National Institute for Health and Care Excellence

Draft for consultation

Urinary incontinence and pelvic organ prolapse in women: management

[D] Evidence reviews for the management of overactive bladder

NICE guideline tbc

Evidence reviews

October 2018

Draft for consultation

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

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ISBN:

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Management of women with overactive bladder

Review questions

This evidence report covers several reviews within subsections. The following are the two review questions that are going to be covered in this document 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 botulinum toxin type A (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 (BoNT-A) treatment?

Introduction

The aim of this review is to determine whether urodynamic assessment provides useful information in addition to clinical assessment when deciding whether to offer botulinum toxin to women with overactive bladder (OAB). The aim was to compare the effects of botulinum toxin type A (BoNT-A) treatment in women with OAB with and without detrusor overactivity confirmed by urodynamic assessment.

The previous recommendation was that only women who had proven detrusor overactivity identified by urodynamic investigation should be considered for this treatment. There was some concern that some women in whom detrusor overactivity is not demonstrated at urodynamic assessment, might be denied treatment with Botulinum toxin and have either no treatment or more invasive therapy because of this recommendation. The committee were aware of new evidence suggesting that women with OAB who have not had urodynamic investigation can benefit from treatment with botulinum toxin and considered it was important to review this evidence.

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.
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.

Outcomes	**Critical**
	• 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

- 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

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 and for a full description of the methods see supplementary material C.

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 Register of Interests).

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 the use of intravesical botulinum toxin for idiopathic OAB syndrome without detrusor over-activity (DOA) on urodynamic assessment.

See also literature search strategies in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

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	Patients undergoing intravesical	Urodynamic assessment before BoNT	Urodynamic assessment before BoNT	Reduction in mean episodes of	Study included

Study	Population	Intervention	Comparison	Outcomes	Comments
Cohort study N=94 (75 patients with DOA; 19 patients without DOA) UK	botulinum toxin injections for idiopathic OAB between 17 January 2009 and 6 November 2009 at Nottingham City Hospital	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.	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.	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. Reduction in mean voids (95% CI) per day at 3 months. Self-catheterisation rates at 3 months.	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.

Quality assessment of clinical studies included in the evidence review

GRADE analysis was conducted on critical and important outcomes and 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. See supplementary document D for further information.

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

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 in the reduction of incontinence episodes per 24 hours, at 3 months after treatment with 200 U BoNT-A, favouring women with DOA compared to women without DOA (MD 0.20 [95% CI 0.01 to 0.39]), but there is uncertainty around the estimate of effect.

Continence specific health related 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 in mean change in ICIQ-OAB score at 3 months after treatment with 200 U BoNT-A, favouring women with DOA compared to women without DOA (MD -1.20 [95% CI -1.82 to -0.58]), 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) there may be a clinically important difference in the mean change in ICIQ-UI score at 3 months after treatment with 200 U BoNT-A, favouring 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 effects of botulinum toxin

Mean change in voids per day

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

Requirement for self-catheterisation or indwelling catheterisation

Self-catheterisation rates

- Very low quality evidence from one cohort study found no clinically-important difference in self-catheterisation rates at 3 months after treatment with 200 U BoNT-A in women with and without DOA (n=30 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.

Recommendations

D1.1 For women with OAB that has not responded to non-surgical management or treatment with medicine and who wish to discuss further treatment options:

- offer urodynamic investigation to determine whether detrusor overactivity is causing her OAB symptoms **and**
- if detrusor overactivity is causing her OAB symptoms, offer an invasive procedure in line with recommendations 1.4.48 to 1.4.59 in this guideline
- if there is no detrusor overactivity, seek advice on further management from the local MDT. **[2013, amended 2019]**

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

For women undergoing urodynamic assessment, the committee prioritised continence status, adverse effects of urodynamic testing, and continence specific health related quality of life as critical outcomes. It is not known whether women with OAB who have detrusor overactivity demonstrated at urodynamic assessment (UDS) respond better to treatment with Botulinum toxin A than women with the same symptoms in whom detrusor overactivity is not demonstrated during UDS. Continence status was therefore prioritised as a critical outcome as well as continence specific health related quality of life. If there is no benefit to UDS, above clinical assessment, women with OAB could avoid an unnecessary test and the associated adverse effects. The adverse effects of urodynamic testing including urinary tract infection are relatively common although rarely serious, and were also prioritised as critical by the committee.

Adverse effects of surgery, adverse effects of botulinum toxin, patient satisfaction and change in management were prioritised as important outcomes. Urodynamic assessment may detect other conditions that may change the management plan and the committee decided that this was an important outcome.

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

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.

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 in addition to their clinical expertise and experience.

The committee was presented with effectiveness data on the use of urodynamic assessment before BoNT-A in patients 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 local MDT review, to women with OAB caused by proven DOA that has not responded to conservative (non-surgical) management (including OAB drug therapy), as they agreed that it was still in line with current clinical practice.

The committee discussed how the aim of urodynamic testing in patients with OAB symptoms is to show if DOA is the underlying cause of the OAB symptoms. The 2013 guideline recommended treatment with BoNT-A after MDT review for women with OAB caused by DOA, and treatment with percutaneous sacral nerve stimulation (P-SNS) for patients with OAB symptoms not caused by DOA. The committee considered that this inconsistency across the recommendations had the potential to result in women, who might otherwise benefit from treatment with BoNT-A receiving P-SNS or a more invasive treatment, or being offered no further treatment. 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. The committee

agreed that if there is no detrusor overactivity, advice from the local MDT should be sought to ensure the woman receives further help in managing her condition. This recommendation was based on their clinical expertise and experience and developed by consensus. There are a number of significant possible adverse effects associated with the use of Botulinum toxin A for OAB and since the duration of action is prolonged (several months) the committee decided that women should have these risks discussed before deciding whether to have this treatment. The committee were aware that some women would not wish to have a treatment that has a high risk of voiding difficulty as they would not find self- catheterisation possible or acceptable and that this would need to be discussed before treatment. They were also aware that many women already suffer from recurrent urinary tract infection and may consider the increased risk of UTI unacceptable to them.

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 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. They agreed that considering it in women with OAB symptoms in whom DOA has not been demonstrated (using urodynamic testing) and for whom other treatments are not acceptable may have potential cost savings to the NHS because fewer women would receive P-SNS or other more invasive treatments. The committee also explained that the 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 entail expensive specialist NHS care at a later stage.

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 (BoNT-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). New evidence regarding dosing of Boulinum toxin type A 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. In addition the UK licence for BoNT-A is for a starting dose of 100 U and it was considered important to update this recommendation.

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
	  ○ anticholinergic 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
Outcomes	**Critical** • 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** • 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.

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 and for a full description of the methods see supplementary material C.

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 Register of Interests).

Clinical evidence

Included studies

Three studies were included in the review (Abdelwahab, 2015; Brubaker, 2012; Dmochowski, 2010).

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

See also literature search strategies in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

Excluded studies

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

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 prospective trial N=80 Egypt	Patients with idiopathic overactive bladder refractory to previous anticholinergics with different types of anticholinergic agents, either as a single	BoNT-A Type: Botox Dilution: 100U/1.0ml N=40 Injection technique: Cystoscopic intra detrusor	BoNT-A Type: Botox Dilution: 200U/1.0ml N=40 Injection technique: Cystoscopic intra detrusor	Mean change urge urinary incontinence per day at months 1, 3, 6 and 9 after treatment. Mean change in quality of life (EQ-5D)[b]	Study included males and females Gender - Female/N (%) N = 63 (78.75%)

Study	Population	Intervention	Comparison	Outcomes	Comments
	drug or a combination for >3 months.	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 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	measured at 1, 3, 6, 9 months after treatment Mean change urgency episodes per day at months 1, 3, 6 and 9 after treatment. Mean change frequency 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. Adverse effects at end of treatment.	
Brubaker 2012 (Secondary article to Dmochowski 2010) Randomised, multicentre, double-blind trial	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, 6, 12, 18, 24, 30, and 36.	

Study	Population	Intervention	Comparison	Outcomes	Comments
N= 313 (of which 272 completed the study) USA, Canada, UK, Germany, Belgium, Poland					
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=55 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=52 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.	Change from baseline in UUI episodes at week 12 Self-reported rate of absolute symptom reduction (episodes of incontinence) at week 24 PVR volume ≥ 200 ml and need for self-catheterisation Adverse effects during study period.	Gender - Female/N (%): N = 288/313 (92%)

Fr: French; BoNT-A: Onabotulinum toxin A; EQ-5D: EuroQoL Five Dimensions Questionnaire; OAB: Overactive Bladder; OAB-PSTQ: Overactive Bladder Patient Satisfaction with Treatment Questionnaire; OABSS: Overactive Bladder Symptom Score; 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, nighttime 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.

Also see clinical evidence tables in appendix D.

Quality assessment of clinical studies included in the evidence review

GRADE analysis was conducted on critical and important outcomes and 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. See supplementary document D for further information.

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

- 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) in women with OAB at 1 month, (MD 0.05 [95% CI -0.52 to 0.62]), 3 months (MD 0.13 [95% CI -0.70 to 0.96]), 6 months (MD 0.08 [95% CI -0.89 to 1.05]) and 9 months (MD 0.71 [95% CI -0.22 to 1.64]).

Continence specific health related quality of life

- 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 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 months (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

Urinary 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 urinary frequency at 1 month (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.
- Very low quality 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 months (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 month (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.
- Very low quality 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 months (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

- 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.
- Very low quality 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 PVR urine volume at 3 months (MD -1.12 [95% CI -4.91 to 2.67]), 6 months (MD -1.26 [95% CI -6.39 to 3.87]) and 9 months (MD -3.35 [95% CI -7.42 to 0.72]) 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 of 100 U BoNT-A for nocturia at 1 month (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.
- Very low quality 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 month (MD 0.03 [95% CI -0.66 to 0.72]), 3 months (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]) and 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 0.95 [95% CI 079 to 1.13], 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 there may be a 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 showed there may be a 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: n=95, RR 0.82 (95% CI 0.55 to 1.24).

Economic evidence statements

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

Recommendations

D2.1 After a local MDT review, offer bladder wall injection with botulinum toxin A[Error! Bookmark not defined.Error! Bookmark not defined.] to women with OAB caused by detrusor overactivity that has not responded to non-surgical management, including pharmacological treatments. **[2019]**

D2.2 Consider treatment with botulinum toxin A[Error! Bookmark not defined.Error! Bookmark not defined.] after a local MDT review for women with symptoms of OAB in whom urodynamics has not demonstrated detrusor overactivity, if the symptoms have not responded to non-surgical management and the woman does not wish to have other invasive treatments. **[2019]**

D2.3 After a local MDT review, discuss the risks and benefits of treatment with botulinum toxin A[Error! Bookmark not defined.] with women and explain:

- the likelihood of complete or partial symptom relief
- the process of clean intermittent catheterisation, the risks, and how long it might need to be continued
- the risk of adverse effects, including an increased risk of urinary tract infection
- that there is not much evidence about how long the injections work for, how well they work in the long term and their long-term risks. **[2019]**

D2.4 Start treatment with botulinum toxin A only if the woman is willing, in the event of developing significant voiding dysfunction:

- to perform clean intermittent catheterisation on a regular basis for as long as needed, or
- to accept a temporary indwelling catheter if the woman is unable to perform clean intermittent catheterisation **[2013, amended 2019]**

D2.5 Use 100 units as the initial dose of botulinum toxin type A[Error! Bookmark not defined.] to treat OAB in women. **[2019]**

D2.6 Offer a face-to-face or telephone review within 12 weeks of the first treatment with botulinum toxin A[3] to assess the response to treatment and adverse effects, and

- if there is good symptom relief, tell the woman how to self-refer for prompt specialist review if symptoms return, and offer repeat treatment as necessary
- if there is inadequate symptom relief, consider increasing subsequent doses of botulinum toxin type A[3] to 200 units and review within 12 weeks
- if there was no effect, discuss with the local MDT. **[2019]**

D2.7 If following injection of 100 units of botulinum toxin type A there has been adequate symptom relief but this has lasted for less than 6 months, consider increasing subsequent doses of botulinum toxin type A3 to 200 units and review within 12 weeks.

D2.8 Do not offer botulinum toxin B to women with proven detrusor overactivity. **[2019]**

Research recommendations

What is the long-term effectiveness of bladder wall injection with botulinum toxin A for overactive bladder in women?

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 BoNT-A treatment for OAB. Symptom reduction (clinical improvement), adverse effects of treatment and patient satisfaction (patient rated improvement) were agreed by the committee to be important outcomes of treatment with BoNT-A.

The committee agreed that these are the most important aspects of treating overactive bladder and urgency urinary incontinence, as women want to have fewer symptoms or to become continent. A relatively low risk but significant risk of BoNT-A is the need for a catheter which is an important consideration, and some women decline Botulinum toxin because of the risk of needing a catheter.

The quality of the evidence

For women treated with different doses of BoNT-A, the two RCT 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 RCT was available for inclusion in this review (Abdelwahab, 2015; Brubaker, 2012; Dmochowski, 2010). Brubaker (2012), was a secondary publication to Dmochowski (2010) and only two of the five 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.

Benefits and harms

The committee based their recommendations on the data presented in addition to 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 BoNT-A, and that there is insufficient good quality evidence about the most appropriate dose, whether the duration of effect is dose dependent, or what the optimal frequency is.

The committee was presented with effectiveness data on BoNT-A 100 units versus 200 units from two RCT. The committee was aware that the evidence available was drawn from low quality trials. The recommendation to use 100 units as the initial dose of BoNT-A was supported by the recommendation in the Summary of Product Characteristics of the licensed drug and the committee agree that there is insufficient good quality evidence to suggest that the main outcomes are inferior when starting treatment with 100 units of BoNT-A. However; there may be a longer duration of effect in women treated with 200 units and there are possible cost savings.

Despite the limited 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 if it does not, usual practice is to increase the dose.

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 opinion. Although the lower dose (100 units BoNT-

A) may result in some patients requiring more injections, the committee agreed 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 if symptom relief is inadequate or has not lasted for the six weeks, consider a dose of 200 units if women are willing to tolerate an increase in side effects. A further follow up after 12 weeks would then take place 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. 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 developed by consensus.

The committee was also 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.

With regard to reviewing treatment with botulinum toxin A, the committee noted that, the previous guideline had recommended a follow up at 6 months when treatment is effective or sooner if symptoms return for repeat treatment without an MDT referral. The committee discussed current clinical practice for follow up and it was suggested that most 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 usually be offered as late as 6 months. The committee also agreed to add that if treatment has no effect, or some effect, but which is considered not to provide adequate symptom relief, then it should be discussed with the local MDT. The changes to the recommendation were based on clinical experience and developed by consensus.

Due to the limited evidence relating to long-term effectiveness, the committee made a research recommendation about the long-term effectiveness of bladder wall injections of botulinum toxin A as treatment for overactive bladders in women. This is important because currently there is no long-term evidence. This research would be of high priority as it is an expensive treatment with no clear long-term effectiveness data or the need for re-treatment or continued self-catheterisation etc. The committee were particularly interested in treatment naïve patients and following their treatments over time.

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.

References

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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.

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Appendices

Appendix A – Review protocols

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

Table 5: Review protocol for 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.

Field (based on PRISMA-P	Content
	Patients with neurological diseases will be excluded.
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** 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** 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 (RCT)

Field (based on PRISMA-P	Content
	RCT Conference abstracts of RCT 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

Field (based on PRISMA-P	Content
	Dates from 1990.
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]

Field (based on PRISMA-P	Content
	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] 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 2014.
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 2014. 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 2014.
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 2014. 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.

Field (based on PRISMA-P	Content
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 2014.
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 2014. 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.

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

Table 6: review protocol for 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** • 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))

Field (based on PRISMA-P	Content
	• Requirement for self-catheterisation or indwelling catheterisation **Important** • 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 RCT • RCT • 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.

Field (based on PRISMA-P	Content
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. 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 2014.
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).

Field (based on PRISMA-P	Content
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 2014.
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 2014. 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 2014.
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 2014. 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.

Field (based on PRISMA-P	Content
PROSPERO registration number	Not registered with PROSPERO.

1

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.

#	Searches
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/
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)

ID	Search
#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)
#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

#	Searches
48	or/36-39,41-46 use oemezd
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
92	33 or 49
93	91 and 92

Database: Cochrane Library via Wiley Online

Date of last search: 17th March 2017.

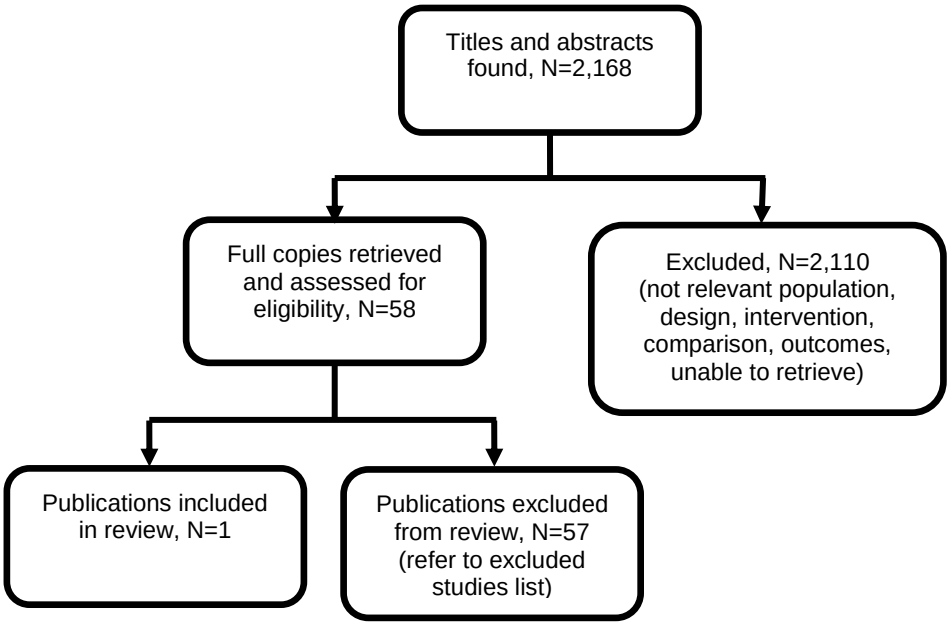
ID	Search
#1	MeSH descriptor: [Urinary Incontinence] this term only
#2	MeSH descriptor: [Urinary Incontinence, Urge] this term only
#3	MeSH descriptor: [Urinary Incontinence, Stress] this term only
#4	MeSH descriptor: [Urinary Bladder, Overactive] this term only
#5	MeSH descriptor: [Nocturia] this term 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)

ID	Search
#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)
#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

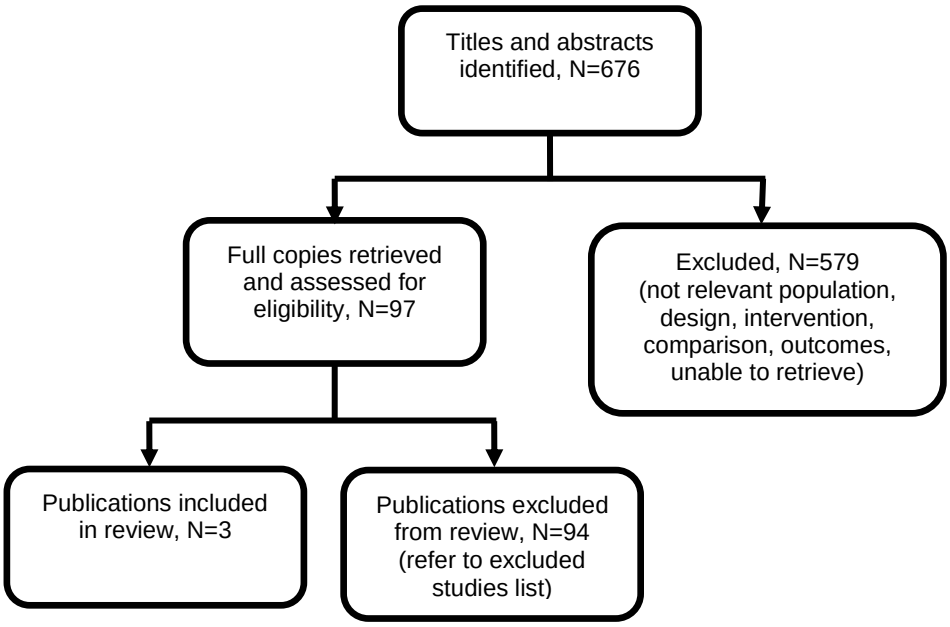
Clinical evidence study selection for review question: What is the value of urodynamic assessment before botulinum toxin type A treatment?

Figure 1: PRISMA flow chart for review question: what is the value 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: PRISMA flow chart for review question: 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?

Table 6: Clinical evidence tables for review: 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	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	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.	Results 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)	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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
A single hospital's experience of intravesical botulinum toxin for idiopathic overactive bladder syndrome (OAB) without detrusor overactivity (DOA) on urodynamic assessment. Study dates 17 January 2009 to 6 November 2009. Source of funding None stated	Inclusion criteria All patients undergoing intravesical botulinum toxin 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		Urodynamic assessment consisted of standard, non-ambulatory, non-video filling cystometry and pressure-flow studies 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.	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) Patients without DOA: (6.1, 9.8 to 2.5) 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)	(>50% missing data 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 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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			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.	Patients without DOA: 5.9 (7.3 to 4.5) Self-catheterisation rates (n/N) Patients with DOA: 23/75 (31%) Patients without DOA: 4/19 (21%)	acknowledged by the authors: Incomplete data available Randomised, placebo-controlled trial required to formally evaluate use of BoNT in patients with 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?

Table 7: Clinical evidence table for 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	Sample size N = 80 BoNT-A 100U: N=40 BoNT-A 200U: N=40 Characteristics Gender - Female/N (%) N = 63 (78.75%)	Interventions BoNT-A Type: Botox Dilution: 100U/1.0 ml or 200U/1.0ml Injection technique: Cystoscopic intra detrusor injection performed in 20	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.	Results 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)*	Limitations Random sequence generation: Unclear r isk of bias (not mentioned in text) Allocation concealment: Unclear risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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 (100U or 200U) in patients with idiopathic overactive bladder Study dates May 2011 to February 2014 Source of funding No funding sources reported	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) Detrusor overactivity - n/N (%) Not reported Duration of OAB - Mean ± SD Not reported Frequency - Mean ± SD	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	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. 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;	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)* QoL (EQ-5D) - 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)* Requirement of self-catheterisation or indwelling catheterisation Not reported. Frequency - Mean ± SD At 1 month BoNT-A 100U = 0.45 (0.503)*	(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)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	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 previous anticholinergics with different types of anticholinergic agents, either as a single drug or a combination for >3 months.		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.	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)* 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)*	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
	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 antineoplastic treatment			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 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". 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)*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				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)* BoNT-A 200U = 0.13 (0.342)* *significant in intragroup comparison to "before intervention". OABSS - Mean ± SD At 1 month BoNT-A 100U = 2.85 (2.537)* BoNT-A 200U = 3.32 (2.092)* 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))* Self-reported rate of absolute symptom reduction per day - Mean ± SD	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Not reported 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) Patient satisfaction with treatment Not reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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 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	Sample size See Dmochowski 2010 for details Characteristics See Dmochowski 2010 for details Inclusion criteria See Dmochowski 2010 for details Exclusion 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 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	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 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	Limitations See Dmochowski 2010 for details Other information See Dmochowski 2010 for details Also associated with Fowler 2012 and Rovner 2011 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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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 See Dmochowski 2010 for details			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 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	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 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	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
			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 patients requiring catheterisation for 1 day or more.	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 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%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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 100191 Country/ies where the study was carried out USA, Canada, UK, Germany, Belgium, Poland Study type Randomised, multicentre, double-blind trial	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 Duration of OAB - Median > 5 years Detrusor overactivity - n/N (%) N = 238/313 (76%) Inclusion criteria	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. 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	Results Change from baseline in UUI episodes at week 12 BoNT-A 100U = -20.7 BoNT-A 200U = -23.0 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 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%) Adverse effects (n/N; %) BoNT-A 100U = 44/55 (80.0%)	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% 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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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 "Supported by Allergan, Inc."	• 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 micturitions/day) • To have not been adequately managed with anticholinergi		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 observation adjusted by the ratio of means for the preceding and current visit for all non-missing values for all patients.	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%) Patient satisfaction with treatment (Week 12) Not reported	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 The authors acknowledged the following limitations: • Lack of requirement to confirm

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	c treatment (de fined as an inadequate response to or intolerable side effects) Exclusion criteria • Used clean intermittent catheterizatio n (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 volume voided > 3,000 ml or post-void residual				UTI by culture; • PVR of 200ml or greater recorded as an adverse effect of urinary retnetion regardless of symptoms or need for intervention; • No standardisati on regarding the initiation and cessation of catheterisati on provided, which most likely contributed to the variation among patients in the duration of catheterisati on and may

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(PVR) urine volume > 200 ml at screening				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 conducted 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 conducted 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 8: 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 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]	serious[3]	none	28	13	-	MD 0.2 higher (0.01 to 0.39 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[4]	none	21	9	-	MD 1.2 lower (1.82 to 0.58 lower)	⨁⊖⊖⊖ VERY LOW	CRITICAL
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]	no serious inconsistency[5]	none	21	9	-	MD 1.3 higher (0.27 to 2.33 higher)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Mean change in voids per day (follow-up 3 months; measured with: Patient reported diaries ; Better indicated by lower values)												

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**
1	observational studies	very serious [1]	no serious inconsistency	very serious[2]	very serious[6]	none	28	13	-	MD 0.3 higher (0.85 lower to 1.45 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Self-catheterisation rates (follow-up 3 months; measured with: Patient reported)												
1	Observational studies	very serious [1]	no serious inconsistency	very serious[2]	very serious[7]	None	21	9	-	RR 1.46 (0.57 to 3.71)	⨁⊖⊖⊖ 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
[3] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals cross one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.2).
[4] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals cross both default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.27).
[5] Evidence not downgraded, 95% confidence intervals do not cross default MID for continuous outcomes, MID 2.52, from Stenlund et al 2014.
[6] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals cross both default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.29).
[7] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals crosses both default MID for dichotomous outcomes, (0.8 and 1.25)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 9: 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]	very serious[3]	none	40	40	-	MD 0.05 higher (0.52 lower to 0.62 higher)	⨁⊖⊖⊖ VERY 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]	very serious[3]	none	40	40	-	MD 0.13 higher (0.7 lower to 0.96 higher)	⨁⊖⊖⊖ VERY 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]	serious[4]	none	40	40	-	MD 0.08 higher (0.89 lower to 1.05 higher)	⨁⊖⊖⊖ VERY 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)												

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]	no serious imprecision	none	40	40	-	MD 1.1 lower (5.85 lower to 3.65 higher)	⨁⨁⊖⊖ LOW	CRITICAL
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[5]	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[5]	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[5]	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[16]	no serious inconsistency	serious[2]	very serious[6]	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)												

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[7]	none	40	40	-	MD 0.10 higher (0.16 lower to 0.36 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
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[7]	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[7]	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]	no serious imprecision	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)												

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[8]	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)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[8]	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[9]	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[10]	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]	very serious[11]	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)												

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]	very serious[11]	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]	very serious[11]	none	40	40	-	MD 3.35 lower (7.42 lower to 0.72 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
PVR urine volume 200ml or greater (follow-up 9 months)												
1	randomised trials	serious[16]	no serious inconsistency	serious[2]	serious[12]	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[13]	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[13]	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)												

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[13]	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[13]	none	40	40	-	MD 0.57 higher (0.19 to 0.95 higher)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
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]	no serious imprecision	none	40	40	-	MD 0.22 higher (0.42 lower to 0.86 higher)	⨁⨁⊖⊖ 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[14]	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)												

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]	very serious[15]	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[6]	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)												
1	randomised trials	serious[16]	no serious inconsistency	serious[2]	very serious[6]	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[6]	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[12]	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)												

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[16]	no serious inconsistency	serious[2]	very serious[6]	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[16]	no serious inconsistency	serious[2]	serious[12]	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)												
1	randomised trials	serious[16]	no serious inconsistency	serious[2]	serious[12]	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[16]	no serious inconsistency	serious[2]	serious[12]	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[16]	no serious inconsistency	serious[2]	serious[12]	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

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
Modified OAB-PSTQ Q.16 Patients reporting that treatment "significantly met" or "exceeded" their primary expectation (follow-up 12 weeks)												
1	randomised trials	serious[16]	no serious inconsistency	serious[2]	serious[12]	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 found).

[2] Total number of women reporting this outcome not stated (includes both men and women).

[3] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals cross both default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (1.0)

[4] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (1.0).

[5] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (3.41).

[6] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals crosses both default MID for dichotomous outcomes, (0.8 and 1.25)

[7] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.26).

[8] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.24).

[9] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals cross both default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.24)

[10] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (7.52).

[11] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals cross both default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (7.52)

[12] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for dichotomous outcomes, (0.8 or 1.25)

[13] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (0.6).

[14] Evidence downgraded by 1 due to risk of serious imprecision, 95% confidence intervals crosses one default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (1.0).

[15] Evidence downgraded by 2 due to risk of very serious imprecision, 95% confidence intervals cross both default MID for continuous outcomes, calculated as 0.5 of SD of baseline control (1.0)

[16] 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 conducted for this review question. See supplementary material D for further information.

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 conducted for this review question. See supplementary material D for further information.

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 for 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 for 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 for 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 for 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 studies were identified 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 studies were identified for this review question.

Appendix K – Excluded studies

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

Clinical studies

Table 10: Excluded studies with reasons for exclusions

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, 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	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
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

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

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

Excluded studies: What is the value of urodynamic assessment before botulinum toxin type A treatment?	
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.
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.

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

Clinical studies

Table 11: Excluded studies with reasons for their exclusions

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
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

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

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

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
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 the absence of urodynamically demonstrable detrusor overactivity (Abstract number: Poster# 64), Neurourology and Urodynamics, 28, 144-5, 2009	Comparison is not relevant to protocol - no comparison to 200 units botulinum toxin
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	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?	
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	
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
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

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

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

Excluded studies: What is the most effective initial dose of botulinum toxin type A for treating overactive bladder?	
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 botulinum toxin type A: results from a randomised, double blind, placebo-controlled trial (Abstract number 675), European Urology, Supplements, 5, 191, 2006	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?	
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?

No economic studies were identified for this review question. See supplementary material D for further information.

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

No economic studies were identified for this review question. See supplementary material D for further information.

Appendix L – Research recommendations

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

No research recommendation was made for this review question.

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

1. What is the long-term effectiveness of bladder wall injection with botulinum toxin A for overactive bladder in women?

Why is this important?

No long term evidence from review. High priority because it's an expensive treatment and there is no clear long term effectiveness data on need for re-treatment, continued self-catheterisation etc. Treatment naïve patients at beginning, then treatments over time.

Table 12: Research recommendation rationale

Research question	What is the long-term effectiveness of bladder wall injection with Botulinum toxin A for OAB?
Importance to 'patients' or the population	Many women start treatment with Botulinum toxin A for OAB but there is little information as to the long-term effectiveness of the treatment and it is not known how many patients discontinue treatment due to loss of efficacy or side effects
Relevance to NICE guidance	No evidence was found in this review
Relevance to the NHS	Treatment with Botulinum toxin for OAB is an expensive treatment and there are significant known side effects but there is little evidence about how helpful the treatment is in the long term
National priorities	Medium
Current evidence base	Minimal
Equality	None known

Table 13: Research recommendation modified PICO table

Criterion	Explanation
Population	Women with OAB starting treatment with botulinum toxin A (treatment naïve)
Intervention	Treatment for OAB with botulinum toxin A
Comparator	Non Botulinum toxin A treatment for OAB
Outcome	Discontinuation of Botulinum toxin A therapy, complications such as recurrent UTI, rate of CISC, change in dose, need for alternative treatment
Study design	Prospective cohort study looking at long term (>5 years) effectiveness
Timeframe	>5 years
Additional information	Subgroups – dose dependent,