0.5cc at each site). Type of Anaesthesia: Spinal anaesthesia	Injection technique: Cystoscopic intra detrusor injection performed in 20 sites, using 30-degree lens and a rigid scope with a 6 Fr. injection needle without side holes. Injection sites determined after mapping of the bladder at the anterior, left lateral, right lateral, posterior walls and the tirgone (0.5cc at each site). Type of Anaesthesia: Spinal anaesthesia	Mean change frequency per day at months 1, 3, 6 and 9 after treatment. Mean change urge urinary incontinence per day at months 1, 3, 6 and 9 after treatment. Mean change post void residual urine volume at months 1, 3, 6 and 9 after treatment. Mean change nocturia at months 1, 3, 6 and 9 after treatment. Mean change in patient symptoms (OABSS)[a] measured at 1, 3, 6, 9 months after treatment. Mean change in quality of life (EQ-5D)[b] measured at 1, 3, 6, 9 months after treatment Urodynamic outcomes measured at 3, 6, 9 months after treatment. Adverse effects at end of treatment.	N = 63 (78.75%)
Brubaker 2012 (Secondary article to Dmochowski 2010) Randomised, multicentre,	See Dmochowski 2010	See Dmochowski 2010	See Dmochowski 2010	Mean change from baseline in patient satisfaction (modified OAB-PSTQ[c]) assessed at baseline (day 0) and weeks 2,	

Study	Population	Intervention	Comparison	Outcomes	Comments
double-blind trial N= 313 (of which 272 completed the study) USA, Canada, UK, Germany, Belgium, Poland				6, 12, 18, 24, 30, and 36.	
Dmochowski 2010 Randomised, multicentre, double-blind trial N= 313 (of which 272 completed the study) USA, Canada, UK, Germany, Belgium, Poland	Patients aged 18 to 85 years with symptoms of OAB with UUI for at least 6 months immediately prior to screening, ≥ 8 UUI episodes per week with no more than 1 incontinence-free day/week, urinary frequency (defined as an average ≥ 8 micturitions/day), and not adequately managed with anticholinergic treatment (defined as an inadequate response to or intolerable side effects).	BoNT-A Type: Botox Dilution: 100U N=54 BoNT-A as 20 intradetrusor injections of 0.5 ml per site, evenly distributed into the detrusor muscle, avoiding the trigone and dome, via cystoscopy.	BoNT-A Type: Botox Dilution: 200U N=53 BoNT-A as 20 intradetrusor injections of 0.5 ml per site, evenly distributed into the detrusor muscle, avoiding the trigone and dome, via cystoscopy.	Patient bladder diary assessed on day 7, and at weeks 2, 6, 12, 18, 24, 30 and 36, for weekly UUI episodes. Adverse effects during study period.	Gender - Female/N (%): N = 288/313 (92%)

OAB-PSTQ: overactive bladder patient satisfaction with treatment questionnaire; OABSS: overactive bladder symptom score; PVR: post-void residual; QoL: quality of life; U: units; UUI: urge urinary incontinence

(a) OABSS is a single symptom score that employs a self-report questionnaire. There were 4-symptoms evaluated: daytime frequency, night time frequency, urgency and urge incontinence for the questionnaire. The score is the simple sum of the 4-symptom scores.
(b) Patient's current health-related QoL state was measured using EuroQoL (EQ-5D) visual analogue scale (VAS); both scales range from 0 to 100 (worst to best).
(c) OAB-PSTQ is a 16-item questionnaire, the 12-item validated questionnaire main module (Q2–Q13) constituted the total OAB-PSTQ score and included content assessing medication impact on various symptoms of OAB and incontinence; impact of medication on the ability to interact more freely in social situations, activities, and relationships; and cost. In the modified OAB-PSTQ instrument, the additional unvalidated questions expanded the content to include: (Q1) patient satisfaction with their most recent treatment (note that for assessment at baseline [day 0], patients rated their satisfaction with their most recent treatment [e.g., oral anticholinergic] prior to study enrolment); (Q14) patient subjective assessment of the severity of side effects; (Q15) patient personal treatment goals (limit of 2) and achievement of these goals; and (Q16) patient personal expectations (limit of 2) of treatment and achievement of these expectations.

See also the study evidence tables in appendix D. No meta-analysis was conducted for this review (and so there are no forest plots in appendix E).

Quality assessment of clinical studies included in the evidence review

GRADE analysis was conducted for critical and important outcomes, including effectiveness of different treatment doses and short term complications. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical Evidence statements

Continence status

Urge urinary incontinence

Low and very low quality evidence from one RCT (n=80) showed no clinically-important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A on urge urinary incontinence (UUI) at 1 (MD 0.05 [95% CI -0.52 to 0.62]), 3 (MD 0.13 [95% CI -0.70 to 0.96]), 6 (MD 0.08 [95% CI -0.89 to 1.05]) and 9 months (MD 0.71 [95% CI -0.22 to 1.64]) in women with OAB.

Quality of life

Continence specific quality of life

Very low quality evidence from one RCT (n=80) showed no clinically-important difference between a dose of 200 U BoNT and the standard licensed dose of 100 U BoNT on QoL (measured using EQ-5D) at 1 month in women with OAB: MD -1.10 (95% CI -5.85 to 3.65). Very low quality evidence from the same RCT (n=80) showed that there may be a clinically important difference favouring the standard licensed dose of 100 U BoNT -A over 200 U BoNT-A on QoL at 3 (MD -6.80 [95% CI -13.91 to 0.31]) and 6 months (MD -5.80 [95% CI -11.77 to 0.17]) in women with OAB, but there is uncertainty around the estimates.

Very low quality evidence from the same RCT (n=80) showed a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A on QoL at 9 months in women with OAB: MD -10.50 (95% CI -15.66 to -5.34).

Requirement for self-catheterisation or indwelling catheterisation

PVR related catheterisation

Very low quality evidence from one RCT (n=107) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 BoNT-A in the number of women requiring PVR related catheterisation (CIC or indwelling) at 9 months: RR 0.52 (95% CI 0.21 to 1.29).

Symptom reduction

Frequency

Very low quality evidence from one RCT (n=80) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A on frequency at 1 (MD 0.10 [95% CI -0.16 to 0.36]) and 3 months (MD 0.16 [95% CI -0.15 to 0.47]) in women with OAB Evidence from the same RCT (n=80) showed that there may be a clinically important difference favouring a dose of 200 U BoNT-A over the standard licensed dose of 100 U BoNT-A on urinary frequency at 6 (MD 0.28 [95% CI -0.03 to 0.59]) and 9 months (MD 0.85 [95% CI 0.54 to 1.16]) in women with OAB, but there is uncertainty around the estimate.

Urgency

Very low quality evidence from one RCT (n=80) showed a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A on urgency episodes at 1 (MD -0.53 [95% CI -0.95 to -0.11]) and 3 months (MD -0.41 [95% CI -0.77 to -0.05]) in women with OAB. Evidence from the same RCT (n=80) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A on urgency episodes at 6 (MD -0.31 [95% CI -0.70 to 0.08]) and 9 months (MD 1.07 [95% CI 1.07 [95% CI 0.72 to 1.42]) in women with OAB.

PVR urine volume

Very low quality evidence from one RCT (n=80) showed a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A on post-void residual (PVR) urine volume at 1 month (MD -5.72 [95% CI -11.18 to -0.26]) in women with OAB. The same RCT (n=80) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A on PVR urine volume at 3 (MD -0.41 [95% CI -0.77 to -0.05]), 6 (MD -0.31 [95% CI -0.70 to 0.08]) and 9 months (MD 1.07 [95% CI 0.72 to 1.42]) in women with OAB.

PVR urine volume 200ml or greater

Very low quality evidence from one RCT (n=107) showed that there may be a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A on the number of women with PVR urine volume 200ml or greater at 9 months: RR 0.50 (95% CI 0.23 to 1.09) but there is uncertainty around the estimate.

Nocturia

Very low quality evidence from one RCT (n=80) showed a clinically important difference favouring a dose of 200 U BoNT-A over the standard licensed dose of100 U BoNT-A for nocturia at 1 (MD 0.41 [95% CI 0.04 to 0.78]) and 9 months (MD 0.57 [95% CI 0.19 to 0.95]) in women with OAB. Evidence from the same RCT (n=80) showed that there may be a clinically important difference favouring a dose of 200 U BoNT-A over the standard dose of 100 U BoNT-A for nocturia at 3 months (MD 0.33 [95% CI -0.04 to 0.70]) in women with OAB, but showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A at 6 months in women with OAB: MD 0.34 (95% CI -0.07 to 0.75).

OAB Symptom Score

Low and very low quality evidence from one RCT (n=80) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A on overactive bladder symptom scores (OABSS) at 1 (MD 0.03 [95% CI -0.66 to 0.72]), 3 (MD 0.22 [95% CI -0.42 to 0.86]) and 6 months (MD 0.41 [95% CI -0.49 to 1.31]) in women with OAB. Very low quality evidence from the same RCT (n=80) showed a clinically important difference favouring a dose of 200 U BoNT-A over the standard licensed dose of 100 U BoNT-A on OABSS at 9 months in women with OAB: MD 3.20 (95% CI 2.40 to 4.00).

Adverse events

Very low quality evidence from a single RCT (n=76) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A in the number of women reporting UTIs (RR 0.40 [95% CI 0.08 to 1.94]), haematuria (RR 0.67 [95% CI 0.20 to 2.18]) at 9 months in women with OAB. Very low quality evidence from a second single RCT (n=107) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A in the number of women reporting urinary retention (RR 0.79 [95% CI 0.37 to 1.67]), treatment related adverse events (RR 0.95 [95% CI 0.58 to 1.54]) or total number of adverse events (RR 0.95 [95% CI 0.79 to 1.13]) at 9 months in women with OAB.

Very low quality evidence from a single RCT (n=76) showed there may be a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A in the number of women reporting dysuria at 9 months: RR 0.42 (95% CI 0.16 to 1.07), but there is uncertainty around the estimate.

Satisfaction

Modified overactive bladder patient satisfaction with treatment questionnaire (OAB-PSTQ)

Very low quality evidence from one RCT (n=97) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A in the proportion of women reporting being “somewhat satisfied” or “ very satisfied” at 12 weeks : RR 0.86 (95% CI 0.67 to 1.10).

Very low quality evidence from one RCT (n=96) showed a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A in the proportion of women reporting “mild side effects” or “no side effects” at 12 weeks: RR 1.18 (95% CI 1.03 to 1.34).

Very low quality evidence from one RCT (n=96) showed that there may be a clinically important difference favouring the standard licensed dose of 100 U BoNT-A over 200 U BoNT-A in the number of women reporting “significant progress” toward or “complete achievement” of primary goal of treatment after 12 weeks: RR 0.72 (95% CI 0.50 to 1.03), respectively), but there is uncertainty around the estimate.

Very low quality evidence from one RCT (n=95) showed no clinically important difference between a dose of 200 U BoNT-A and the standard licensed dose of 100 U BoNT-A in the proportion of women reporting that treatment “significantly met” or “exceeded” their primary expectation at 12 weeks: RR

Economic evidence statements

No economic evidence was identified which was applicable to the review question.

Research recommendations

1. What is the long-term effectiveness of bladder wall injection with Botulinum toxin A for OAB?

2. Is the duration of effect of Botulinum toxin A dose dependant? / What is the optimal frequency of repeat therapy?

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

For women treated with BoNT-A, the committee prioritised self-reported continence status, improvements in quality of life and requirement for self-catheterisation or indwelling catheterisation as critical outcomes following Botulinum toxin treatment for OAB. Symptom reduction (clinical improvement), adverse effects of treatment and patient satisfaction (patient related improvement) were agreed by the committee to be important outcomes of treatment with Botulinum toxin.

Committee consensus is that these are the most important aspects of treating overactive bladder and urgency urinary incontinence, as women want to have symptom reduction or become continent. A relatively low risk but significant risk of botox is the need for a catheter – this is an important consideration, and some women decline botox because of the risk of needing a catheter

The quality of the evidence

For women treated with different doses of BoNT-A, the two RCTs were assessed using the Cochrane Collaborations tool for assessing risk of bias. In addition, the evidence in the pairwise comparisons was assessed using the GRADE methodology.

Low and very low quality evidence from three reports of two RCTs was available for inclusion in this review (Abdelwahab, 2015; Brubaker, 2012; Dmochowski, 2010). Brubaker (2012) was a secondary publication to Dmochowski (2010) and only 2 of the 5 treatment arms of the phase II RCT were relevant to this review. Evidence was downgraded for risk of bias as well as for indirectness because the number of women included in each treatment group was not reported for each outcome, although over 66% of the overall study populations were women.

The overall study population was small, and no results could be pooled. Outcomes were reported at multiple time points up to 9 months.

No evidence was identified to assess continence specific health-related quality of life.

Benefits and harms

The committee based their recommendations on the data presented and using their clinical expertise and experience.

The committee was aware that there is no evidence available on the long-term effectiveness of bladder wall injection of Botulinum toxin, and there is no strong evidence regarding the dose, duration of effect being dose dependent, or what the optimal frequency is.

The committee was aware that at the time of the previous guidance, most BoNT-A preparations had not been licensed. However, it has subsequently been licensed and the Summary of Product Characteristics recommends the lower, standard licensed dose of 100 units for the management of overactive bladder with symptoms of urinary incontinence,

urgency and frequency. A 200 unit dose is recommended for the management of urinary incontinence due to neurogenic detrusor overactivity. The committee agreed that the recommendations should state that if prescribing off-label, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

The committee was presented with effectiveness data on BoNT A 100 units versus 200 units from two RCTs. The committee was aware that the evidence available was drawn from low quality trials. The committee agreed that there is no strong evidence to suggest that the main outcomes are inferior when starting treatment with 100 units of BoNT-A , but there may be a longer duration of effect in women treated with 200 units and there is potential for cost savings. Despite the weak evidence, the committee concluded that in women who have had only a short duration of response (less than 6 months) to 100 units, it was appropriate to offer an increased dose of 200 units. The committee noted that it is usual to expect the treatment to last for 6 months, and hence if it does not, an increase in dose is usually standard practice. The recommendation to use 100 units as the initial dose of BoNT-A was also informed by the recommendation in the Summary of Product Characteristics of the licensed drug.

The committee agreed that there was a lack of evidence available on the risk of adverse effects associated with the two different doses of BoNT-A, particularly in relation to self-catheterisation. The committee was aware from their own experience that there may be an increased risk of self-catheterisation with 200 units BoNT-A and that patients usually wish to avoid self-catheterisation if possible, and therefore may consent to start on the lower dose, but there was no evidence to support this. Although the lower dose (100 units BoNT-A) may result in some patients requiring more injections, the committee felt that on balance it was better to make recommendations to use 100 units as the initial dose of BoNT-A. The committee discussed presenting the recommendations in a clear and logical manner to provide a pathway to be followed in clinical practice, i.e. recommend the use of 100 units as the initial dose of BoNT-A, follow-up within 12 weeks and consider a dose of 200 units if women are willing to tolerate an increase in side effects. Follow up after 12 weeks if this approach is used.

The committee was aware that there was no strong evidence to support an increase in treatment dose to 200 units. The committee discussed whether to keep the statement concerning starting treatment with BoNT-A only if women have been trained in clean intermittent catheterisation and agreed that this was not necessary as recommendations regarding catheterisation remained unchanged from the previous guideline. Despite the limited evidence, the committee agreed that increasing subsequent doses of BoNT-A to 200 units is an effective strategy to generate improved response in women who have not had a satisfactory response to 100 units and in women who had a response lasting less than 6 months to 100 units. The recommendation to consider increasing subsequent doses of BONT-A to 200 units in these women was based on clinical experience and consensus.

The committee discussed recommendation “If the first botulinum toxin A treatment has no effect discuss with the MDT”, and suggested changing the recommendation to ‘If the botulinum toxin A treatment has no effect discuss with the MDT’. The change in recommendation was based on clinical experience and consensus.

The committee discussed the previous guideline recommendation “If botulinum toxin A treatment is effective, offer follow up at 6 months or sooner if symptoms return for repeat treatment without an MDT referral”. The committee discussed the process for follow up of women in clinical practice and it was suggested that women received a telephone call at 6 weeks or were seen at 3 months after their first injection. The committee agreed that the recommendation should be changed as follow up would not be offered as late as 6 months.

Cost effectiveness and resource use

There was no economic evidence on the cost-effectiveness of different doses of BoNT-A for treating overactive bladder. The committee considered the acquisition costs of BoNT-A i.e. £138.20 and £276.40, for a 100 unit and a 200 unit dose, respectively (BNF, 2018). The committee noted that the duration of effect associated with 200 unit dose is likely to be longer at approximately 9 months (versus 6 months for a 100 unit dose). The committee also estimated, based on their clinical experience, that approximately 70% of women with OAB are successfully managed using the lower 100 unit dose (that is, only 30% of women initiated on 100 unit dose need their dose increased to 200 units due to the lack of effect).

It was noted that the shorter duration of effect would imply the need for more frequent dosing that could be costly in terms of consumables and health professionals' time. However, the committee explained that the benefits of giving a 100 unit dose would not generally be offset by increasing the frequency of injections, as the treatment dose would be adjusted to a higher level rather than continuing with more frequent 100 unit treatments.

The committee noted the lower rate of dysuria associated with a 100 unit dose. This may result in fewer investigations (such as, urine dipstick, microscopy and culture, ultrasound, X-rays, urodynamic studies, and in some cases cystoscopy in a specialist setting) and cost savings to the NHS. A 100 unit dose was also associated with a reduction in post-void residual urine volume at 1 month after treatment and fewer women had a post-void residual urine volume of 200ml or more. As a result, there may be small cost savings associated with self-catheterisation primarily, through the reduction in consumables. As indicated by the clinical review there may also be potential improvements in QoL (measured using EQ-5D-3L) in women receiving a 100 unit dose. Overall, given the above considerations, the committee were of a view that a strategy where treatment with botulinum toxin type A is initiated at a lower 100 unit dose is likely to result in the cost savings to the NHS and potential improvements in health.

Other factors the committee took into account

None identified.

References

Abdelwahab 2015

Abdelwahab, O., Sherif, H., Soliman, T., Elbarky, I., Eshazly, A., Efficacy of botulinum toxin type A 100 Units versus 200 units for treatment of refractory idiopathic overactive bladder, International Braz J Urol, 41, 1132-40, 2015.

BNF 2018

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on 07/08/2018]

Brubaker 2012

Brubaker,L., Gousse,A., Sand,P., Thompson,C., Patel,V., Zhou,J., Jenkins,B., Sievert,K.D., Treatment satisfaction and goal attainment with onabotulinumtoxinA in patients with incontinence due to idiopathic OAB, International Urogynecology Journal, 23, 1017-1025, 2012.

Dmochowski 2010

Dmochowski,R., Chapple,C., Nitti,V.W., Chancellor,M., Everaert,K., Thompson,C., Daniell,G., Zhou,J., Haag-Molkenteller,C., Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial, Journal of Urology, 184, 2416-2422, 2010.

Appendices

Appendix A – Review protocols

Evidence review protocol for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment

Field (based on PRISMA-P	Content
Review question	What is the value of urodynamic assessment before botulinum toxin type A treatment?
Type of review question	Intervention
Objective of the review	Although a specific review of urodynamic testing before botulinum toxin A (BoNT-A) treatment in women with overactive bladder (OAB) was not performed in the previous guideline CG 171, the Committee concluded that only women who had proven detrusor overactivity identified by urodynamic investigation should be considered for this treatment. This was based on biological plausibility that the pharmacological action of BoNT-A paralyses the detrusor muscle so that it is no longer contracts involuntarily and therefore is probably only effective in women in whom detrusor overactivity is the cause of OAB. Although this had not been analysed by scientific study, it was surmised that BoNT-A treatment is probably not effective for women in whom detrusor overactivity is not the cause of their symptoms. The aim of this review is to determine whether urodynamic assessment provides additional useful information to the clinical assessment of eligibility for botulinum toxin type A in women with OAB and the comparative effects of BoNT-A treatment in women with OAB with and without detrusor overactivity confirmed by urodynamic assessment.
Eligibility criteria – population/disease/condition/issue/domain	Women with overactive bladder (OAB) who may be eligible for botulinum toxin type A to manage their symptoms. All women with OAB who have failed to respond to: Conservative interventions (lifestyle, behavioural or bladder retraining) and Anticholinergic drugs or beta-3 agonist drugs. Patients with neurological diseases will be excluded.

Field (based on PRISMA-P	Content
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Botulinum toxin A following: No urodynamic assessment Multichannel urodynamic assessment not indicating detrusor overactivity.
Eligibility criteria – comparator(s)/control or reference (gold) standard	Botulinum toxin A following: Multichannel urodynamic assessment indicating detrusor overactivity
Outcomes and prioritisation	Critical outcomes: Continence status (e.g. number of incontinent episodes per day in first 3 months after treatment) Adverse effects of urodynamic testing urinary infection dysuria haematuria Continence specific health-related quality of life (ICIQ, BFLUTS, I-QOL, SUIQQ, UISS, SEAPI-QMM, ISI and KHQ (all from previous guideline) and E-PAQ (new)). Important outcomes: Adverse effects of surgery Urgency Urgency incontinence Voiding difficulties Adverse effects of botulinum toxin Urinary tract infection Requirement of self-catheterisation Satisfaction Patient Global Impression of Improvement (PGI-I) Change of management
Eligibility criteria – study design	Systematic reviews of randomised controlled trials (RCTs) RCTs

Field (based on PRISMA-P	Content
	Conference abstracts of RCTs Comparative observational studies
Other inclusion exclusion criteria	Patients with neurological diseases will be excluded.
Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: older women women with physical disabilities women with cognitive impairment Special consideration of women who are considering future pregnancy was not prioritised for this question. The following groups will be assessed separately: Population subgroups: Urgency incontinence (OAB wet) Urgency without incontinence (OAB dry)
Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question, although there will be senior supervision of the selection process. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates from 1990.

Field (based on PRISMA-P	Content
Identify if an update	This is a new question in the guideline that is part of a broader chapter with other recommendations. It has impact on the following current recommendations in CG171 on urodynamic testing : 1.1.20 After undertaking a detailed clinical history and examination, perform multi-channel filling and voiding cystometry before surgery in women who have: • symptoms of OAB leading to a clinical suspicion of detrusor overactivity, or • symptoms suggestive of voiding dysfunction or anterior compartment prolapse, or • had previous surgery for stress incontinence. [2006, amended 2013] As well as recs 1.9.1 – 1.9.9 Red in particular 1.9.1 After an MDT review, offer bladder wall injection with botulinum toxin A to women with OAB caused by proven detrusor overactivity that has not responded to conservative management (including OAB drug therapy). [new 2013] 1.9.2 Discuss the risks and benefits of treatment with botulinum toxin A[6] with women before seeking informed consent, covering: • the likelihood of being symptom free or having a large reduction in symptoms • the risk of clean intermittent catheterisation and the potential for it to be needed for variable lengths of time after the effect of the injections has worn off • the absence of evidence on duration of effect between treatments and the long term efficacy and risks • the risk of adverse effects, including an increased risk of urinary tract infection. [new 2013] 1.9.3 Start treatment with botulinum toxin A[6] only if women: • have been trained in clean intermittent catheterisation and have performed the technique successfully, and • are able and willing to perform clean intermittent catheterisation on a regular basis for as long as needed. [new 2013] 1.9.4 Use 200 units when offering botulinum toxin A[6]. [new 2013] 1.9.5 Consider 100 units of botulinum toxin A[for women who would prefer a dose with a lower chance of catheterisation and accept a reduced chance of success. [new 2013] 1.9.6 If the first botulinum toxin A[6] treatment has no effect discuss with the MDT. [new 2013] 1.9.7 If botulinum toxin A[6] treatment is effective, offer follow up at 6 months or sooner if symptoms return for repeat treatment without an MDT referral. [new 2013]

Field (based on PRISMA-P	Content
	1.9.8 Tell women how to self refer for prompt specialist review if symptoms return following a botulinum toxin A[6] procedure. Offer repeat treatment as necessary. [new 2013] 1.9.9 Do not offer botulinum toxin B to women with proven detrusor overactivity. [2006]
Author contacts	Developer: The National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10035.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	The GRADE approach was used. For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – Current management	For details please see the introduction to the evidence review.

Field (based on PRISMA-P	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Dr Fergus Macbeth in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	Not registered with PROSPERO.

Evidence review protocol for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder

Field (based on PRISMA-P	Content
Review question	Amended in GC1= 4.2 What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?
Type of review question	Intervention
Objective of the review	The aim of this review is to determine the clinical and cost effectiveness of an initial dose of 100-unit botulinum toxin type A (new dose) compared with 200-unit botulinum toxin type A (dose recommended in CG171) in women with OAB.

Eligibility criteria – population/disease/condition/issue/domain	Women over 18 years of age with OAB who may be eligible for botulinum toxin type A to manage their symptoms:
	
	• All women with OAB who have failed to respond to:
	  ○ conservative interventions (lifestyle behavioural or bladder retraining) and
	  ○ anticholinergic drugs or beta-3 agonist drugs
	
	Women with OAB irrespective of whether urodynamic testing was carried out before treatment.
	
	Treatment naïve to botulinum toxin type A.

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	100 Botulinum toxin type A (BOTOX®)
Eligibility criteria – comparator(s)/control or reference (gold) standard	200-units Botulinum toxin type A (BOTOX®)
Outcomes and prioritisation	**Critical outcomes:** • Continence status (e.g. number of incontinent episodes per day in first 3 months after treatment) • Continence specific health-related quality of life (ICIQ, BFLUTS, I-QOL, SUIQQ, UISS, SEAPI-QMM, ISI and KHQ (all from previous guideline) and E-PAQ (new)) • Requirement for self-catheterisation or indwelling catheterisation

Field (based on PRISMA-P	Content
	Important Outcomes: • Symptom reduction (e.g. number of urgency and frequency episodes per day in first 3 months after treatment) • Adverse effects (e.g. urinary infection, retention) • Satisfaction (patient rated improvement)
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Comparative cohort studies will be included if no RCT evidence is retrieved.
Other inclusion exclusion criteria	Exclude • women who have previously been treated with botulinum toxin A for OAB • women with neurological disease
Proposed sensitivity/sub-group analysis, or meta-regression	Groups that will be reviewed and analysed separately, if possible: Population subgroups: • wet versus dry OAB Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • older women • women with physical disabilities • women with cognitive impairment Special consideration of women who are considering future pregnancy was not prioritised for this question.
Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question, although there will be senior supervision of the selection process. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.

Field (based on PRISMA-P	Content
	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates from 1990. For details please see appendix B.
Identify if an update	This area will update current recommendations in CG171 in red: This review is part of a broader chapter with other recommendations: 1.9.4 Use 200 units when offering botulinum toxin A[6]. [new 2013] 1.9.5 Consider 100 units of botulinum toxin A[for women who would prefer a dose with a lower chance of catheterisation and accept a reduced chance of success. [new 2013]
Author contacts	Developer: The National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10035.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix F.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P	Content
	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	The GRADE approach was used. For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Dr Fergus Macbeth in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	Not registered with PROSPERO.

Appendix B – Literature search strategies

Literature search strategies for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Database: Medline & Embase (Multifile)
Last searched on Embase 1974 to 2017 March 17, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date of last search: 17th March 2017.

#	Searches
1	Urinary Incontinence/ use ppez
2	urine incontinence/ use oemezd
3	Urinary Incontinence, Urge/ use ppez
4	urge incontinence/ use oemezd
5	mixed incontinence/ use oemezd
6	Urinary Bladder, Overactive/ use ppez
7	overactive bladder/ use oemezd
8	bladder instability/ use oemezd
9	Nocturia/ use ppez
10	nocturia/ use oemezd
11	exp Enuresis/ use ppez
12	exp enuresis/ use oemezd
13	((mix$ or urg$ or urin$) adj5 incontinen$).tw.
14	(bladder$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$ or incontinen$)).tw.
15	(detrusor$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$)).tw.
16	OAB.tw.
17	((urgency adj2 frequency) or (frequency adj2 urgency)).tw.
18	((urin$ or bladder$) adj2 (urg$ or frequen$)).tw.
19	(nocturia$ or enuresis$).tw.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Botulinum Toxins/ use ppez
22	exp botulinum toxin/ use oemezd
23	exp botulinum toxin A/ use oemezd
24	botulinum$.tw.
25	(botul$ adj2 tox$).tw.
26	(BTA or BTX or CNBTX or BoNT$ or BoTx).tw.
27	(botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum$ or abobotuli$ or onabotulinum$ or Neuronox or Meditoxin).tw.
28	21 or 22 or 23 or 24 or 25 or 26 or 27
29	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
30	29 use ppez
31	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
32	31 use oemezd
33	30 or 32
34	meta-analysis/
35	meta-analysis as topic/
36	systematic review/
37	meta-analysis/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
41	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43	(search* adj4 literature).ab.
44	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
45	cochrane.jw.
46	((pool* or combined) adj2 (data or trials or studies or results)).ab.
47	or/34-35,38,40-45 use ppez
48	or/36-39,41-46 use oemezd

#	Searches
49	47 or 48
50	letter/
51	editorial/
52	news/
53	exp historical article/
54	Anecdotes as Topic/
55	comment/
56	case report/
57	(letter or comment*).ti.
58	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59	randomized controlled trial/ or random*.ti,ab.
60	58 not 59
61	animals/ not humans/
62	exp Animals, Laboratory/
63	exp Animal Experimentation/
64	exp Models, Animal/
65	exp Rodentia/
66	(rat or rats or mouse or mice).ti.
67	60 or 61 or 62 or 63 or 64 or 65 or 66
68	letter.pt. or letter/
69	note.pt.
70	editorial.pt.
71	case report/ or case study/
72	(letter or comment*).ti.
73	68 or 69 or 70 or 71 or 72
74	randomized controlled trial/ or random*.ti,ab.
75	73 not 74
76	animal/ not human/
77	nonhuman/
78	exp Animal Experiment/
79	exp Experimental Animal/
80	animal model/
81	exp Rodent/
82	(rat or rats or mouse or mice).ti.
83	75 or 76 or 77 or 78 or 79 or 80 or 81 or 82
84	67 use ppez
85	83 use oemezd
86	84 or 85
87	20 and 28
88	remove duplicates from 87
89	limit 88 to english language
90	86 and 89
91	89 not 90

Database: Cochrane Library via Wiley Online
Date of last search: 17th March 2017

ID	Search
#1	MeSH descriptor: [Urinary Incontinence] this term only
#2	MeSH descriptor: [Urinary Incontinence, Urge] this term only
#3	MeSH descriptor: [Urinary Incontinence, Stress] this term only
#4	MeSH descriptor: [Urinary Bladder, Overactive] this term only
#5	MeSH descriptor: [Nocturia] this term only
#6	MeSH descriptor: [Enuresis] explode all trees
#7	((stress* or mix* or urg* or urin*) near/5 incontinen*):ti,ab,kw (Word variations have been searched)
#8	(bladder* near/5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex* or incontinen*)):ti,ab,kw (Word variations have been searched)
#9	OAB:ti,ab,kw (Word variations have been searched)
#10	((urgency near/2 frequency) or (frequency near/2 urgency)):ti,ab,kw (Word variations have been searched)
#11	((urin* or bladder*) near/2 (urg* or frequen*)):ti,ab,kw (Word variations have been searched)
#12	(detrusor* near/5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex*)):ti,ab,kw (Word variations have been searched)
#13	(nocturia* or enuresis*):ti,ab,kw (Word variations have been searched)
#14	SUI:ti,ab,kw (Word variations have been searched)
#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	MeSH descriptor: [Botulinum Toxins] explode all trees
#17	botulinum*:ti,ab,kw (Word variations have been searched)
#18	(botul* near/2 tox*):ti,ab,kw (Word variations have been searched)

ID	Search
#19	(BTA or BTX or CNBTX or BoNT* or BoTx):ti,ab,kw (Word variations have been searched)
#20	(botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum* or abobotuli* or onabotulinum* or Neuronox or Meditoxin):ti,ab,kw (Word variations have been searched)
#21	#16 or #17 or #18 or #19 or #20
#22	#15 and #21

Literature search strategies for review Question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Database: Medline & Embase (Multifile)
Last searched on Embase 1974 to 2017 March 16, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date of last search: 17th March 2017.

#	Searches
1	Urinary Incontinence/ use ppez
2	urine incontinence/ use oemezd
3	Urinary Incontinence, Urge/ use ppez
4	urge incontinence/ use oemezd
5	mixed incontinence/ use oemezd
6	Urinary Bladder, Overactive/ use ppez
7	overactive bladder/ use oemezd
8	bladder instability/ use oemezd
9	Nocturia/ use ppez
10	nocturia/ use oemezd
11	exp Enuresis/ use ppez
12	exp enuresis/ use oemezd
13	((mix$ or urg$ or urin$) adj5 incontinen$).tw.
14	(bladder$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$ or incontinen$)).tw.
15	(detrusor$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$)).tw.
16	OAB.tw.
17	((urgency adj2 frequency) or (frequency adj2 urgency)).tw.
18	((urin$ or bladder$) adj2 (urg$ or frequen$)).tw.
19	(nocturia$ or enuresis$).tw.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Botulinum Toxins/ use ppez
22	exp botulinum toxin/ use oemezd
23	exp botulinum toxin A/ use oemezd
24	botulinum$.tw.
25	(botul$ adj2 tox$).tw.
26	(BTA or BTX or CNBTX or BoNT$ or BoTx).tw.
27	(botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum$ or abobotuli$ or onabotulinum$ or Neuronox or Meditoxin).tw.
28	21 or 22 or 23 or 24 or 25 or 26 or 27
29	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
30	29 use ppez
31	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
32	31 use oemezd
33	30 or 32
34	meta-analysis/
35	meta-analysis as topic/
36	systematic review/
37	meta-analysis/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
41	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43	(search* adj4 literature).ab.
44	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
45	cochrane.jw.
46	((pool* or combined) adj2 (data or trials or studies or results)).ab.
47	or/34-35,38,40-45 use ppez
48	or/36-39,41-46 use oemezd
49	47 or 48
50	letter/
51	editorial/
52	news/

#	Searches
53	exp historical article/
54	Anecdotes as Topic/
55	comment/
56	case report/
57	(letter or comment*).ti.
58	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59	randomized controlled trial/ or random*.ti,ab.
60	58 not 59
61	animals/ not humans/
62	exp Animals, Laboratory/
63	exp Animal Experimentation/
64	exp Models, Animal/
65	exp Rodentia/
66	(rat or rats or mouse or mice).ti.
67	60 or 61 or 62 or 63 or 64 or 65 or 66
68	letter.pt. or letter/
69	note.pt.
70	editorial.pt.
71	case report/ or case study/
72	(letter or comment*).ti.
73	68 or 69 or 70 or 71 or 72
74	randomized controlled trial/ or random*.ti,ab.
75	73 not 74
76	animal/ not human/
77	nonhuman/
78	exp Animal Experiment/
79	exp Experimental Animal/
80	animal model/
81	exp Rodent/
82	(rat or rats or mouse or mice).ti.
83	75 or 76 or 77 or 78 or 79 or 80 or 81 or 82
84	67 use ppez
85	83 use oemezd
86	84 or 85
87	20 and 28
88	remove duplicates from 87
89	limit 88 to english language
90	86 and 89
91	89 not 90
92	33 or 49
93	91 and 92

Database: Cochrane Library via Wiley Online
Date of last search: 17th March 2017.

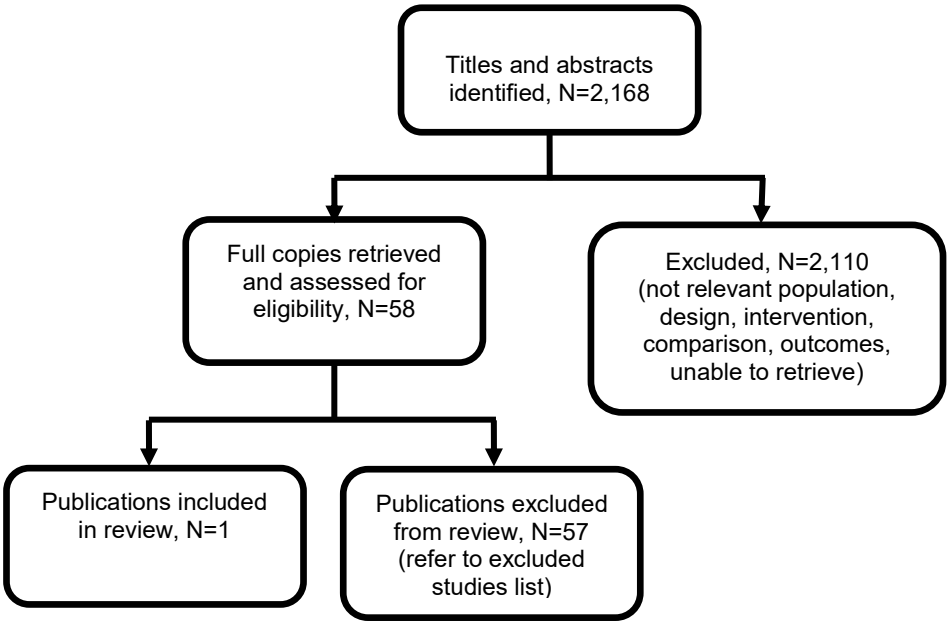
ID	Search
#1	MeSH descriptor: [Urinary Incontinence] this term only
#2	MeSH descriptor: [Urinary Incontinence, Urge] this term only
#3	MeSH descriptor: [Urinary Incontinence, Stress] this term only
#4	MeSH descriptor: [Urinary Bladder, Overactive] this term only
#5	MeSH descriptor: [Nocturia] this term only
#6	MeSH descriptor: [Enuresis] explode all trees
#7	((stress* or mix* or urg* or urin*) near/5 incontinen*):ti,ab,kw (Word variations have been searched)
#8	(bladder* near/5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex* or incontinen*)):ti,ab,kw (Word variations have been searched)
#9	OAB:ti,ab,kw (Word variations have been searched)
#10	((urgency near/2 frequency) or (frequency near/2 urgency)):ti,ab,kw (Word variations have been searched)
#11	((urin* or bladder*) near/2 (urg* or frequen*)):ti,ab,kw (Word variations have been searched)
#12	(detrusor* near/5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex*)):ti,ab,kw (Word variations have been searched)
#13	(nocturia* or enuresis*):ti,ab,kw (Word variations have been searched)
#14	SUI:ti,ab,kw (Word variations have been searched)
#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	MeSH descriptor: [Botulinum Toxins] explode all trees
#17	botulinum*:ti,ab,kw (Word variations have been searched)
#18	(botul* near/2 tox*):ti,ab,kw (Word variations have been searched)
#19	(BTA or BTX or CNBTX or BoNT* or BoTx):ti,ab,kw (Word variations have been searched)

ID	Search
#20	(botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum* or abobotuli* or onabotulinum* or Neuronox or Meditoxin):ti,ab,kw (Word variations have been searched)
#21	#16 or #17 or #18 or #19 or #20
#22	#15 and #21

Appendix C – Clinical evidence study selection

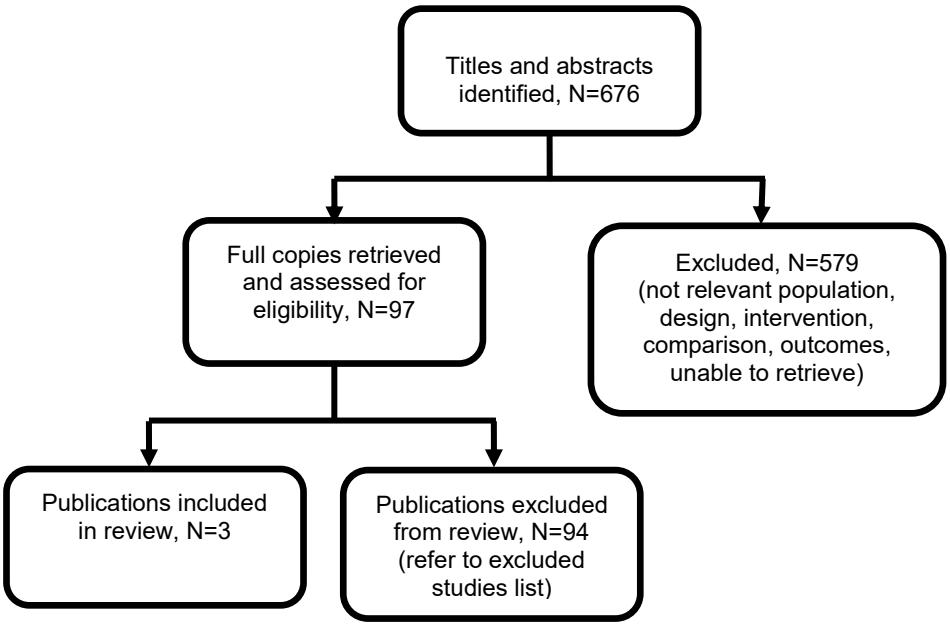
Clinical evidence study selection for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Figure 1: Flow chart of clinical evidence study selection for "what is the values of urodynamic assessment before botulinum toxin type A treatment?"



Clinical evidence study selection for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Figure 2: Flow chart of clinical evidence study selection for "what is the most effective initial dose of botulinum toxin type A for treating overactive bladder?"



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Jackson,B.L., Burge,F., Bronjewski,E., Parkinson,R.J., Intravesical botulinum toxin for overactive bladder syndrome without detrusor overactivity, British Journal of Medical and Surgical Urology, 5, 169-173, 2012 Ref Id 194807 Country/ies where the study was carried out UK Study type Prospective cohort Aim of the study A single hospital's experience of intravesical botulinum toxin for idiopathic overactive bladder syndrome (OAB) without detrusor overactivity (DOA) on	Sample size N = 94 patients 75 patients with DOA 19 patients without DOA Characteristics Gender - Female/N (%) N = 78 (83%) Without DOA on urodynamics: 16 (84%) female Age - Mean ± SD 59 (range 24 to 84) years Without DOA on urodynamics: 56 (range 37 to 81) years Inclusion criteria All patients undergoing intravesical botulinum toxin	Interventions Urodynamic assessment before BoNT 200U in patients with and without DOA Dilution: 20 x 1 ml Injection technique: Intra detrusor injection. Type of Anaesthesia: Local anaesthesia using flexible cystoscopy, and a non trigone-sparing approach.	Details All patients underwent treatment on a day case basis, and reviewed at 3 months to assess response. In addition, all patients underwent post-void residual volume estimation at 2 weeks, with intermittent self-catheterisation (ISC) being considered where residual volumes of over 150 ml were associated with symptoms of voiding dysfunction or urinary tract infections though to be due to incomplete bladder emptying in the opinion of the consultant urologist. Patients with asymptomatic high residuals were not commenced on ISC. Urodynamic assessment consisted of standard, non-ambulatory, non-video filling cystometry and pressure-flow studies	Results Reduction in mean (95% CI) voids per day - measured using bladder diaries Pre-treatment (N=41): 11.2 (12.6 to 9.9); Patients with DOA (N=28): 11.3 (13.1 to 9.5) Patients without DOA (N=13): 11 (13.1 to 8.9) Post-treatment: 6.3 (7.0 to 5.6) Patients with DOA: 6.5 (7.9 to 5.1) Patients without DOA: 5.9 (7.3 to 4.5) Reduction in mean (95% CI) episodes of nocturia Pre-treatment: 2.66 (3.2 to 2.1) Patients with DOA: 2.6 (3.3 to 2.0) Patients without DOA: 2.6 (3.7 to 1.6) Post-treatment: 1.35 (1.7 to 1.0) Patients with DOA: 1.4 (2.0 to 0.8) Patients without DOA: 1.2 (1.9 to 0.6)	Limitations Confounding bias: Low risk of bias Selection of participant's bias: Moderate risk of bias (only patients who had undergone urodynamic testing included) Classification of interventions bias: Low risk of bias Deviations from intended interventions bias: Low risk of bias Missing data bias: High risk of bias (>50% missing data for some outcomes) Measurement of outcomes bias: Serious risk of bias (self-reported

urodynamic assessment. Study dates 17 January 2009 to 6 November 2009. Source of funding None stated	injections for idiopathic OAB between 17 January 2009 and 6 November 2009 at Nottingham City Hospital Exclusion criteria Patients undergoing treatment for: • neuropathic bladder dysfunction • bypassing catheters, or • painful bladder syndrome Patients undergoing treatment without prior urodynamic assessment		carried out according to the standards of practice established by the International Continence Society. Patients were asked to discontinue anticholinergic medication 2 weeks prior to the test. Randomisation Not applicable Statistical analysis Primary outcome - patient-reported subjective improvement: binary outcome (Yes or No) to indicate responders (improved symptoms following treatment, with no additional treatment required). Response rates were calculated for patients with and without DOA on urodynamic assessment. The majority of outcome data were recorded at the 3-month follow-up visit, with some missing follow-up data obtained by contacting patients by telephone.	Reduction in mean (95% CI) episodes of incontinence per 24 hr period Pre-treatment: 3.6 (4.3 to 2.8) Patients with DOA: 3.8 (4.8 to 2.8) Patients without DOA: 3.1 (4.5 to 1.7) Post-treatment: 0.8 (1.3 to 0.3) Patients with DOA: 1.0 (2.0 to 0.0) Patients without DOA: 0.3 (0.7 to -0.1) Mean (95% CI) International Consultation on Incontinence Modular Questionnaire (ICIQ) scores Pre-treatment Patients with DOA (N=21): (13.2, 17.0 to 9.4) Patients without DOA (N=9): (12.0, 13.6 to 10.4) Post-treatment Patients with DOA: (4.8, 6.0 to 3.6) Patients without DOA: (4.8, 6.4 to 3.2) Mean (95% CI) ICIQ-UI scores Pre-treatment Patients with DOA (N=21): (14.4, 16.6 to 12.2) Patients without DOA (N=9): (15.8, 18.3 to 13.0) Post-treatment Patients with DOA: (6.0, 8.3 to 3.7)	outcomes and assessors aware of intervention) Selection of the reported results bias: Low risk of bias Other information Only a small proportion of patients within each group for whom data were available for the following outcomes: mean voids per day; incontinence episodes; mean ICIQ-OAB score; Mean ICIQ-UI score) The following limitations were acknowledged by the authors: • Incomplete data available • Randomised, placebo-controlled trial required to formally evaluate use of BoNT in patients with

				Patients without DOA: (6.1, 9.8 to 2.5) Self-catheterisation rates (n/N) Patients with DOA: 23/75 (31%) Patients without DOA: 4/19 (21%)	OAB symptoms without DOA on conventional urodynamic assessment

Clinical evidence tables for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abdelwahab, O., Sherif, H., Soliman, T., Elbarky, I., Eshazly, A., Efficacy of botulinum toxin type A 100 Units versus 200 units for treatment of refractory idiopathic overactive bladder, International Braz J Urol, 41, 1132-40, 2015 Ref Id 542110 Country/ies where the study was carried out Egypt Study type Randomised prospective study Aim of the study To evaluate the efficacy and safety of a single intra detrusor injection of botulinum neurotoxin type A (BoNT-A) comparing two different doses	Sample size N = 80 BoNT-A 100U: N=40 BoNT-A 200U: N=40 Characteristics Gender - Female/N (%) N = 63 (78.75%) Age - Mean ± SD BoNT-A 100U: 30.22 (8.37) years BoNT-A 200U: 31.35 (7.61) years Incontinence episodes / day - Mean ± SD Not reported Urgency episodes / day - Mean ± SD BoNT-A 100U = 4.7 (0.464) BoNT-A 200U = 4.67 (0.474)	Interventions BoNT-A Type: Botox Dilution: 100U/1.0 ml or 200U/1.0ml Injection technique: Cystoscopic intra detrusor injection performed in 20 sites, using 30-degree lens and a rigid scope with a 6 Fr. injection needle without side holes. Injection sites determined after mapping of the bladder at the anterior, left lateral, right lateral, posterior walls and the tirgone (0.5cc at each site). Type of Anaesthesia: Spinal anaesthesia	Details Patients underwent intra detrusor injection of 100U or 200U BTX-A. Additional use of anticholinergics was not allowed during the study period. Following injection, a 16 Fr. Foley's catheter was inserted, to be removed the following morning after surgery. All patients received peri-operative intravenous antibiotics. Patients were assessed by taking a history, a physical examination, overactive bladder symptom score (OABSS) at 1, 3, 6, and 9 months, EuroQol (EQ-5D) visual analogue scale (VAS), measuring the patient's current health-related quality of life (QoL) state, urine analysis, routine laboratory investigations, KUB and pelviabdominal spiral CT and IVP if indicated.	Results Patient satisfaction with treatment Not reported Self-reported rate of absolute symptom reduction per day - Mean ± SD Not reported QoL - Mean ± SD At 1 month BoNT-A 100U = 83.6 (7.54)* BoNT-A 200U = 82.8 (7.60)* At 3 months BoNT-A 100U = 72.4 (16.45)* BoNT-A 200U = 77.3 (11.67)* At 6 months BoNT-A 100U = 73.4 (12.21)* BoNT-A 200U = 77.3 (10.12)* At 9 months BoNT-A 100U = 68.5 (7.57)* BoNT-A 200U = 77.1 (10.00)* OABSS - Mean ± SD At 1 month BoNT-A 100U = 2.85 (2.537)* BoNT-A 200U = 3.32 (2.092)*	Limitations Random sequence generation: Unclear r isk of bias (not mentioned in text) Allocation concealment: Unclear risk of bias (not mentioned in text) Blinding: High risk of bias (the study was not blinded) Incomplete outcome data: Low risk of bias (Less than 15% of patients lost to follow-up. Of the 80 initially included patients, 4 dropped out - 2 from the BoNT-A 100U group after 6 and 9 months follow-up, and 2 from the BoNT-A 200U group after 9 months follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(100U or 200U) in patients with idiopathic overactive bladder Study dates May 2011 to February 2014 Source of funding No funding sources reported	Detrusor overactivity - n/N (%) Not reported Duration of OAB - Mean ± SD Not reported Frequency - Mean ± SD BoNT-A 100U = 1.6 (0.496) BoNT-A 200U = 1.67 (0.525) UUI - Mean ± SD BoNT-A 100U = 1.67 (1.899) BoNT-A 200U = 1.8 (2.002) Post Void Residual (PVR) - Mean ± SD BoNT-A 100U = 25.75 (12.83) BoNT-A 200U = 27.4 (15.05) Inclusion criteria Idiopathic overactive bladder refractory to		Urodynamic evaluation was done in the form of flowmetry and cystometry at 3, 6, and 9 months. Randomisation Patients were randomly classified into 100U or 200U BTX-A groups. Statistical analysis Categorical data presented as number of percentages; quantitative data expressed as mean and standard deviation. Chi square test (X2) and Student "t" tests used as tests of significance, analysed using SPSS version 16. P<0.05 considered significant. Power calculation None reported. Intention to treat analysis Not reported.	At 3 months BoNT-A 100U = 2.27 (2.391)* BoNT-A 200U = 2.55 (2.417)* At 6 months BoNT-A 100U = 2.28 (2.361))* BoNT-A 200U = 2.37 (2.518)* At 9 months BoNT-A 100U = 5.3 (2.11))* BoNT-A 200U = 2.6 (2.307))* Frequency - Mean ± SD At 1 month BoNT-A 100U = 0.45 (0.503)* BoNT-A 200U = 0.42 (0.5)* At 3 months BoNT-A 100U = 0.42 (0.5)* BoNT-A 200U = 0.33 (0.474)* At 6 months BoNT-A 100U = 0.51 (0.506)* BoNT-A 200U = 0.3 (0.464))* At 9 months BoNT-A 100U = 1.1 (0.508)* BoNT-A 200U = 0.32 (0.471)* Urgency episodes - Mean ± SD At 1 month BoNT-A 100U = 1.4 (1.37)* BoNT-A 200U = 1.9 (1.12)* At 3 months BoNT-A 100U = 1.07 (1.163)*	Selective reporting: Low risk of bias (All outcomes reported) Other bias: Low risk of bias (no other potential source of bias identified) Other information The following limitations were acknowledged by the authors: • No control arm • Small number of patients • Further studies required to confirm the effectiveness of BoNT-A 100U and 200U

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous anticholinergics with different types of anticholinergic agents, either as a single drug or a combination for >3 months. Exclusion criteria • Pregnant women • Uncorrectable coagulopathies • Active urinary tract infection (UTI) • Bladder outlet obstruction; • Neurogenic bladder, or • Having a post void residual (PVR) >150 mL at the time of enrolment, and • Previous radiotherapy or			BoNT-A 200U = 1.45 (1.131)* At 6 months BoNT-A 100U = 0.97 (1.135))* BoNT-A 200U = 1.25 (1.031))* At 9 months BoNT-A 100U = 2.57 (0.948)* BoNT-A 200U = 1.47 (1.202)* UUI - Mean ± SD At 1 month BoNT-A 100U = 0.77 (1.073)* BoNT-A 200U = 0.85 (1.098)* At 3 months BoNT-A 100U = 0.65 (0.975)* BoNT-A 200U = 0.65 (0.948)* At 6 months BoNT-A 100U = 0.67 (0.982)* BoNT-A 200U = 0.72 (1.085)* At 9 months BoNT-A 100U = 1.26 (1.171)* BoNT-A 200U = 0.68 (0.162)* Post-void residual (PVR) urine volume - Mean ± SD At 1 month BoNT-A 100U = 40.0 (21.42)* BoNT-A 200U = 47.37 (11.87)* At 3 months	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	antineoplastic treatment			BoNT-A 100U = 39.23 (12.48)* BoNT-A 200U = 42.00 (10.05)* At 6 months BoNT-A 100U = 38.88 (12.22)* BoNT-A 200U = 41.79 (10.77)* At 9 months BoNT-A 100U = 24.21 (8.58) BoNT-A 200U = 29.21 (11.30) *significant in intragroup comparison to "before intervention". Requirement of self-catheterisation or indwelling catheterisation Not reported. Nocturia - Mean ± SD At 1 month BoNT-A 100U = 0.23 (0.422)* BoNT-A 200U = 0.15 (0.361)* At 3 months BoNT-A 100U = 0.13 (0.334)* BoNT-A 200U = 0.13 (0.334)* At 6 months BoNT-A 100U = 0.13 (0.338)* BoNT-A 200U = 0.12 (0.334)* At 9 months BoNT-A 100U = 0.36 (0.488)*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				BoNT-A 200U = 0.13 (0.342)* *significant in intragroup comparison to "before intervention". Adverse effects Haematuria (Female n/N) BoNT-A 100U N = 4/(unclear number of female patients) BoNT-A 200U N = 6/(unclear number of female patients) Dysuria (Female n/N) BoNT-A 100U N = 5/(unclear number of female patients) BoNT-A 200U N = 12/(unclear number of female patients) UTI (Female n/N) BoNT-A 100U N = 2/(unclear number of female patients) BoNT-A 200U N = 5/(unclear number of female patients)	
Full citation Brubaker,L., Gousse,A., Sand,P., Thompson,C., Patel,V., Zhou,J., Jenkins,B., Sievert,K.D., Treatment satisfaction and goal attainment with onabotulinumtoxinA in patients with	Sample size See Dmochowski 2010 for details Characteristics See Dmochowski 2010 for details Inclusion criteria See Dmochowski 2010 for details	Interventions See Dmochowski 2010 for details	Details Statistical analysis For the modified overactive bladder-patient satisfaction with treatment questionnaire (OAB-PSTQ), Q1 was analysed as a single item using patients who responded with a score of 1-5 (a score of 6 meant the question did not apply to the patient) and population	Results Mean change from baseline in the modified OAB-PSTQ at week 12 Q1: Proportion of patients reporting being "somewhat satisfied" or "very satisfied" BoNT-A 100U = 32/48 (66.7%); p=0.031 BoNT-A 200U = 38/49 (77.6%); p=0.001	Limitations See Dmochowski 2010 for details Other information See Dmochowski 2010 for details Also associated with Fowler 2012 and Rovner 2011

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
incontinence due to idiopathic OAB, International Urogynecology Journal, 23, 1017-1025, 2012 Ref Id 215540 Country/ies where the study was carried out USA, Canada, UK, Germany, Belgium, Poland Study type See Dmochowski 2010 for details Aim of the study See Dmochowski 2010 for details Study dates See Dmochowski 2010 for details To investigate the effect of BoNT-A treatment on patient satisfaction and patient goal and expectation attainment. Source of funding	Exclusion criteria See Dmochowski 2010 for details		information computed only from patients listing values of 1-5. Change from baseline in score in Q1 was analysed by an analysis of covariance model at each visit with factors for treatment group and investigator, using baseline as a covariate. The main module OAB-PSTQ score comprised Q2-Q13 and was computed only according to the rule that >50% of the items of the 12-item scale are non-missing. The score was computed as (((total score/12)-1)/(5-1))*100. Group means and distributions were then compared as continuous variables. Q14 of the modified OAB-PSTQ, which analyses overall severity of side effects, was analysed as a single item. Group means were calculated at each time point. For assessments of modified OAB-PSTQ Q15 (patient goal) and Q16 (patient expectation), mean group scores were calculated at each time point and compared across groups, and a categorical data analysis was performed grouping the percentage of patients in each	Q14: Proportion of patients reporting "mild side effects" or "no side effects" BoNT-A 100U = 47/48 (97.9%); p=0.867 BoNT-A 200U = 40/48 (83.3%); p=0.035 Q.15 Proportion of patients at week 12 reporting a "significant progress" toward or "complete achievement" of primary goal of treatment BoNT-A 100U = 22/47 (46.8%) BoNT-A 200U = 32/49 (65.3%) Q.16 Patients reporting that treatment "significantly met" or "exceeded" their primary expectation BoNT-A 100U = 21/47 (44.7%) BoNT-A 200U = 26/48 (54.2%) PGA item/score (n, %) at week 12 Symptoms - improvement BoNT-A 100U = 24/48 (50.0%) BoNT-A 200U = 31/49 (63.3%) Symptoms - unchanged	The authors acknowledged the following limitations: • The PGA instrument used, along with the questions added to the main module OAB-PSTQ, are not validated • Patients had to be willing to perform clean intermittent catheterisation (CIC) in order to be enrolled into the study • Only 8% of patients enrolled in the study were male

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Dmochowski 2010 for details			category at each time point of follow-up. For the patient global assessment (PGA) questions, an analysis was performed of the number and percentage of individuals who recorded a PGA score categorised as "improvement" (score >+1), "unchanged" (score of +1, 0 or -1), or "deterioration" (score <-1) by treatment group at the primary efficacy time point of week 12. Modified OAB-PSTQ subgroup analyses An analysis of the overall satisfaction score (Q1) was performed in the subgroup of patients who needed to perform catheterisation for >1 day during the study versus those who either did not need catheterisation or required it for 1 day or less (i.e. a single catheterisation event not related to elevated PVR). The overall satisfaction score was reported for the visit in which, or immediately after which, catheterisation was used in the analysis for patients requiring catheterisation for >1 day. Week 12 data were used for	BoNT-A 100U = 16/48 (33.3%) BoNT-A 200U = 12/49 (24.5%) Symptoms - deterioration BoNT-A 100U = 8/48 (16.7%) BoNT-A 200U = 6/49 (12.2%) Quality of life - improvement BoNT-A 100U = 24/48 (50.5%) BoNT-A 200U = 30/49 (61.2% Quality of life - unchanged BoNT-A 100U = 20/48 (41.7%) BoNT-A 200U = 17/49 (34.7%) Quality of life - deterioration BoNT-A 100U = 4/48 (8.3%) BoNT-A 200U = 2/49 (4.1%) Activity limitations - improvement BoNT-A 100U = 21/48 (43.8%) BoNT-A 200U = 26/49 (53.1%) Activity limitations - unchanged BoNT-A 100U = 24/48 (50.0%) BoNT-A 200U = 20/49 (40.8%) Activity limitations - deterioration	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			patients requiring catheterisation for 1 day or more.	BoNT-A 100U = 3/48 (6.3%) BoNT-A 200U = 3/49 (6.1%) Emotions - improvement BoNT-A 100U = 20/47 (42.6%) BoNT-A 200U = 29/49 (58.2% Emotions - unchanged BoNT-A 100U = 19/47 (40.4%) BoNT-A 100U = 16/49 (32.7%) Emotions - deterioration BoNT-A 100U = 8/47 (17.0%) BoNT-A 200U = 4/49 (8.2%)	
Full citation Dmochowski,R., Chapple,C., Nitti,V.W., Chancellor,M., Everaert,K., Thompson,C., Daniell,G., Zhou,J., Haag-Molkenteller,C., Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial, Journal of Urology, 184, 2416-2422, 2010 Ref Id	Sample size N = 313 (of which 272 completed the study) BoNT-A 50U = 56 BoNT-A 100U = 55 BoNT-A 150U = 50 BoNT-A 200U = 52 BoNT-A 300U = 55 Placebo = 43 Characteristics Gender - Female/N (%) N = 288/313 (92%) Age - Mean ± SD 58.8 years	Interventions BoNT-A as 20 intradetrusor injections of 0.5 ml per site, evenly distributed into the detrusor muscle, avoiding the trigone and dome, via cystoscopy.	Details Before injection, the bladder was instilled with 1% to 2% lidocaine (or similar agent) to achieve sufficient anaesthesia. The bladder was drained, rinsed and then instilled with sufficient saline to achieve adequate visualisation for the injections. Anticholinergic medication was not permitted within 21 days of entry into the study or after treatment. Sedatives could be used. Randomisation Eligible patients were randomised on a 1:1:1:1:1:1 basis.	Results Patient satisfaction with treatment (Week 12) Not reported Self reported rate of absolute symptom reduction per day - Assessed at Week 24 Episodes of incontinence - weekly - Mean - no sd reported BoNT-A 100U: 8.6 BoNT-A 200U: 4.1 Change from baseline in UUI episodes at week 12 BoNT-A 100U = -20.7 BoNT-A 200U = -23.0	Limitations Random sequence generation: Low risk of bias (randomly assigned on a 1:1:1:1:1:1 basis) Allocation concealment: Unclear risk of bias (not mentioned in text) Blinding: Low risk of bias (double blinded) Incomplete outcome data: Low risk of bias (Of 313 patients, 272 (86.9%) completed the study; 41 (13.1%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
100191 Country/ies where the study was carried out USA, Canada, UK, Germany, Belgium, Poland Study type Randomised, multicentre, double-blind trial Aim of the study To assess the safety and efficacy of a range of doses of a single treatment of intradetrusor onabotulinumtoxinA versus placebo in patients with idiopathic overactive bladder (OAB) and urinary urgency incontinence (UUI) whose symptoms were not adequately managed with anticholinergics Study dates July 2005 to June 2008 Source of funding	Duration of OAB - Median > 5 years Detrusor overactivity - n/N (%) N = 238/313 (76%) Inclusion criteria • Male and female patients aged 18 to 85 years old • Symptoms of OAB with UUI for at least 6 months immediately prior to screening • ≥ 8 UUI episodes/week with no more than 1 incontinence-free day/week • Urinary frequency (defined as an average ≥ 8		Statistical analysis Primary outcome ANCOVA model without adjustment for multiplicity used. Dose response relationship explored using categorical data analysis, graphically, and using non-parametric rank ANOVA. Secondary outcomes Same ANCOVA model used for primary outcome without imputation. Subgroup analysis by presence of detrusor overactivity performed for weekly UUI episodes, weekly micturition episodes and volume per micturition at week 12. PVR analysed with descriptive statistics and summarising change from baseline. Power calculation A formal power calculation was not performed, but a power of 61% to 92% to detect a between group difference of 4 to 6 weekly UUI episodes was the basis for the sample size of 42 patients per group. Intention-to-treat analysis Missing values up to week 12 were replaced by the last	Adverse effects (n/N; %) BoNT-A 100U = 44/55 (80.0%) BoNT-A 200U = 44/52 (84.6%) No. treatment related adverse effects (n/N; %) BoNT-A 100U = 20/55 (36.4%) BoNT-A 200U = 20/52 (38.5%) No. UTIs (n/N; %) BoNT-A 100U = 20/55 (36.4%) BoNT-A 200U = 25/52 (48.1%) No. urinary retention (n/N; %) BoNT-A 100U = 10/55 (18.2%) BoNT-A 200U = 12/52 (23.1%) No. PVR 200ml or greater BoNT-A 100U = 8/55 (14.5%) BoNT-A 200U = 15/52 (28.8%) No. PVR related catheterisation BoNT-A 100U = 6/55 (10.9%) BoNT-A 200U = 11/52 (21.2%)	discontinued prematurely) Other reasons BoNT-A 100U = 0 BoNT-A 200U = 3 Personal reasons BoNT-A 100U = 1 BoNT-A 200U = 2 Lack of efficacy BoNT-A 100U = 3 BoNT-A 200U = 0 Lost to follow-up BoNT-A 100U = 1 BoNT-A 200U = 1 Adverse effects BoNT-A 100U = 0 BoNT-A 200U = 0 Protocol violation BoNT-A 100U = 1 BoNT-A 200U = 0 Selective reporting: Low risk of bias (All outcomes reported) Other bias: Low risk of bias (no other potential source of bias identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
"Supported by Allergan, Inc."	micturitions/day) • To have not been adequately managed with anticholinergic treatment (defined as an inadequate response to or intolerable side effects) Exclusion criteria • Used clean intermittent catheterization (CIC) • History or evidence of pelvic or urologic abnormalities • Diseases affecting bladder function • Treated for≥ 2 UTIs within 6 months • Had 24-hr total urine		observation adjusted by the ratio of means for the preceding and current visit for all non-missing values for all patients.		The authors acknowledged the following limitations: • Lack of requirement to confirm UTI by culture; • PVR of 200ml or greater recorded as an adverse effect of urinary retnetion regardless of symptoms or need for intervention; • No standardisation regarding the initiation and cessation of catheterisation provided, which most likely contributed to the variation among patients in the duration

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	volume voided > 3,000 ml or post-void residual (PVR) urine volume > 200 ml at screening				of catheterisation and may have contributed to the occurrence of UTIs Supplementary data available from the primary author.

Appendix E – Forest plots

Forest plots for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

No meta-analysis was undertaken for this review so there are no forest plots.

Forest plots for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

No meta-analysis was undertaken for this review so there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Table 5: Clinical evidence profile for botulinum toxin type A treatment

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patients with positive confirmation of DOA	Patients with negative confirmation of DOA	Relative (95% CI)	Absolute	Quality	Importance
Mean change in voids per day (follow-up 3 months; measured with: Patient reported diaries ; Better indicated by lower values)												
1	observational studies	very serious [1]	no serious inconsistency	very serious[2]	very serious[3,4]	none	28	13	-	MD 0.3 higher (0.85 lower to 1.45 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Mean change in incontinence episodes (follow-up 3 months; measured with: Patient reported diaries; Better indicated by lower values)												
1	observational studies	very serious [1]	no serious inconsistency	very serious[2]	very serious[3]	none	28	13	-	MD 0.2 higher (0.01 to 0.39 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Mean change in nocturia episodes (follow-up 3 months; measured with: Patient reported diaries; Better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	very serious[2]	very serious[3,4]	none	28	13	-	MD 0 higher (0.24 lower to 0.24 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Mean change in ICIQ-OAB score (follow-up 3 months; measured with: ICIQ-OAB score; Better indicated by lower values)												
1	observational studies	very serious [1]	no serious inconsistency	very serious[2]	very serious[3,4]	none	21	9	-	MD 1.2 lower (1.82	⨁⊖⊖⊖	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Patients with positive confirmation of DOA**	**Patients with negative confirmation of DOA**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										to 0.58 lower)	VERY LOW	
Mean change in ICIQ-UI score (follow-up 3 months; measured with: ICIQ-UI score; Better indicated by lower values)												
1	observational studies	very serious [1]	no serious inconsistency	very serious[2]	serious[3]	none	21	9	-	MD 1.3 higher (0.27 to 2.33 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

[1] Confounding bias: Low risk of bias; Selection of participant's bias: Moderate risk of bias (patients selected on basis of having undergone a urodynamic study); Classification of interventions bias: Low risk of bias; Deviations from intended interventions bias: Low risk of bias; Missing data bias: High risk of bias (missing data (>50%) for some outcomes); Measurement of outcomes bias: Serious risk of bias (self-reported outcomes and assessors aware of intervention); Selection of the reported results bias: Low risk of bias.
[2] Proportion of women with and without DOA not reported (i.e. includes both men and women); small proportion within each group with available data.
[3] The upper estimate of the 95% CI crosses MD threshold
[4] The lower estimate of the 95% CI crosses the MD threshold

GRADE tables for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Table 6: Clinical evidence profile for the most effective initial dose of botulinum toxin type A for treating overactive bladder

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
UUI Mean change from baseline (follow-up 1 month; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	40	-	MD 0.05 higher (0.52 lower to 0.62 higher)	⨁⨁⊖⊖ LOW	CRITICAL
UUI Mean change from baseline (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	40	-	MD 0.13 higher (0.7 lower to 0.96 higher)	⨁⨁⊖⊖ LOW	CRITICAL
UUI Mean change from baseline (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	40	-	MD 0.08 higher (0.89 lower to 1.05 higher)	⨁⨁⊖⊖ LOW	CRITICAL
UUI Mean change from baseline (follow-up 9 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.71 higher (0.22 lower to 1.64 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
QoL Mean change from baseline (follow-up 1 month; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 1.1 lower (5.85 lower to 3.65 higher)	⨁⊖⊖⊖	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
											VERY LOW	
QoL Mean change from baseline (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 6.8 lower (13.91 lower to 0.31 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
QoL Mean change from baseline (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 5.8 lower (11.77 lower to 0.17 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
QoL Mean change from baseline (follow-up 9 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 10.5 lower (15.66 to 5.34 lower)	⨁⊖⊖⊖ VERY LOW	CRITICAL
PVR related catheterisation (follow-up 9 months)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	very serious[3]	none	6/55 (10.9 %)	11/52 (21.2 %)	RR 0.52 (0.21 to 1.29)	102 fewer per 1000 (from 167 fewer to 61 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Frequency mean change from baseline (follow-up 1 month; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.10 higher (0.16 lower to 0.36 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Frequency Mean change from baseline (follow-up 3 months; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.16 higher (0.15 lower to 0.47 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Frequency Mean change from baseline (follow-up 6 months; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.28 higher (0.03 lower to 0.59 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Frequency Mean change from baseline (follow-up 9 months; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.85 higher (0.54 to 1.16 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Urgency episodes Mean change from baseline (follow-up 1 month; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.53 lower (0.95 to 0.11 lower)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Urgency episodes Mean change from baseline (follow-up 3 months; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.41 lower (0.77 to 0.05 lower)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Urgency episodes Mean change from baseline (follow-up 6 months; measured per day; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.31 lower (0.7 lower to 0.08 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Urgency episodes Mean change from baseline (follow-up 9 months; measured per day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	40	40	-	MD 1.07 higher (0.72 to 1.42 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
PVR urine volume Mean change from baseline (follow-up 1 month; measured in mls; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 5.72 lower (11.18 to 0.26 lower)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
PVR urine volume Mean change from baseline (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 1.12 lower (4.91 lower to 2.67 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
PVR urine volume Mean change from baseline (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 1.26 lower (6.39 lower to 3.87 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
PVR urine volume Mean change from baseline (follow-up 9 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 3.35 lower (7.42	⨁⊖⊖⊖	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										lower to 0.72 higher)	VERY LOW	
PVR urine volume 200ml or greater (follow-up 9 months)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious[4]	none	8/55 (14.5 %)	15/52 (28.8 %)	RR 0.5 (0.23 to 1.09)	144 fewer per 1000 (from 222 fewer to 26 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Nocturia Mean change from baseline (follow-up 1 month; measured per night; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.41 higher (0.04 to 0.78 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Nocturia Mean change from baseline (follow-up 3 months; measured per night; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.33 higher (0.04 lower to 0.7 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Nocturia Mean change from baseline (follow-up 6 months; measured per night; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.34 higher (0.07 lower to 0.75 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Nocturia Mean change from baseline (follow-up 9 months; measured per night; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.57 higher (0.19 to 0.95 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OABSS Mean change from baseline at 1 month (follow-up 1 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	40	-	MD 0.03 higher (0.66 lower to 0.72 higher)	⨁⨁⊖⊖ LOW	IMPORTANT
OABSS Mean change from baseline at 3 months (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.22 higher (0.42 lower to 0.86 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
OABSS Mean change from baseline (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40	40	-	MD 0.41 higher (0.49 lower to 1.31 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
OABSS Mean change from baseline (follow-up 9 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	40	40	-	MD 3.2 higher (2.4 to 4 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Adverse Events - UTIs (follow-up at 9 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/38 (5.3%)	5/38 (13.2 %)	RR 0.4 (0.08 to 1.94)	79 fewer per 1000 (from 121 fewer to 124 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Adverse Events - Urinary retention (follow-up at 9 months)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	very serious[3]	none	10/55 (18.2 %)	12/52 (23.1 %)	RR 0.79 (0.37 to 1.67)	48 fewer per 1000 (from 145 fewer to 155 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Adverse Events – Haematuria (follow-up at 9 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	4/38 (10.5 %)	6/38 (15.8 %)	RR 0.67 (0.2 to 2.18)	52 fewer per 1000 (from 126 fewer to 186 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Adverse Events – Dysuria (follow-up at 9 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	5/38 (13.2 %)	12/38 (31.6 %)	RR 0.42 (0.16 to 1.07)	183 fewer per 1000 (from 265 fewer to 22 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Adverse Events - Treatment related adverse effects (follow-up at 9 months)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	very serious[3]	none	20/55 (36.4 %)	20/52 (38.5 %)	RR 0.95 (0.58 to 1.54)	19 fewer per 1000 (from 162 fewer to 208 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Adverse Events - Total no. AEs (follow-up at 9 months)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious[4]	none	44/55 (80%)	44/52 (84.6 %)	RR 0.95 (0.79 to 1.13)	42 fewer per 1000 (from 178 fewer to 110 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Modified OAB-PSTQ Q1: Proportion of patients reporting being "somewhat satisfied" or "very satisfied" (follow-up 12 weeks)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BoNT-A 100U**	**BoNT-A 200U**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious[4]	none	32/48 (66.7 %)	38/49 (77.6 %)	RR 0.86 (0.67 to 1.1)	109 fewer per 1000 (from 256 fewer to 78 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Modified OAB-PSTQ Q14: Proportion of patients reporting "mild side effects" or "no side effects" (follow-up 12 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious[4]	none	47/48 (97.9 %)	40/48 (83.3 %)	RR 1.18 (1.03 to 1.34)	142 more per 1000 (from 25 more to 283 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Modified OAB-PSTQ Q.15: Proportion of patients reporting a "significant progress" toward or "complete achievement" of primary goal of treatment (follow-up 12 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious[4]	none	22/47 (46.8 %)	32/49 (65.3 %)	RR 0.72 (0.5 to 1.03)	183 fewer per 1000 (from 327 fewer to 20 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Modified OAB-PSTQ Q.16 Patients reporting that treatment "significantly met" or "exceeded" their primary expectation (follow-up 12 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	serious[2]	serious[4]	none	21/47 (44.7 %)	26/48 (54.2 %)	RR 0.82 (0.55 to 1.24)	98 fewer per 1000 (from 244 fewer to 130 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

[1] Random sequence generation: Unclear risk of bias (not mentioned in text). Allocation concealment: Unclear risk of bias (not mentioned in text). Blinding: High risk of bias (the study was not blinded). Incomplete outcome data: Low risk of bias (Less than 15% of patients lost to follow-up. Of the 80 initially included patients, 4 dropped out - 2 from the BoNT-A 100U group after 6 and 9 months follow-up, and 2 from the BoNT-A 200U group after 9 months follow-up. Selective reporting: Low risk of bias (All outcomes reported). Other bias: Low risk of bias (no other potential source of bias identified).
[2] Total number of women reporting this outcome not stated (includes both men and women).
[3] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 default MIDs.
[4] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 default MID.
[5] Random sequence generation: Low risk of bias (randomly assigned on a 1:1:1:1:1:1 basis). Allocation concealment: Unclear risk of bias (not mentioned in text). Blinding: Low risk of bias (double blinded). Incomplete outcome data: Low risk of bias (Of 313 patients, 272 (86.9%) completed the study; 41 (13.1% discontinued prematurely)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

One global search was undertaken – please see supplementary material D for details on study selection.

Economic evidence study selection for review question: What is the most effective initial dose of botulinum toxin type A for treating OAB?

One global search was undertaken – please see supplementary material D for details on study selection.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

No economic studies were identified which were applicable to this review question.

Economic evidence tables for review question: What is the most effective initial dose of botulinum toxin type A for treating OAB?

No economic studies were identified which were applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

No economic studies were identified which were applicable to this review question.

Economic evidence profiles for review question: What is the most effective initial dose of botulinum toxin type A for treating OAB?

No economic studies were identified which were applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

No economic analysis was undertaken for this review question.

Economic analysis for review question: What is the most effective initial dose of botulinum toxin type A for treating OAB?

No economic analysis was undertaken for this review question.

Appendix K – Excluded studies

Clinical studies

Excluded clinical studies list for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
Study	**Reason for Exclusion**
Abdelwahab, O., Sherif, H., Soliman, T., Elbarky, I., Eshazly, A., Efficacy of botulinum toxin type A 100 Units versus 200 units for treatment of refractory idiopathic overactive bladder, International Braz J Urol, 41, 1132-40, 2015	Intervention and comparator not relevant to the protocol
Altaweel,W., Mokhtar,A., Rabah,D.M., Prospective randomized trial of 100u vs 200u botox in the treatment of idiopathic overactive bladder, Urology Annals, 3, 66-70, 2011	Intervention and comparator not relevant to the protocol
American Urogynecological Society's Guidelines Development, Committee, Diagnosis and treatment of overactive bladder, Female Pelvic Medicine & Reconstructive Surgery, 19, 316, 2013	Conference abstract
Anonymous,, Society for Urodynamics and Female Urology 2013 Winter Meeting, Neurourology and Urodynamics. Conference: Society for Urodynamics and Female Urology, 32, 2013	Conference abstracts
Anonymous,, OnabotulinumtoxinA for Injection For the Treatment of Overactive Bladder, Canadian Agency for Drugs and Technologies in Health, OnabotulinumtoxinA for Injection, For the Treatment of Overactive Bladder CADTH Common Drug Reviews, 2015	Intervention and comparator not relevant to the protocol
Bayoud, Y., Menard, J., Staerman, F., Impact on quality of life of botulinum toxin-a in non-neurogenic detrusor overactivity refractory to anticholinergics, Urology, 1), S91-S92, 2010	Intervention and comparator not relevant to protocol.
Bayoud, Y., Menard, J., Staerman, F., Outcomes and complications of botulinum toxin-A in non-neurogenic detrusor overactivity refractory to anticholinergics, Urology, 1), S46, 2010	Intervention and comparator not relevant to the protocol
Cardozo,L., The overactive bladder syndrome: Treating patients on an individual basis, BJU International, 99, 1-7, 2007	Narrative literature review

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
Caruso, D, Kanagarajah, P, Gousse, A, 100 vs. 150 units of intra-detrusor Botox (trademark): dose differences in OAB-wet patients? (Abstract number 316), Proceedings of the 39th Annual Meeting of the International Continence Society (ICS), 2009 Sep 29 - Oct 3, San Francisco, CA, 2009	Intervention and comparator not relevant to the protocol
Chibelean, C., Nechifor-Boila, I. A., Botulinum neurotoxin A for overactive bladder treatment: advantages and pitfalls, Canadian Journal of Urology, 22, 7681-9, 2015	Systematic review - interventions included do not have relevant interventions
Cohen, BI, Barboglio, P, Gousse, Ae, Can we predict who will respond to botulinum toxin-A injections for idiopathic overactive bladder? (Abstract number 18), Neurourology and Urodynamics, 27, 132-3, 2008	Intervention and comparator not relevant to the protocol
Cohen,B.L., Barboglio,P., Rodriguez,D., Gousse,A.E., Preliminary results of a dose-finding study for botulinum toxin-A in patients with idiopathic overactive bladder: 100 versus 150 units, Neurourology and Urodynamics, 28, 205-208, 2009	Intervention and comparator not relevant to the protocol
Cohen,B.L., Caruso,D.J., Kanagarajah,P., Gousse,A.E., Predictors of response to intradetrusor botulinum toxin-A injections in patients with idiopathic overactive bladder, Advances in Urology, 328364-, 2009	Intervention and comparator not relevant to the protocol
Denys, P., Le Normand, L., Ghout, I., Costa, P., Chartier-Kastler, E., Grise, P., Hermieu, J. F., Amarenco, G., Karsenty, G., Saussine, C., Barbot, F., Vesitox study group in France, 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, European Urology, 61, 520-9, 2012	Intervention is not relevant to protocol - all women have detrusor overactivity
Denys,P., Lenormand,L., Costa,P., Chartier-Kastler,E., Grise,P., Hermieu,J., Amarenco,G., Karsenty,G., Saussine,C., Barbot,F., Efficacy and safety of low doses of onabotulinumtoxina for the treatment of refractory idiopathic overactive bladder: A multicenter, double-blind, randomised, placebo controlled study, Neurourology and Urodynamics, 30, 924-926, 2011	Conference abstract
Dmochowski,R., Chapple,C., Nitti,V.W., Chancellor,M., Everaert,K., Thompson,C., Daniell,G., Zhou,J., Haag-Molkenteller,C., Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial, Journal of Urology, 184, 2416-2422, 2010	Subgroup analysis only - outcomes not reported on all women
Duggan, P, The BIDO (Botulinum toxin for Idiopathic Detrusor Overactivity) trial, Australasian Gynaecological Endoscopy & Surgery Society Ltd (AGES) at http://www.ages.com.au/fund2010.htm (accessed on 10.2.2011), 2011	Unable to obtain full text
Fine, M., Kanagarajah, P., Gomez, C., Gousse, A., Repeated intra-detrusor injection of onabotulinum toxin-A in patients with idiopathic overactive bladder, Neurourology and Urodynamics, 31 (2), 267-268, 2012	Intervention and comparator not relevant to the protocol

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
Furuta, A., Chancellor, M. B., Health care usage, botulinum toxin for overactive bladder, Reviews in Urology, 8, 234-5, 2006	Study design not relevant to protocol
Ghalayini, I. F., Al-Ghazo, M. A., Intradetrusor injection of botulinum-A toxin in patients with idiopathic and neurogenic detrusor overactivity: Urodynamic outcome and patient satisfaction, Neurourology and Urodynamics, 26, 531-536, 2007	Intervention and comparator not relevant to the protocol
Gilleran, J. P., Nguyen, L., Killinger, K., Bartley, J., Gaines, N. P., Sirls, L. T., Boura, J., Peters, K. M., Clinical and urodynamic factors associated with subsequent botulinum toxin a injection after neuro modulation, Neurourology and Urodynamics, 36, S98, 2017	Intervention and comparator not relevant to the protocol
Gormley, E. A., Lightner, D. J., Burgio, K. L., Chai, T. C., Clemens, J. Q., Culkin, D. J., Das, A. K., Foster Jr, H. E., Scarpero, H. M., Tessier, C. D., Vasavada, S. P., Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline, Journal of Urology, 188, 2455-2463, 2012	Guideline paper
Gormley, E. A., Lightner, D. J., Faraday, M., Vasavada, S. P., Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment, Journal of Urology, Part S. 193, 1572-1580, 2015	Guideline update paper
Gousse, A, Barboglio, P, Cohen, B, Rodriguez, D, Caruso, D, Botox (R) for idiopathic overactive bladder patients refractory to antimuscarinic therapy in the absence of detrusor overactivity (Abstract number 133), Neurourology and Urodynamics, 27, 724-5, 2008	Comparator not relevant to the protocol - no women with detrusor overactivity
Gousse, A, Barboglio, P, Cohen, B, Rodriguez, D, Caruso, D, Can we predict who will respond to botulinum toxin-A injections for idiopathic overactive bladder? (Abstract number 538), Proceedings of the 38th Annual Meeting of the International Continence Society (ICS), 2008 Oct 20-24, Cairo, Egypt, 2008	Intervention and comparator not relevant to the protocol
Gousse, A, Shirodkar, S, Gomez, C, Kanagarajah, P, Barboglio, P, Caruso, D, Botox (trademark) for idiopathic overactive bladder patients refractory to antimuscarinic therapy in the absence of urodynamically demonstrable detrusor overactivity (Abstract number: Poster# 64), Neurourology and Urodynamics, 28, 144-5, 2009	Comparator not relevant to the protocol
Guggenbuehl-Roy, S., Schurch, B., Sulser, T., Schmid, D. M., Effect of repeated intradetrusor injections of botulinum-a toxin on bladder capacity, detrusor pressure and compliance for treating patients with idiopathic detrusor overactivity, follow-up, Journal of Urology, 1), 571, 2009	Study design not relevant to the protocol - no comparator group
Harris,M.A., Umez-Eronini,N., Rogers,A., Harding,C., Fulford,S., Whiteway,J., Clinical and urodynamic predictors of success of intravesical botulinum a treatment, European Urology, Supplements, 8, 242-, 2009	Intervention and comparator not relevant to the protocol
Hsiao, S. M., Lin, H. H., Kuo, H. C., Urodynamic prognostic factors for large post-void residual urine volume after intravesical injection of onabotulinumtoxinA for overactive bladder, Scientific Reports, 7, 43753, 2017	Intervention and comparator not relevant to the protocol

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
Jiang, Y. H., Ke, Q. S., Chen, Y. C., Kuo, H. C., Baseline urodynamic parameters do not affect the treatment outcome of intravesical 100u onabotulinumtoxina injection for patients with idiopathic detrusor overactivity, Journal of Urology, 1), e934, 2012	Intervention and comparator not relevant to the protocol
Jiang, Y. H., Kuo, H. C., Reduction of urgency severity is the most important factor in the subjective therapeutic outcome of intravesical onabotulinumtoxinA injection for overactive bladder, Neurourology and Urodynamics, 36, 338-343, 2017	Study design not relevant to protocol - no comparator group
Kanagarajah,P., Ayyathurai,R., Caruso,D.J., Gomez,C., Gousse,A.E., Role of botulinum toxin-A in refractory idiopathic overactive bladder patients without detrusor overactivity, International Urology and Nephrology, 44, 91-97, 2012	Comparator not relevant to protocol
Ke, Q. S., Chen, Y. C., Kuo, H. C., Do baseline urodynamic parameters affect the treatment outcome after intravesical 100 U onabotulinumtoxinA injection in patients with idiopathic detrusor overactivity?, Tzu Chi Medical Journal, 24, 121-126, 2012	Intervention not relevant to the protocol
Ksibi,I., Godard,A.L., Azouvi,P., Denys,P., Dziri,C., Botulinum toxin and refractory non-neurogenic overactive detrusor, Annals of Physical and Rehabilitation Medicine, 52, 668-683, 2009	Intervention and comparator not relevant to the protocol
Kuo, H. C., Urodynamic evidence of effectiveness of botulinum a toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents, Urology, 63, 868-872, 2004	Intervention not relevant to the protocol
Kuo,H.C., Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity?, Urology, 68, 993-997, 2006	Intervention and comparator not relevant to the protocol
Marinkovic,S.P., Rovner,E.S., Moldwin,R.M., Stanton,S.L., Gillen,L.M., Marinkovic,C.M., The management of overactive bladder syndrome, BMJ (Online), 344, -, 2012	Narrative literature review
Nct,, Kuo, H-C, Tang, D-L, Comparative Study of Safety and Efficacy Between 100 U Suburothelial Injection and 50 U Suburothelial Plus 50 U Urethral Injections of Botulinum Toxin A in Treatment of Patients With Detrusor Overactivity and Impaired Contractility, Http://clinicaltrials.gov/show/NCT02135341, 2014	Study protocol
Onyeka, B. A., Shetty, A., Ilangovan, K., Saxena, A., Submucosal injections of botulinum toxin A in women with refractory idiopathic detrusor overactivity, International Journal of Gynecology and Obstetrics, 110, 68-69, 2010	Study design not relevant to protocol - no comparator group
Ospina-Galeano, I. A., Medina-Polo, J., de la Rosa-Kerhmann, S., Villacampa-Auba, F., Guerrero-Ramos, F., Passas-Martinez, J. B., Use of onabotulinum toxin A in patients with idiopathic overactive bladder and a lack of efficacy, intolerance or contraindication with anticholinergics, Urologia Colombiana., 12, 2015	Unable to obtain full text

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
Pannek,J., Pieper,P., Clinical usefulness of ambulatory urodynamics in the diagnosis and treatment of lower urinary tract dysfunction, Scandinavian Journal of Urology and Nephrology, 42, 428-432, 2008	Ineligible patient population - fewer than 66% of the population are women
Patel, D., Ferry, E., Sammarco, A., Mahajan, S., Hijaz, A., Urodynamics: A poor predictor of repeat onabotulinumtoxin a injection, Neurourology and Urodynamics, 33 (2), 245, 2014	Study design not relevant to protocol - no comparator group
Rachaneni, S., Champaneria, R., Latthe, P., Does the outcome of botulinum toxin treatment differ in OAB patients with detrusor overactivity compared to those without detrusor overactivity?:A systematic review, International Urogynecology Journal and Pelvic Floor Dysfunction, 1), S32-33, 2015	Conference abstract
Rachaneni, S., Latthe, P., Effectiveness of BTX-A and neuromodulation in treating OAB with or without detrusor overactivity: a systematic review, International urogynecology journal, 12, 12, 2017	Systematic review of non-randomised studies
Rovner,E., Kennelly,M., Schulte-Baukloh,H., Zhou,J., Haag-Molkenteller,C., Dasgupta,P., Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder, Neurourology and Urodynamics, 30, 556-562, 2011	Insufficient outcome data presented
Rovner,E., Kennelly,M., Schulte-Baukloh,H., Zhou,J., Molkenteller,C.H., Dasgupta,P., Urodynamic RESULTS and clinical outcomes with intravesical botulinum toxin a (onabotuliumtoxina) in a randomized, placebo controlled dose-finding Study in idiopathic overactive bladder, Journal of Urology, 183, e591-e592, 2010	Conference abstract
Rudd, I., Kavia, R., Jenks, J., Hamid, R., Ockrim, J., Shah, J., Greenwell, T., Patient treatment preferences for symptomatic refractory urodynamic idiopathic detrusor overactivity (IDO), BJU international, 109, 45, 2012	Intervention and comparator not relevant to the protocol
Sahai, A., Khan, M. S., Le Gall, N., Dasgupta, P., Urodynamic Assessment of Poor Responders After Botulinum Toxin-A Treatment for Overactive Bladder, Urology, 71, 455-459, 2008	Intervention and comparator not relevant to the protocol
Sahai,A., Sangster,P., Kalsi,V., Khan,M.S., Fowler,C.J., Dasgupta,P., Assessment of urodynamic and detrusor contractility variables in patients with overactive bladder syndrome treated with botulinum toxin-A: is incomplete bladder emptying predictable?, BJU International, 103, 630-634, 2009	Study design not relevant to the protocol
Smith, A., Bevan, D., Douglas, H. R., James, D., Management of urinary incontinence in women: Summary of updated NICE guidance, BMJ (Online), 347 (7925) (no pagination), 2013	Summary guideline paper
Thuroff,J.W., Abrams,P., Andersson,K.E., Artibani,W., Chapple,C.R., Drake,M.J., Hampel,C., Neisius,A., Schroder,A., Tubaro,A., EAU guidelines on urinary incontinence, European Urology, 59, 387-400, 2011	Study design not relevant to protocol - Guideline summary.

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
Van Breda, H. M. K., Heesakkers, J. P. F. A., Botulinum Toxin A in Clinical Practice, the Technical Aspects and What Urologists Want to Know about It, Urologia Internationalis, 95, 411-416, 2015	Study design not relevant to protocol.
Wang, C. C., Lee, C. L., Kuo, H. C., Efficacy and Safety of Intravesical OnabotulinumtoxinA Injection in Patients with Detrusor Hyperactivity and Impaired Contractility, Toxins, 8, 18, 2016	Intervention and comparator not relevant to protocol.
Wang, C. C., Liao, C. H., Kuo, H. C., Diabetes mellitus does not affect the efficacy and safety of intravesical onabotulinumtoxinA injection in patients with refractory detrusor overactivity, Neurourology & Urodynamics, 33, 1235-9, 2014	Intervention and comparator not relevant to protocol.
Wang,C., Kuo,H., Efficacy and safety of intravesical onabotuliumtoxin a injection on patients with idiopathic detrusor overactivity and diabetes mellitus, Neurourology and Urodynamics, 31, 821-822, 2012	Intervention and comparator not relevant to protocol.
Wang,C.C., Kuo,H.C., Diabetes mellitus does not affect the efficacy and safety of intravesical botunilum toxin type a injection on patients with oaveractive bladder, Journal of Urology, 187, e794-, 2012	Intervention and comparator not relevant to protocol.
Wu, S. Y., Wang, C. C., Kuo, H. C., Safety and efficacy of botulinum toxin a treatment for patients with detrusor overactivity and inadequate contractility, Journal of Urology, 1), e1018, 2016	Intervention and comparator not relevant to protocol.
Yamaguchi,O., Nishizawa,O., Takeda,M., Yokoyama,O., Homma,Y., Kakizaki,H., Obara,K., Gotoh,M., Igawa,Y., Seki,N., Yoshida,M., Clinical guidelines for overactive bladder: Guidelines, International Journal of Urology, 16, 126-142, 2009	Narrative review and treatment algorithm
Yared, J. E., Gormley, E. A., The Role of Urodynamics in Elderly Patients, Clinics in Geriatric Medicine, 31, 567-579, 2015	Study design not relevant to protocol - not a systematic review.

Excluded clinical studies list for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Study	**Reason for Exclusion**
Botulinum toxin type A (Botox®) (Structured abstract), Health Technology Assessment Database, 2013	Conference abstract
Codependent with PBAC- intravesical injection of botulinum toxin (Botox) into the bladder wall for urinary incontinence due to idiopathic overactive bladder (Structured abstract), Health Technology Assessment Database, 2013	Government website - only protocol and final decision documents are presented
Abdallah, O, Othman, T, Sherif, H, Habous, M, Safety and efficacy of botulinium toxin A intravesical instillation in treatment of refractory overactive bladder (Abstract number 121), Proceedings of the 45th Annual Meeting of the International Continence Society (ics), 2015 Oct 6-9, Montreal, Canada, 2015	Comparison is not relevant to protocol
Adile, B, Gugliotta, G, Adile, G, Passalacqua, D, Vella, M, Melloni, D, Botox (Trademark) for idiopathic overactive bladder patients refractory to antimuscarinic therapy: a 53 patients randomized double blind placebo controlled trial (Abstract number 667), Proceedings of the 41st annual meeting of the international continence society (ics), 2011 aug 29 to sept 2, glasgow, scotland, 2011	Conference abstract
Allahdin,S., Oo,N., An overview of treatment of overactive bladder syndrome in women, Journal of Obstetrics and Gynaecology, 32, 217-221, 2012	Narrative literature review
Altaweel,W., Mokhtar,A., Rabah,D.M., Prospective randomized trial of 100u vs 200u botox in the treatment of idiopathic overactive bladder, Urology Annals, 3, 66-70, 2011	Population does not meet the inclusion criteria - unclear what proportion of women are included in the study
Andrade, R., Silva, A. S., Viana, R., Viana, S., Mascarenhas, T., Effectivity of botulinum toxin a in improving qol, decreasing the daily episodes of UI and in achieving full continence: A systematic review, Female Pelvic Medicine and Reconstructive Surgery, 20, S336, 2014	Population does not meet the inclusion criteria - population have neurogenic overactive bladder syndrome

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Anger,J., Weinberg,A., Suttorp,M., Litwin,M., Shekelle,P., Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: A systematic review of the literature, Neurourology and Urodynamics, 29, 325-, 2010	Systematic review - references checked for inclusion
Anonymous,, 44th Annual Meeting of the International Continence Society, ICS 2014, Neurourology and Urodynamics. Conference: 44th Annual Meeting of the International Continence Society, ICS, 33, 2014	Summary of conference proceedings - references checked for inclusion
Anonymous,, 33rd Annual Scientific Meeting of the American Urogynecologic Society, AUGS 2012, Female Pelvic Medicine and Reconstructive Surgery. Conference: 33rd Annual Scientific Meeting of the American Urogynecologic Society, AUGS, 18, 2012	Conference abstract
Anonymous,, 34th Annual Scientific Meeting of the American Urogynecologic Society, AUGS 2013, 19, 2013	Conference abstract
Anonymous,, 2014 AUGS-IUGA Scientific Meeting, International Urogynecology Journal and Pelvic Floor Dysfunction. Conference, 25, 2014	Summary of conference proceedings - references checked for inclusion
Apostolidis,A., Pharmacotherapy for overactive bladder: Minimally invasive treatment-botulinum toxins, Expert Opinion on Pharmacotherapy, 12, 1029-1039, 2011	Narrative literature review
Bertapelle, Mp, Vottero, M, Popolo, Gd, Mencarini, M, Ostardo, E, Spinelli, M, Giannantoni, A, D'Ausilio, A, Sacral neuromodulation and Botulinum toxin A for refractory idiopathic overactive bladder: a cost-utility analysis in the perspective of Italian Healthcare System (Provisional abstract), World journal of urology, epub, 2014	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Brubaker, L, Refractory urge urinary incontinence and botulinum A toxin injection trial (Abstract number 101), Neurourology and Urodynamics, 26, 728, 2007	Comparison is not relevant to protocol - placebo controlled study
Brubaker, L, Refractory urge urinary incontinence and botulinum A toxin injection (RUBI) trial (Abstract number 2 Oral), Journal of Pelvic Medicine & Surgery, 13, 224-5, 2007	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Cardozo,L., Systematic review of overactive bladder therapy in females, Canadian Urological Association Journal, 5, S139-S142, 2011	Systematic review - references checked for inclusion
Casanova, N., McGuire, E., Fenner, D. E., Botulinum toxin: A potential alternative to current treatment of neurogenic and idiopathic urinary incontinence due to detrusor overactivity, International Journal of Gynecology and Obstetrics, 95, 305-311, 2006	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Chancellor, M. B., Elovic, E., Esquenazi, A., Naumann, M., Segal, K. R., Schiavo, G., Smith, C. P., Ward, A. B., Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions, Toxicon, 67, 129-40, 2013	Systematic review - references checked for inclusion
Chappie, C. R., Dmochowski, R., Nitti, V., Chancellor, M., Everaert, K., Thompson, C. R., Daniell, G., Zhou, J., Haag-Molkenteller, C., Dose ranging phase 2 study of botox (onabotulinumtoxina) in idiopathic oab: Benefit risk assessment, European Urology, Supplements, 9 (2), 62, 2010	Population does not meet the inclusion criteria - unclear what proportion of women are included in the study
Chapple, C, Thompson, C, Nardo, C, Yan, X, Haag-Molkenteller, C, OnabotulinumtoxinA significantly decreases urinary incontinence and provides treatment benefit in patients with idiopathic overactive bladder (Abstract number 550), Proceedings of the 42nd Annual Meeting of the International Continence (ics), 2012 Oct 15 to 19, Beijing, China, 2012	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Chibelean, C., Nechifor-Boila, I. A., Botulinum neurotoxin A for overactive bladder treatment: advantages and pitfalls, Canadian Journal of Urology, 22, 7681-9, 2015	Systematic review - references checked for inclusion
Chua, Michael Erlano, Lapitan, Marie Carmela M, Silangcruz, Jan Michael A, Luna, Jr Saturnino, Morales, Jr Marcelino Lopeztan, Beta-3 adrenergic receptor agonist for adult with overactive bladder, Cochrane Database of Systematic Reviews, 2015	Cochrane systematic review - references checked for inclusion
Chuang,Y.C., Kuo,H.C., Chancellor,M.B., Botulinum toxin for the lower urinary tract, BJU International, 105, 1046-1058, 2010	Systematic review - references checked for inclusion
Cohen, Bl, Barboglio, P, Gousse, Ae, Can we predict who will respond to botulinum toxin-A injections for idiopathic overactive bladder? (Abstract number 18), Neurourology and Urodynamics, 27, 132-3, 2008	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Cornu, J. N., Re: OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women: A Randomized Clinical Trial, European Urology., 2017	Commentary paper
Cui, Y., Wang, L., Liu, L., Zeng, F., Niu, J., Qi, L., Chen, H., Botulinum toxin-A injections for idiopathic overactive bladder: a systematic review and meta-analysis, Urologia Internationalis, 91, 429-38, 2013	Systematic review - studies included do not have the appropriate comparator

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Cui, Y., Zhou, X., Zong, H., Yan, H., Zhang, Y., The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: A systematic review and meta-analysis, Neurourology & Urodynamics, 34, 413-9, 2015	Systematic review - studies included do not have the appropriate comparator
da Silva, C. M., Chancellor, M. B., Smith, C. P., Cruz, F., Use of botulinum toxin for genitourinary conditions: What is the evidence?, Toxicon, 107, 141-7, 2015	Systematic review -references checked for inclusion
Dowson,C., Sahai,A., Watkins,J., Dasgupta,P., Khan,M.S., The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: a randomised double-blind placebo-controlled trial, International Journal of Clinical Practice, 65, 698-704, 2011	Comparison is not relevant to protocol - 100 units botulinum toxin versus saline
Drug, company, A multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study of the safety and efficacy of a single treatment of BOTOX® (botulinum toxin type A) purified neurotoxin complex in patients with idiopathic overactive bladder with urinary urge incontinence, Https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-001936-59, 2005	Website - population does not meet the inclusion criteria, data not presented for women
Duggan, P, The BIDO (Botulinum toxin for Idiopathic Detrusor Overactivity) trial, Australasian Gynaecological Endoscopy & Surgery Society Ltd (AGES) at http://www.ages.com.au/fund2010.htm (accessed on 10.2.2011), 2011	Unable to obtain full text article
Duthie, James B, Vincent, Michael, Herbison, G Peter, Wilson, David Iain, Wilson, Don, Botulinum toxin injections for adults with overactive bladder syndrome, Cochrane Database of Systematic Reviews, 2011	Cochrane systematic review - references checked for inclusion
Duthie,J., Vincent,M., Herbison,P., Wilson,D., Intravesical botulinum toxin injections for overactive bladder syndrome-a cochrane review, International Urogynecology Journal and Pelvic Floor Dysfunction, 22, S140-, 2011	Conference abstract of excluded Cochrane review (Duthie 2011)
Duthie,J., Vincent,M., Herbison,P., Wilson,P., The safety and efficacy of intravesical botulinum toxin for OAB in adults: Preliminary findings of a Cochrane Review, BJU International, 107, 21-, 2011	Conference abstract
Eldred-Evans, D., Seth, J., Dowson, C., Malde, S., Watkins, J., Khan, M. S., Dasgupta, P., Sahai, A., Licensed and approved vs traditional dose of onabotulinumtoxinA in refractory overactive bladder?, European Urology, Supplements, 15 (3), e878+e878a, 2016	Population does not meet inclusion criteria - unclear what proportion of women are included in the study

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Eldred-Evans, D., Seth, J., Khan, M. S., Chapple, C., Dasgupta, P., Sahai, A., Adverse events with botox and dysport for refractory overactive bladder: A systematic review, Neurourology and Urodynamics, 34, S105-S106, 2015	Systematic review - references checked for inclusion
Flynn, M, Amundsen, C, Perevich, M, Webster, G, Short-term outcomes of a randomized, double-blind placebo controlled trial of botulinum A toxin for the management of severe idiopathic detrusor overactivity incontinence (Abstract number 33, poster), Neurourology and Urodynamics, 27, 151-2, 2008	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Flynn, M, Amundsen, C, Webster, G, Short-term outcomes of a randomized, double-blind placebo controlled tiral of botulinum A toxin for the management of severe idiopathic detrusor overactivity incontinence (Abstract number 3 Oral), Journal of Pelvic Medicine & Surgery, 13, 225-6, 2007	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Flynn, M, Amundsen, C, Webster, G, Short-term outcomes of a randomized, double-blind placebo controlled trial of botulinum A toxin for the management of severe idiopathic detrusor overactivity incontinence (Abstract number 317), Proceedings of the 37th annual meeting of the international continence soceity (ics), 20-24 aug 2007, rotterdam, netherlands, 2007	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Flynn,M.K., Amundsen,C.L., Perevich,M., Liu,F., Webster,G.D., Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder, Journal of Urology, 181, 2608-2615, 2009	Comparison is not relevant to protocol - 200 and 300 units botulinum toxin combined
Fowler,C., Auerbach,S., Ginsberg,D., Hale,D., Radziszewski,P., Rechberger,T., Kowalski,J., Zhou,J., Botulinum toxin a (BOTOX) demonstrates dose-dependent improvements in health-related quality-of-life measures in idiopathic overactive bladder, Journal of Urology, 181, 558-, 2009	Abstract publication to included study (Dmochowski 2010)
Fowler,C.J., Auerbach,S., Ginsberg,D., Hale,D., Radziszewski,P., Rechberger,T., Patel,V.D., Zhou,J., Thompson,C., Kowalski,J.W., OnabotulinumtoxinA Improves Health-Related Quality of Life in Patients With Urinary Incontinence Due to Idiopathic Overactive Bladder: A 36-Week, Double-Blind, Placebo-Controlled, Randomized, Dose-Ranging Trial, European Urology, 62, 148-157, 2012	No relevant outcomes presented

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Freemantle, N., Ginsberg, D. A., McCool, R., Fleetwood, K., Arber, M., Khalaf, K., Loveman, C., Ni, Q., Glanville, J., Comparative assessment of onabotulinumtoxinA and mirabegron for overactive bladder: an indirect treatment comparison, BMJ Open, 6, e009122, 2016	Systematic review - references checked for inclusion
Geoffrion, R., Society of, Obstetricians, Gynaecologists of, Canada, Treatments for overactive bladder: focus on pharmacotherapy, Journal of Obstetrics & Gynaecology Canada: JOGC, 34, 1092-101, 2012	Systematic review - references checked for incluison
Ghei, M, Maraj, B, Miller, R, Nathan, S, Shah, J, O'Sullivan, C, Fowler, C, Malone-Lee, J, Effects of botulinum toxin B on refractory detrusor overactivity: a randomised, double-blind, placebo controlled, cross over trial (Abstract), Neurourology and Urodynamics, 24, 548-9, 2005	Intervention is not relevant to protocol - Botulinum B
Giannantoni, A., Bini, V., Dmochowski, R., Hanno, P., Nickel, J. C., Proietti, S., Wyndaele, J. J., Contemporary management of the painful bladder: A systematic review, European Urology, 61, 29-53, 2012	Systematic review - references checked for inclusion
Gormley, E. A., Lightner, D. J., Burgio, K. L., Chai, T. C., Clemens, J. Q., Culkin, D. J., Das, A. K., Foster Jr, H. E., Scarpero, H. M., Tessier, C. D., Vasavada, S. P., Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline, Journal of Urology, 188, 2455-2463, 2012	Non-systematic review
Gormley, E. A., Lightner, D. J., Faraday, M., Vasavada, S. P., Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment, Journal of Urology, Part S. 193, 1572-1580, 2015	Systematic review - references checked for inclusion
Gousse, A, Barboglio, P, Cohen, B, Rodriguez, D, Caruso, D, Botox (R) for idiopathic overactive bladder patients refractory to antimuscarinic therapy in the absence of detrusor overactivity (Abstract number 133), Neurourology and Urodynamics, 27, 724-5, 2008	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Gousse, A, Cohen, B, Rodriguez, D, Barboglio, P, Botulinum toxin A: intradetrusor re-injections in idiopathic overactive bladder every 6 months - 3 years follow up (Abstract number 102), Neurourology and Urodynamics, 26, 728-9, 2007	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Gousse, A, Shirodkar, S, Gomez, C, Kanagarajah, P, Barboglio, P, Caruso, D, Botox (trademark) for idiopathic overactive bladder patients refractory to antimuscarinic therapy in	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
the absence of urodynamically demonstrable detrusor overactivity (Abstract number: Poster# 64), Neurourology and Urodynamics, 28, 144-5, 2009	
Gousse, A, Tunuguntla, Hsgr, Rodriguez, D, Velazquez, D, Dose-finding prospective randomized study to evaluate the efficacy and safety of botulinum-a toxin for refractory idiopathic overactive bladder (Abstract number 254), Proceedings of the 35th Annual Meeting of the International Continence Society (ICS); 2005 Aug 28 - Sept 2; Montreal, 2005	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Gousse, Ae, Tununguntia, Hsgr, Bateman, D, Velasquez, D, Dose-finding prospective randomized study to evaluate the efficacy and safety of botulinum-A toxin for refractory non-neurogenic overactive bladder (Abstract), Neurourology and Urodynamics, 24, 161, 2005	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Gries,K.S., Campbell,J.D., Watanabe,J.H., Dmochowski,R.R., Sullivan,S.D., Characterization of treatment success for overactive bladder with urinary urge incontinence refractory to oral antimuscarinics, Journal of Urology, 181, 85-, 2009	Conference abstract
Hanna-Mitchell, A. T., Kashyap, M., Chan, W. V., Andersson, K. E., Tannenbaum, C., Pathophysiology of idiopathic overactive bladder and the success of treatment: a systematic review from ICI-RS 2013, Neurourology & Urodynamics, 33, 611-7, 2014	Systematic review - references checked for inclusion
Hartmann,K.E., McPheeters,M.L., Biller,D.H., Ward,R.M., McKoy,J.N., Jerome,R.N., Micucci,S.R., Meints,L., Fisher,J.A., Scott,T.A., Slaughter,J.C., Blume,J.D., Treatment of overactive bladder in women, Evidence Report/Technology Assessment, 1-120, v, 2009	Interventions not relevant to protocol - not botulinum toxin
Hayes,, Inc,, Botulinum toxin treatment for detrusor instability (Structured abstract), Health Technology Assessment Database, 2011	Unable to obtain full text article
Jiang, Y, Lee, C, Kuo, H, Intravesical instillation of liposome encapsulated onabotulinumtoxinA for patients with overactive bladder - a pilot clinical study (Abstract number 569), Proceedings of the 44th Annual Meeting of the International Continence Society (ics), 2014 Oct 20-24, Rio de Janeiro, Brazil, 2014	Comparison is not relevant to protocol - saline
Jiang, Y. H., Kuo, H. C., Liu, H. T., Chuang, Y. C., Birder, L. A., Chancellor, M., Pilot study of liposome encapsulated onabotulinumtoxinA for patients with overactive bladder-clinical results and changes of urothelial sensory proteins in a single centre, European Urology, Supplements, 13 (1), e579-e579a, 2014	Comparison is not relevant to protocol - saline

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Kalsi, V, Popat, R B, Apostolidis, A, Kavia, R, Odeyemi, I A O, Dakin, H A, Warner, J, Elneil, S, Fowler, C J, Dasgupta, P, Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre (Structured abstract), European Urology, 49, 519-527, 2006	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Kessler,T.M., Words of wisdom. Re: Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial, European Urology, 52, 1793-1794, 2007	Commentary paper
Khan, Ms, The effects of botulinum toxin A on patients with idiopathic detrusor overactivity. A double-blind, randomised, placebo-controlled trial, Http://isrctn.org/ISRCTN16995641, 2005	Comparison is not relevant to protocol - placebo controlled
Killock, D., Incontinence: Liposomal onabotulinumtoxinA instillation piloted for OAB, Nature Reviews Urology, 11, 185, 2014	Comparison is not relevant to protocol - saline
King, J, Neville, J, A randomised, double-blind, placebo-controlled trial of botulinum toxin type A injections for the treatment of refractory idiopathic detrusor overactivity (Abstract number 130), International Urogynecology Journal and Pelvic Floor Dysfunction, 18, S77, 2007	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Ksibi,I., Godard,A.L., Azouvi,P., Denys,P., Dziri,C., Botulinum toxin and refractory non-neurogenic overactive detrusor, Annals of Physical and Rehabilitation Medicine, 52, 668-683, 2009	Systematic review - references checked for inclusion
Kuo, H, Liu, H, Will suburothelial injection of different dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? (Abstract number 145), Proceedings of the International Continence Society (ICS), 36th Annual Meeting, 2006 Nov 27-Dec 1, Christchurch, New Zealand, 2006	Population does not meet inclusion criteria - the majority of participants were male
Kuo, H. C., Botulinum toxin injection for overactive bladder, International journal of urology, 19, 406, 2012	Outcomes are not relevant to protocol
Kuo, H-C, Comparative study of the therapeutic effects of different intravesical injections of botulinum toxin A on overactive bladder (Poster abstract number 1190), Journal of Urology, 177, 2007	Unable to obtain full text article

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Kuo,H.C., Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity?, Urology, 68, 993-997, 2006	Population does not meet the inclusion criteria - the majority of participants were male
Leong, Rk, Wachter, Sg, Joore, Ma, Kerrebroeck, Pe, Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder (Structured abstract), BJU international, 108, 558-564, 2011	Comparison is not relevant to protocol - sacral neuromodulation
Lopez Ramos, H., Torres Castellanos, L., Ponce Esparza, I., Jaramillo, A., Rodriguez, A., Moreno Bencardino, C., Management of Overactive Bladder With OnabotulinumtoxinA: Systematic Review and Meta-analysis, Urology, 100, 53-58, 2017	Systematic review - references checked for inclusion
Lucioni, A, Rapp, De, Reynolds, Ws, Gong, Em, Fedunok, Pa, Bales, Gt, Evaluation of the effect of injection volumes of intravesical botulinum-A toxin injections in patients with overactive bladder symptoms (Abstract number 17), Neurourology and Urodynamics, 27, 132, 2008	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Moga, M. A., Banciu, S., Dimienescu, O., Bigiu, N. F., Scarneciu, I., Botulinum-A Toxin's efficacy in the treatment of idiopathic overactive bladder, JPMA - Journal of the Pakistan Medical Association, 65, 76-80, 2015	Narrative literature review
Naser, O., Mohamed, O., Zein, H., Hassan, O., Kamel, M., Al Nahrawi, S., Negida, A., Ali, W., Omar, A., Ashraf, B., Gana, B., Safety and efficacy of onabotulinumtoxina for the treatment of neurogenic and idiopathic overactive bladder: A meta-analysis of ten randomized controlled trials, Neurourology and Urodynamics, 34, S110, 2015	Conference abstract
Ndegwa, S, Cunningham, J, Botulinum toxin A for the management of pelvic pain and urinary incontinence in women: a review of the clinical-effectiveness and safety (Structured abstract), Health Technology Assessment Database, 2009	Systematic review - references checked for inclusion
Obloza, A., Toozs-Hobson, P., Kirby, J., Yates, D. J., Indirect treatment comparison of medical therapies for an overactive bladder, International Urogynecology Journal and Pelvic Floor Dysfunction, 1), S33-S35, 2015	Systematic review - references checked for inclusion
Owen, R. K., Tincello, D. G., Bujkiewicz, S., Abrams, K., Comparative efficacy of interventions for overactive bladder syndrome: A systematic review and network meta-analysis, Value in health, 18 (3), A186, 2015	Systematic review - references checked for inclusion

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
Owen, R. K., Tincello, D. G., Bujkiewicz, S., Abrams, K., Hierarchical network meta-analysis incorporating ordering constraints on increasing doses of interventions-application to overactive bladder syndrome, Value in health, 17 (7), A543, 2014	Conference abstract
Patel,A.K., Patterson,J.M., Chapple,C.R., The emerging role of intravesical botulinum toxin therapy in idiopathic detrusor overactivity, International journal of clinical practice, 60, 27-32, 2006	Systematic review - references checked for inclusion
Rachaneni, S., Champaneria, R., Latthe, P., Does the outcome of botulinum toxin treatment differ in OAB patients with detrusor overactivity compared to those without detrusor overactivity?:A systematic review, International Urogynecology Journal and Pelvic Floor Dysfunction, 1), S32-33, 2015	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Rachaneni, S., Latthe, P., Effectiveness of BTX-A and neuromodulation in treating OAB with or without detrusor overactivity: a systematic review, International urogynecology journal, 12, 12, 2017	Comparison is not relevant to protocol - Dysport
Rovner,E., Kennelly,M., Schulte-Baukloh,H., Zhou,J., Haag-Molkenteller,C., Dasgupta,P., Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder, Neurourology and Urodynamics, 30, 556-562, 2011	Outcomes not relevant to the protocol
Rovner,E., Kennelly,M., Schulte-Baukloh,H., Zhou,J., Molkenteller,C.H., Dasgupta,P., Urodynamic RESULTS and clinical outcomes with intravesical botulinum toxin a (onabotuliumtoxina) in a randomized, placebo controlled dose-finding Study in idiopathic overactive bladder, Journal of Urology, 183, e591-e592, 2010	Outcomes not presented separately for women
Roxburgh,C., Cook,J., Dublin,N., Anticholinergic drugs versus other medications for overactive bladder syndrome in adults, Cochrane Database of Systematic Reviews, -, 2007	Systematic review -references checked for inclusion
Sahai, A, Khan, M, Smith, K, Dasgupta, P, Botulinum toxin-A for patients with idiopathic detrusor overactivity: early results from a randomised, double-blind, placebo-controlled trial (Abstract number 428), Proceedings of the International Continence Society (ICS), 35th Annual Meeting, 2005 Aug 28-Sep 2, Montreal, Canada, 2005	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Sahai, A, Khan, S, Dasgupta, P, Quality of life in patients with symptoms of overactive bladder and refractory idiopathic detrusor over activity following intradetrusor injections of	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
botulinum toxin type A: results from a randomised, double blind, placebo-controlled trial (Abstract number 675), European Urology, Supplements, 5, 191, 2006	
Sahai, A., Dowson, C., Khan, M. S., Dasgupta, P., Repeated Injections of Botulinum Toxin-A for Idiopathic Detrusor Overactivity, Urology, 75, 552-558, 2010	Comparison is not relevant to protocol - no comparison to 100 units botulinum toxin
Sun, Y., Luo, D., Tang, C., Yang, L., Shen, H., The safety and efficiency of onabotulinumtoxinA for the treatment of overactive bladder: a systematic review and meta-analysis, International Urology & Nephrology, 47, 1779-88, 2015	Systematic review - references checked for inclusion
Tincello,D.G., Botulinum toxin treatment for overactive bladder and detrusor overactivity in adults, World Journal of Urology, 30, 451-456, 2012	Narrative literature review
Toth,P.P., Treatment of urge urinary incontinence with botulinum toxin A, Journal of Applied Research, 6, 258-259, 2006	Editorial
Truzzi, Jc, Bruschini, H, Simonetti, R, Miguel, S, What is the best dose for intravesical botulinum-A toxin injection in overactive bladder treatment? A prospective randomized preliminary study (Abstract), Proceedings of the Joint Meeting of the International Continence Society (ICS) (34th Annual Meeting) and the International UroGynecological Association (IUGA), 2004 Aug 23-27, Paris, France, Abstract number 520, 2004	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
Veeratterapillay, R., Lavin, V., Thorpe, A., Harding, C., Posterior tibial nerve stimulation in adults with overactive bladder syndrome: A systematic review of the literature, Journal of Clinical Urology, 9, 120-127, 2016	Systematic review - references checked for inclusion
Wein, A. J., Re: OnabotulinumtoxinA improves health-related quality of life in patients with urinary incontinence due to idiopathic overactive bladder: A 36-week, double-blind, placebo-controlled, randomized, dose-ranging trial, Journal of Urology, 189, 2206, 2013	Editorial

Economic studies

Excluded economic studies list for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

All economic studies were excluded at the initial title and abstract screening stage.

Excluded economic studies list for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

All economic studies were excluded at the initial title and abstract screening stage.

Appendix L – Research recommendations

Research recommendations for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Research recommendations for review question: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?

Research recommendation rationale

Research question	
Why this is needed	
Importance to 'patients' or the population	
Relevance to NICE guidance	
Relevance to the NHS	
National priorities	
Current evidence base	
Equality	
Feasibility	
Other comments	

Research recommendation statements

Criterion	Explanation
Population	
Intervention	
Comparator	
Outcome	
Study design	
Timeframe	