NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Difficulty passing urine or being unable to completely empty the bladder (urinary retention) can happen if the muscle controlling release of urine from the bladder (urethral sphincter) does not relax or the muscle lining the bladder does not contract. In some people, it can happen without any known cause (idiopathic) and with no physical obstruction to the urine flow (non-obstructive). In this procedure, botulinum toxin type A is injected into the urethral sphincter. The aim is to relax it and allow urine to be passed more easily, without needing to use a catheter to empty the bladder. The effects are temporary, and the procedure may need to be repeated every few months.

Contents

Abbreviations

Word or phrase	Abbreviation
Bladder outlet obstruction index	BOOI
Clean intermittent catheterisation	CIC
Cystometric bladder capacity	CBC
Detrusor overactivity with inadequate contractility	DHIC
Detrusor sphincter dyssynergia	DSD
Detrusor underactivity	DU
Dysfunctional voiding	DV
Detrusor voiding pressure	Pdet
Electromyography	EMG
External urethral sphincter	EUS
Functional profile length	FPL
International Prostate Symptom Score	IPSS
IPSS storage sub-score	IPSS-S
IPSS voiding sub-score	IPSS-V
Lower urinary tract symptoms	LUTS
Maximal urethral closure pressure	MUCP
Maximal urinary flow rate	Qmax
Patient Perception of Bladder Condition score	PPBC
Poor relaxation of the urethral sphincter	PRES
Post-void residual urine volume	PVR
Quality of life	QOL
Randomised controlled trial	RCT
Standard deviation	SD
Suprapubic catheter	SPC
Total IPSS score	IPSS-T
Urethral pressure profile	UPP
Urethral sphincter dysfunction	USD

Urinary tract infection	UTI
Video-urodynamic study	VUDS
Voided volume	VV
Voiding efficiency	VE

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2023

Procedure name

- Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Professional societies

- British Society of Urogynaecology
- British Association of Urological Surgeons.

Description of the procedure

Indications and current treatment

Idiopathic non-obstructive urinary retention is the inability to completely empty the bladder when there is no physical obstruction (in the urethra or bladder neck) to normal urine flow. It can be caused by USD. This can be because of DV, urethral sphincter hyperactivity or inadequate relaxation of the urethral sphincter (for example, Fowler's syndrome in younger women and people with female anatomy), or bladder functional problems (detrusor muscle underactivity, or

detrusor hyperreflexia and inadequate contractility). But the specific underlying cause of the condition is unknown. Idiopathic non-obstructive urinary retention is often asymptomatic, but some people have lower abdominal discomfort and pain. Also, it can cause complications such as recurrent UTIs and chronic kidney disease.

Current treatments for non-obstructive urinary retention include urotherapy (that is, education and rehabilitation for bladder and bowel management), an alpha adrenoreceptor-blocker medicine, urethral dilatation or CIC. When the condition is refractory to these treatments, it may be treated with sacral nerve stimulation or urinary diversion procedures.

What the procedure involves

Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention is usually done as an outpatient procedure with the person awake and lying in the lithotomy position. A local anaesthetic is used on either side of the external meatus. Botulinum toxin type A diluted with normal saline is injected directly into the external urethral sphincter using a syringe needle. A transperineal route (EMG guided) is used in women and a transurethral route (using electrical stimulation and cystoscopy guidance) is used in men.

The dose and number of injections, and the depth and position of injections on the EUS, vary and depend on the discretion of the clinician. People have oral antibiotics for a week. The aim of the procedure is to relax the sphincter muscle and restore voiding function. It may be repeated every few months.

Outcome measures

IPSS

The IPSS is a tool for classifying the severity of LUTS and assessing the impact of LUTS on QOL.

The IPSS questionnaire is intended to be completed by the patient. It contains 7 questions relating to symptom severity (each question is scored from 0 [best] to 5 [worst]) and 1 question relating to QOL due to urinary symptoms (scored from 0 [best] to 6 [worst]).

The IPSS severity score is interpreted as:

- Score 20 to 35: severely symptomatic.
- Score 8 to 19: moderately symptomatic.

- Score 0 to 7: mildly symptomatic.

Limitations of the IPSS questionnaire include lack of assessing incontinence, post-micturition symptoms and bother caused by each separate symptom.

Printable versions of the IPSS questionnaire are widely available online, for example, from the Royal United Hospital Bath NHS trust website.

PPBC

PPBC is a single item tool used to measure to assess the patient's subjective perception of urinary (bladder) problems. It is scored on a 6-point rating scale ranging from 1 (no problems) to 6 (many severe problems).

Efficacy summary

Success rate

In an RCT of 73 patients with medically refractory DV or DU comparing the effects of botulinum toxin type A (from now, botulinum) with normal saline urethral sphincter injections, there was an analysis of 62 patients who completed 1 month of follow up. This found that the overall success rate for both groups combined (defined as reduction of PPBC by more than or equal to 2) was 44%. Also, there was no statistically significant difference in success rate between patients who had botulinum injections and those who had saline placebo injections (37% [14/38] compared with 54%, [13/24], p= 0.114). Subgroup analysis showed that there was no statistically significant difference in success rate for the patients with DV (botulinum 44% [7/16] compared with placebo 68% [10/15], p= 0.200) and the patients with DU (botulinum 32% [7/22] compared with placebo 33% [3/9], p=0.935). The success rates after a second botulinum injection increased from 29% to 57% among patients with DV and from 25% to 50% among patients with DU (Jiang 2016).

In a case series of 27 patients with idiopathic low detrusor contractility that was treated with botulinum injection into the urethral sphincter, there was an overall success rate was 89% (24/27; Kuo 2007a).

In a case series of 66 patients who had 50 units (n=33) and 100 units (n=33) of botulinum into the urethral sphincter, there was no statistically significant difference in the overall success rate between the 2 doses (85% [28/33] compared with 91% [30/33], p=0.452; Kuo 2007b).

In a retrospective case series, 81 patients with non-neurogenic DV (55 with midurethral DV, 19 with distal urethral DV, and 7 with bladder neck dysfunction and midurethral DV) had treatment with botulinum injection into the urethral

sphincter. The treatment was successful in 68% (55/81) of patients and failed in 32% (26/81) of patients. Treatment success was defined as an improvement of VE by 10% and patient-reported global response assessment by more than or equal to 1% (Jiang 2021).

Clinical outcomes

IPSS

In the RCT analysis of 62 patients, statistically significant improvements from baseline in IPSS-V, IPSS-S, IPSS-T were seen in the botulinum injection and placebo groups after first EUS injections at 1-month follow up ($p<0.05$). Patients who had botulinum injections had statistically significantly less improvement in IPSS-V, IPSS-S and IPPS-T than patients in the placebo group. Subgroup analysis showed that the outcomes were similar between the DV and DU groups after first injection. There was a statistically significantly greater reduction in IPSS-T in the placebo group than in the botulinum group in patients with DV ($p= 0.026$). In patients with DU, the placebo group had statistically significantly greater reductions in IPSS-V and IPSS-T than the botulinum group ($p=0.036$ and 0.002). Repeated botulinum injection into the urethral sphincter in the botulinum group (n=19) resulted in improvement in IPSS-V, IPSS-S, IPSS-T in patients with DV and DU (Jiang 2016).

In a case series of 10 patients with a primary disorder of urethral sphincter relaxation (Fowler's syndrome) that was treated with 100 units of botulinum injection into the external urethral sphincter, the mean symptom scores on the IPSS questionnaire improved from 25.6 to 14.1. Also, the mean 'bother' score on IPSS reduced from 6.1 to 3.5 at 10-week follow up (Panicker 2016).

PPBC

In the RCT analysis of 62 patients, statistically significant improvements from baseline were seen in both botulinum and placebo groups at 1-month follow up after first injection ($p<0.05$). Repeated botulinum injections into the urethral sphincter in the botulinum group (n=19) resulted in improvement in PPBC in patients with DV and DU (Jiang 2016).

In a retrospective analysis of 56 patients with refractory idiopathic external urethral sphincter dysfunction who had botulinum injections into the external urethral sphincter, patients with DV (n=23) had no statistically significant differences in treatment improvement rates compared with patients with PRES (n=33). The rates of good subjective outcomes (65% [15/23] compared with 64% [21/33], $p=0.903$) and objective outcomes (74% [17/23] compared with 67% [22/33], $p=0.562$) were not statistically significantly different between the 2 groups at 1-month follow up (Ou 2021).

Recovery of detrusor function

In the case series of 27 patients, there was recovery of detrusor contractility in 48% (13/27) of patients (7 with DV and low detrusor contractility with concomitant PRES, 3 with DHIC and 3 with DU) and no recovery in 52% (14/27) of patients. Detrusor contractility recovery was defined as an increase in Pdet and Qmax and reduced PVR volume). Patients with recovery could void without abdominal straining, but patients without recovery continued to void with increased abdominal pressure (Kuo 2007a).

Duration of treatment effect

In the case series of 27 patients, patients with recovery of detrusor contractility (n=13) had a statistically significantly longer duration of treatment effect than those without recovery (n=14; 14±7.6 months compared with 4.6±2.5 months, p<0.001; Kuo 2007a).

In the case series of 66 patients, the mean duration of treatment effect was statistically significantly shorter in the 50 units botulinum injection group than the 100 units group (6.4±3.6 months compared with 8.4±3.4 months, p= 0.022; Kuo 2007b).

QOL

In the RCT analysis of 62 patients, QOL statistically significantly improved from baseline in both botulinum injection and placebo groups at 1-month follow up after first injection (botulinum group from 4.5±1.9 to 3.0±1.9 and placebo group from 5.4±0.9 to 2.4±1.9, p<0.05 compared with baseline or before injection). Compared with placebo, botulinum injection into the urethral sphincter resulted in statistically significantly less improvement in QOL (p<0.01 between the groups after treatment). Repeated botulinum injection into the urethral sphincter (n=19) resulted improvement in QOL index in patients with DV and DU (p<0.05; Jiang 2016).

In the case series of 27 patients, 10 out of 13 patients with recovery of detrusor contractility had an excellent outcome. QOL index assessed using a questionnaire (with a scale ranging from 0 to 6) improved by more than 2 points and reduction in PVR by more than 50%. Three patients had an improved outcome (QOL index improved by 1 point with improvement of urodynamic parameters). Of these who reported no recovery (n=14), 1 had an excellent outcome, 10 had an improved result and 3 had a failed result (no improvement in QOL; Kuo 2007a).

In the case series of 66 patients with voiding dysfunction (of any aetiology) that was treated with botulinum injection into the external urethral sphincter (100 units and 50 units), the overall treatment results were excellent in 61% (20/33) and

70% (23/33) of patients respectively. 'Excellent' was defined as a more than 2-point improvement in the QOL index, 50% or more reduction in PVR and 25% or more reduction in MUCP. The overall treatment results were improved in 30% (10/33) and 15% (5/33) of patients respectively. 'Improved' was defined as an improvement in the QOL index of 1 point, 50% or more reduction in PVR or 25% or more reduction in MUCP. Treatment failed in 9% (3/33) and 15% (5/33) patients respectively. 'Failed' was defined as no improvement in QOL regardless of the urodynamic improvement (Kuo 2007b).

Urodynamic parameters

In the RCT analysis of 62 patients, after first injections in both groups, there was a statistically significant increase ($p<0.05$) in Qmax (botulinum group from 5.3±5.7 to 9.8±9.5 and placebo group from 6.3±5.1 to 9.5±6.6) and in VE (botulinum group from 29.6±28.3 to 44.1±35.3 and placebo group from 34.4 ±34.2 to 56.1±36.4). But there was only a statistically significant improvement in VV in the botulinum group (from 119.9±82.2 ml to 191.0±140.1 ml) and only a statistically significant improvement in PVR in the placebo group (from 279.3±246.9 to 146.6±160.5, $p<0.05$). There were no statistically significant differences in changes in the other VUDS parameters (Pdet cm/H_20, CBC) between the botulinum and placebo groups after the first injection. Subgroup analysis showed that, in patients with voiding dysfunction (n=31), there were only statistically significant improvements in VUD parameters in the botulinum group, including Pdet (from 40.3±23.0 cmH_2O to 31.6±22.3 cmH_2O), Qmax (from 6.4±5.4 ml/sec to 11.1±10.1 ml/sec) and VV (from 119.9±82.2 ml to 191.0±140.1 ml). In patients with DU (n=31), there were statistically significant improvements in Qmax in both groups (botulinum group from 4.5±6.0 ml/sec to 8.8±9.1 ml/sec, and placebo group from 3.4±3.7 ml/sec to 10.6±9.2 ml/sec) and VE (botulinum group from 20.8±28.5 to 39.4±36.0 and placebo group from 17.0±31.5 to 61.6±40.7). In the DU group, reduction in PVR, was statistically significantly greater in the placebo group (from 415.0±304.0 ml to 131±169.1 ml) than in the botulinum group (from 350.0±174.6 ml to 293±233.1 ml, $p=0.046$ between the groups after treatment). There were no statistically significant changes in VUD parameters after repeated botulinum injections (Jiang 2016).

In the case series of 27 patients, there was a statistically significant reduction in the PVR (from 328±134 ml to 31±35 ml, $p<0.05$ compared with baseline or before injection) and a statistically significant increase in the Qmax (from 4.7±5.6 ml/sec to 13±6.6 ml/sec, $p<0.05$ compared with baseline or before injection) in patients with and without recovery of detrusor contractility after urethral injections of botulinum. Pdet statistically significantly reduced (from 47±39 cmH20 to 32±27 cmH20, $p<0.05$ compared with baseline or before injection) in patients without recovery but statistically significantly increased it in patients with recovery (from 7.4±9.2 cmH20 to 24±13.1 cmH20, $p<0.05$ compared with baseline) (Kuo 2007a).

In the case series of 66 patients, there were statistically significant reductions in urodynamic parameters (Pdet, PVR, MUCP), and a statistically significant increase in Qmax with both doses of botulinum (50 units and 100 units) after treatment compared with baseline. But no statistically significant differences were noted between groups after treatment (Kuo 2007b).

In the case series of 10 patients, with 100 units of botulinum injection into the urethral sphincter, there was an improvement in Qmax (from 8.12 ml/sec to 15.8 ml/sec), a decrease in PVR (from 260 ml to 89 ml) and an improvement in the mean static UPP (from 113 cmH_2O to 90 cmH_2O), at 10-week follow up (p value not assessed; Panicker 2016).

In the retrospective case series of 81 patients with DV, patients with a successful treatment outcome after botulinum injection into the urethral sphincter had a statistically significant change in urodynamic parameters (decrease of Pdet, PVR volume and BOOI, and an increase in VE) at follow up compared with the treatment failure group (Jiang 2021).

In the retrospective analysis of 56 patients, for both patients with DV (n=23) and patients with PRES (n=33), botulinum injections into the EUS resulted in statistically significantly improved Qmax (DV: 7.3 to 10.2 ml/sec, $p<0.01$; PRES: 7.4 to 10.2 ml/sec, $p<0.05$) and VE (DV: 0.47 to 0.59 ml/sec, $p<0.01$; PRES: 0.43 to 0.60 ml/sec, $p<0.01$) after the injections. Also, there was a statistically significant decrease in FS ($p=0.023$), US ($p=0.004$) and CBC ($p=0.044$ in the DV group than the PRES group after the injections (Ou 2021).

Safety summary

De novo UTI

New UTIs, which resolved with medical treatment, were reported in 5% (3/62) of patients at 1-month follow up in the RCT. It is not clear whether they were in the treatment or placebo group (Jiang 2016).

A UTI developed in 3 patients (with a history of recurrent UTI) in the case series of 10 patients (Panicker 2016).

Urge urinary incontinence

Urge urinary incontinence, which resolved with medical treatment, was reported in 5% (3/62) of patients at 1-month follow up in the RCT. It is not clear whether they were in the treatment or placebo group (Jiang 2016).

Micturition pain

Pain during micturition, which resolved with medical treatment, was reported in 3% (2/62) of patients at 1-month follow up in the RCT. It is not clear whether they were in the treatment or placebo group (Jiang 2016).

Difficulty in urination (mild and resolved within 3 days after treatment) was reported in 9% (7/81) of patients in the case series of 81 patients (Jiang 2021).

Haematuria

Haematuria, which resolved with medical treatment, was reported in 3% (2/62) of patients at 1-month follow up in the RCT (Jiang 2016).

Haematuria (mild and resolved in 3 days) was reported in 6% (5/81) of patients in the case series of 81 patients (Jiang 2021).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: discomfort during the procedure and a degree of oozing of blood. They did not describe any theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention. The following databases were searched, covering the period from their start to 05-01-2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with idiopathic chronic non-obstructive urinary retention.
Intervention/test	Botulinum toxin type A injection into the urethral sphincter.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 451 patients from 1 RCT and 7 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Study 1 Jiang Y-H (2016)

Study details

Study type	RCT (NCT01733290)
Country	Taiwan, Helsinki

Recruitment period	2012-2014
Study population and number	N=73 patients with DV or DU refractory to medical or behavioural treatment. (48 in botulinum injection group versus 25 in placebo group)
Age and sex	Mean age 65.2±15.2 years (range, 28 to 87 years); botulinum injection group 64.7 years versus placebo injection group 66.9 years; p= 0.562. Sex: overall 66% (48/73) women; At 1 month, botulinum injection group had 76% (29/38) women, placebo injection group had 76% (19/25) women
Patient selection criteria	Inclusion criteria: patients more than 20 years of age with a 3-month history of medically refractory non-neurogenic voiding dysfunction (DV and DU diagnosed by video-urodynamic studies). DV was diagnosed in patients with an open bladder neck and narrow membranous urethra, a poorly relaxed urethral sphincter, and a normal to-high voiding pressure with a low and/or intermittent urinary flow during voiding. DU was diagnosed in patients with low voiding pressure and low flow rate, a post-void residual volume >300 mL, and a low VE (<33%) and the presence of a relaxed urethral sphincter during voiding. **Exclusion criteria:** anatomic bladder outlet obstruction conditions, including benign prostatic obstruction in men, bladder neck obstruction or contracture, and urethral stricture, active UTI, interstitial cystitis, and occult or overt neuropathy (including cerebrovascular accidents, diabetes mellitus, multiple sclerosis, Parkinson's disease, and spinal cord injury).
Technique	All injections were done under general anaesthesia through a transurethral route in men and perineal route in women. Treatment group (n=48) had injections of botulinum (100U diluted was with 5ml saline) into the external urethral sphincter. Men had 10 injections using a 23 gauge needle. Each injection site had 10U of botulinum or 0.5ml of normal saline. Women had 5 urethral sphincter injections of botulinum solution or 1.0ml of normal saline circumferentially into the urethral sphincter using a 27 gauge 1ml syringe needle. Placebo group (n=25) had normal saline (5ml) injections (10 in men and 5 in women) After injections, a Foley catheter was inserted overnight in men but not in women. Patients are discharged next day and oral antibiotics are given for a week. 48 in the botulinum group and 25 in placebo group had first injection, and 19 and 13 patients in each group had a second botulinum injection after 1 month.
Follow up	1 month.
Conflict of interest/source of funding	Study was approved by Tzu-Chi General Hospital. No external funding for this study.

Analysis

Follow-up issues: short follow-up period with high loss to follow-up. 11 patients (10 in botulinum group and 1 in placebo group) were lost to follow-up during the study period. Data were available in 38 patients in botulinum injection group and 24 patients in placebo injection group at 1 month follow-up.
Study design issues: small number of patients were randomly allocated in a 2:1 ratio by block randomisation. Patients, doctors and nurses were blinded. Video-urodynamic studies were done according to International

Continence Society recommendations. Different routes of injection were used for men and women. The primary outcome was change in PPBC score at 1 month from baseline. Other endpoints assessed were changes from baseline in IPSS, QOL (assessed according to IPSS system questionnaire and was scored from 0 to 6, representing excellent to bad), VV, PVR, Pdet and adverse events. If patients were not satisfied with the treatment result, repeated urethral sphincter botulinum injection was done regardless of patient allocation. Patients having a second injection were assessed in the same manner used for the first treatment.
Study population issues: baseline patient characteristics and urodynamic parameters were not statistically significantly different between the 2 study groups. Patients with 2 different indications were included in the study.

Key efficacy findings

Number of patients analysed: 62 (38 botulinum injection versus 24 placebo injection)

Overall success rate (reduction of PPBC ≥2) at 1 month: 43.5%

	Botulinum injection % (n=38)	**Placebo injection % (n=24)**	**P value**
Success rate (PPBC>2)	36.8 (14/38)	54.2 (13/24)	0.114

Subjective clinical outcomes: changes of symptom scores and VUDS parameters after first EUS injection

		Botulinum injection (n=38)	Placebo injection (n=24)	P value (between baseline data of groups)	P value (between the groups after treatment)
IPSS-V	Baseline	15.2±5.6	14.5±6.7	0.468	0.002
	1 month	12.7±7.0*	6.0±6.6*		
IPSS-S	Baseline	10.7±4.0	11.0±4.3	0.518	0.074
	1 month	8.5±3.8*	7.1±4.2*		
IPSS-T	Baseline	25.8±8.2	25.5±8.8	0.776	0.001
	1 month	21.2±8.6*	13.1±9.5*		
QOL-index	Baseline	4.5±1.9	5.4±0.9	0.024	0.014
	1 month	3.0±1.9*	2.4±1.9*		
PPBC	Baseline	4.8±1.7	5.0±1.7	0.761	0.066
	1 month	3.4±2.0*	2.7±2.1*		
CBC (mL)	Baseline	378.9±154.2	397.8±223.5	0.585	0.201
	1 month	404.6±182.4	360.0±140.7		
Pdet (cmH_2O)	Baseline	22.7±24.7	25.3±24.6	0.444	0.161
	1 month	19.2±19.6	30.5±25.1		
Qmax (mL/s)	Baseline	5.3±5.7	6.3±5.1	0.344	0.558
	1 month	9.8±9.5*	9.5±6.6*		
Vol (mL)	Baseline	104.8±112.2	102.4±101.4	0.942	0.627
	1 month	170.7±140.5*	148.5±144.7		
PVR (mL)	Baseline	295.7±194.1	279.3±246.9	0.965	0.141
	1 month	251.7±214.0	146.6±160.5*		
VE (%)	Baseline	29.6±28.3	34.4±34.2	0.530	0.336
	1 month	44.1±35.3*	56.1±36.4*		

Data are presented as mean±SD; *p value <0.05 versus baseline

Subgroup analysis

Changes of symptom scores and VUDS parameters after first EUS injection

		DV (n=31)			DU (n=31)		
		Botulinum (n=16)	Placebo (n=15)	P value^	Botulinum (n=22)	Placebo (n=9)	P value ^
IPSS-V	Baseline	12.7±6.6	14.1±5.8		17.0±3.8	15.1±8.4	

	1 month	8.3±7.6*	5.7±5.8*	0.089	16.0±4.3	6.6±8.2*	0.036
IPSS-S	Baseline	11.4±4.3	12.1±4.0		10.1±3.8	9.8±4.5	
	1 month	8.5±3.7*	6.3±3.9*	0.089	8.5±3.9	8.4±4.5	0.831
IPSS-T	Baseline	24.1±10.3	26.2±7.8		27.1±6.2	24.3±10.7	
	1 month	16.8±10.4*	12.0±8.0*	0.026	24.4±5.2*	15.0±11.8*	0.002
QOL-I	Baseline	4.4±1.7	5.4±1.0		4.6±2.0	5.4±0.9	
	1 month	2.8±2.1*	2.4±2.1*	0.089	3.0±1.9*	2.4±1.8*	0.107
PPBC	Baseline	4.8±1.4	5.4±1.4		4.7±1.9	4.4±1.9	
	1 month	3.3±1.9*	2.5±2.2*	0.085	3.5±2.1*	3.0±1.8*	0.814
CBC (ml)	Baseline	359.0±172.6	334±176		393.9±141	497±262.5	
	1 month	365.0±154.4	354±125.7	0.860	434.7±199.4	369±169.2	0.042
Pdet (cmH2O)	Baseline	40.3±23.0	35.6±25.1		9.2±16.4	9.1±12.8	
	1 month	31.6±22.3*	32.1±22.6	0.473	9.8±10.0	27.9±30.0	0.070
Qmax (mL/s)	Baseline	6.4±5.4	7.9±5.2		4.5±6.0	3.4±3.7	
	1 month	11.1±10.1*	8.9±4.7	0.099	8.8±9.1*	10.6±9.2*	0.445
Vol. (mL)	Baseline	119.9±82.2	136.3±109		93.9±130.9	45.9±54.9	
	1 month	191.0±140.1*	117.5±63.7	0.020	155.0±142.0	200±219.7	0.182
PVR (mL)	Baseline	225.0±200.7	198±168.2		350.0±174.6	415±304.0	
	1 month	198.0±179.1	156±160.5	0.770	293.0±233.1	131±169.1*	0.046
VE (%)	Baseline	42.1±27.8	44.9±32.2		20.8±28.5	17.0±31.5	
	1 month	50.5±34.6	52.8±34.6	0.969	39.4±36.0*	61.6±40.7*	0.094

*p<0.05 versus baseline. ^ p value between groups after treatment. Data are presented as mean±SD.

Changes of symptom scores and VUDS parameters after first and second EUS botulinum injections in botulinum group (n=19)

	DV (n=7)			**DU (n=12)**		
	Changes after 1st injection	**Changes after 2nd injection**	**P value**	**Changes after 1st injection**	**Changes after 2nd injection**	**P value**
IPSS-V	−4.0±5.5	−3.4±5.4	0.848	−1.0±4.0	−6.3±7.0*	0.035
IPSS-S	−2.3±3.9	−3.4±3.3*	0.563	−2.1±3.8	−4.5±5.7*	0.250
IPSS-T	−6.3±6.7*	−6.9±3.5*	0.846	−3.0±5.0	−10.7±10.8*	0.051
QOL-index	−1.0±2.2	−2.0±1.5*	0.337	−1.8±1.8*	−3.1±2.2*	0.144
PPBC	−0.9±2.7	−1.7±1.8*	0.502	−0.9±1.6	−1.8±1.7*	0.202
CBC (ml)	60.6±105.5	143.3±143.0*	0.242	32.1±72.8	77.2±148.5	0.381
Pdet (cmH_20)	−8.1±14.7	−13.4±21.1	0.597.5	2±10.7	3.8±10.0	0.719
Qmax (mL/s)	1.3±5.2	2.6±6.0	0.676	−0.6±3.8	5.4±5.5*	0.008
Vol (mL)	17.9±64.7	29.7±55.8	0.720	−10.3±94.5	57.5±150.5	0.206

PVR (mL)	29.1±104.2	21.3±124.7	0.900	−1.3±174.4	−70.9±179.3	0.367
VE (%)	−7.7±25.8	−1.9±31.8	0.715	−0.2±17.2	19.5±37.1	0.113

*p<0.05 versus baseline.

Changes of symptom scores and VUDS parameters after first placebo injection and second EUS botulinum injections in placebo group (n=13)

	DV (n=9)			**DU (n=4)**		
	Changes after 1st placebo injection	**Changes after 2nd Botulinum injection**	**P value**	**Changes after 1st injection**	**Changes after 2nd injection**	**P value**
IPSS-V	−6.1±4.7*	−4.5±7.1	0.585	−7.0±8.9	−7.8±8.7	0.908
IPSS-S	−5.3±4.4*	−2.9±6.1	0.354	−0.0±3.6	−2.3±5.1	0.498
IPSS-T	−11.4±7.9*	−7.4±12.1	0.419	−7.0±6.3	−10.0±4.5*	0.468
QOL-index	−2.3±2.1*	−1.1±2.5	0.289	−1.75±1.5	−2.5±2.1	0.580
PPBC	−2.4±2.1*	−1.6±3.7	0.578	−1.25±1.0	−2.5±2.1	0.317
CBC (ml)	−10.0±245.7	−29.6±225.9	0.876	−133.5±336.7	−88.5±274.7	0.843
Pdet (cmH_20)	−3.3±14.1	−8.7±7.9*	0.719	33.8±47.0	10.8±28.8	0.436
Qmax (mL/s)	1.0±5.4	1.6±4.5	0.800	3.8±4.3	2.5±4.1	0.691
Vol (mL)	2.2±123.6	−5.0±88.6	0.893	180.0±260.6	69.5±102.2	0.462
PVR (mL)	−54.0±201.7	−107.6±236.3	0.621	−400.2±309.2	−251.3±296.5	0.513
VE (%)	16.6±27.3	15.5±27.6	0.936	64.5±38.9*	22.3±29.1	0.133

*p<0.05 versus baseline.

Key safety findings

Complications at 1 month	% (n)
De novo urgency urinary incontinence*	4.8 (3/62)
De novo stress urinary incontinence*	n=1
UTI*	4.8 (3/62)
Micturition pain*	3.2 (2/62)
Haematuria*	3.2 (2/62)

No serious adverse events were reported. All complications resolved after medical treatment.

Study 2 Kuo H-C (2007a)

Study details

Study type	Case series
Country	Taiwan
Recruitment period	2002-2005
Study population and number	N=27 patients with idiopathic low detrusor contractility (3 had DV, 5 had low detrusor contractility with PRES 10 had DHIC, and 9 had DU)
Age	Mean age not reported; 81% (22/27) women.
Patient selection criteria	Inclusion criteria: presence of bladder and urethral dysfunction (idiopathic low detrusor contractility confirmed on VUD studies and defined no evident neuropathy, no functional or anatomic bladder outlet obstruction, a low or no Pdet combined with a Qmax of less than 10 mL/s, and a large PVR of more than 150 mL or urinary retention difficult urination, with a hyperactive or poorly relaxed urethral sphincter), patients in whom treatment with conventional medications had failed. Exclusion criteria: with bladder outlet obstruction.
Technique	urethral injection of botulinum (50 units or 100 units) done under general anaesthesia and cystoscopy guidance, directly into the urethral sphincter in men and periurethrally in women.100 units is diluted with 8ml saline.
Follow up	More than 1 year
Conflict of interest/source of funding	Allergan company provided botulinum injections.

Analysis

Follow-up issues: 2 weeks after injection and thereafter regular monthly follow-up.

Study design issues: small retrospective study. Video-urodynamic studies were done at baseline and after treatment. Patients were randomly assigned to have of either 50 units or 100 units of botulinum injection. Video-urodynamic studies were done according to International Continence Society recommendations. The outcomes (changes in urodynamic parameters) were compared between patients with and without recovery of detrusor contractility. The QoL index was assessed according to the IPSS (scored from 0 to 6, representing excellent to bad).

Study population issues: patients with different indications were included. Results for each indication were not presented separately. Authors state that age was not statistically significantly different between the 2 groups.

Other issues: patients were advised not to use alpha-adrenergic blockers or skeletal muscle relaxants during study period.

Key efficacy findings

- Number of patients analysed: 27

Changes in urodynamic parameters in patients with and without recovery of detrusor contractility after botulinum injections

Recovery of detrusor contractility^	First bladder sensation (ml)	Pdet or Pves (cm H_2O)	Qmax (mL/s)	PVR (mL)	Duration of effect^^ (months)
Yes 48% (13/27)					
Baseline	233 ± 106	7.4 ± 9.2	4.7 ± 5.6	328 ± 134	
After treatment	191 ± 87	24 ± 13.1*	13 ± 6.6*	31 ± 35*	14 ± 7.6
No 52% (14/27)					
Baseline	368 ± 132	47 ± 39†	4.8± 4.3	228 ± 122	
After treatment	297 ± 121	32 ± 27*	7.0± 3.6	132 ± 71*	4.6 ± 2.5 (p<0.001)

*p<0.05 between baseline and after treatment. Data are presented as mean±SD.

^ defined as an increase in Pdet and Qmax and reduced PVR volume (in 7 patients with DV or low detrusor contractility combined with PRES, 3 with DHIC, and 3 with DU)

^^ length of time from treatment and return of voiding symptoms to pre-treatment level.

Treatment outcomes

	Recovery of detrusor contractility^	Without detrusor contractility recovery^^
Excellent (QOL index improved by >2 and reduction in PVR by >50%)	N=10	N=1
Statistically significantly improved (QOL index improved by >2 and reduction in PVR by <50%)	-	-
Improved (QOL index improved by 1 and improvement of UD parameters)	N=3	N=10
Failed (no improvement in QOL)	-	N=3

^all could void without the aid of abdominal straining.

^^ continued to void with increased abdominal pressure

Overall success rate of treatment was 89% (24/27)

Key safety findings

None reported

Study 3 Kuo H-C (2007b)

Study details

Study type	Case series
Country	Taiwan
Recruitment period	Not reported
Study population and number	N=66 patients with voiding dysfunction that was treated with botulinum injections into the EUS. (50 unit injection group [n=33] versus 100 unit injection group [n=33]) (DSD n=6, DV [n=21], PRES [n=11], or DU with non-relaxation of the urethral sphincter [n=28])
Age and sex	Mean age: 64.8 years and 60.0 years in the 50 and 100 units injection groups, (p> 0.05). Sex: 54% (18/33) and 58% (19/33) women in the 50 and 100 units injection groups, (p>0.05)
Patient selection criteria	Inclusion criteria: presence of bladder and urethral dysfunction (idiopathic low detrusor contractility) confirmed on VUD studies (no anatomic bladder outlet obstruction, difficult urination, and urinary retention or a large PVR volume, and low detrusor pressure with a hyperactive or poorly relaxed urethral sphincter), patients with voiding dysfunction in whom treatment with conventional medications (such as α-blockers and skeletal muscle relaxants) had failed. Exclusion criteria: with bladder outlet obstruction.
Technique	botulinum injections into the urethral sphincter (50 units in 33 patients or 100 units in 33 patients) done under light intravenous general anaesthesia and cystoscopy guidance transurethrally in men at the 3, 6, 9 and 12 o'clock positions at a depth of about 5 mm and transcutaneously and periurethrally in women at a depth of 15mm.100 units is diluted with 8ml saline. Both groups had same volume of injection but different doses.
Follow up	More than 12 months
Conflict of interest/source of funding	Allergan company provided botulinum injections. Study was supported by grants from the National Science Council of Taiwan.

Analysis

Follow-up issues: 2 weeks after injection and regular monthly follow-up thereafter.

Study design issues: small retrospective study. Video-urodynamic studies and urethral pressure profilometry were done according to International Continence Society recommendations at baseline and after treatment. Patients were randomly assigned to have of either 50 units or 100 units of botulinum injection. The outcomes (changes in urodynamic parameters and treatment effect) were compared from baseline to after treatment in each group and also between the 2 groups of patients. The QOL index was assessed according to the IPSS questionnaire (and scored from 0 to 6, representing excellent to bad).

Study population issues: patients with voiding dysfunction of different aetiologies were included but the allocation of patients with different aetiologies in the 50 unit and 100 unit treatment groups was not equal.

Other issues: other medications such as alpha-adrenergic blockers or skeletal muscle relaxants were not used during study period. No repeat injections were given to patients.

Key efficacy findings

- Number of patients analysed: 66

Changes in urodynamic parameters and QOL in patients with 50 units and 100 units of botulinum injections

	MCUP (cm H_2O)	**FPL (cm)**	**Pdet (cm H_2O)**	**Qmax (mL/s)**	**PVR (mL)**	**QOL index**	**Mean duration of effect (months)^^**
50 units injection (n=33)							
Baseline	66.6 ± 34.4	3.3 ± 0.5	51.6 ± 40.7	5.6 ± 5.3	285 ± 154	4.1 ± 0.9	
After treatment	48.9 ± 27.3 (p<0.001)	3.1 ± 0.3 (p=0.186)	37.5 ± 35.4 (p<0.001)	8.3 ± 5.4 (p=0.016)	120 ± 145 (p<0.001)	1.9 ± 1.2 (p<0.001)	6.4 ± 3.6
100 units injection (n=33)							
Baseline	61.9 ± 26.0	3.8 ± 1.0	53.8 ± 38.9	5.8 ± 4.8	261 ± 157	4.0 ± 1.0	
After treatment	49.5 ± 21.5 (p=0.049)	4.1 ± 1.0 (p=0.493)	33.0 ± 31.7 (p=0.006)	10.5 ± 5.9 (p<0.001)	114 ± 107 (p<0.001)	2.2 ± 1.2 (p<0.001)	8.4 ± 3.4 (p=0.022)*

*between the 2 groups; Data are presented as mean±SD.
^^ length of time from treatment and return of voiding symptoms to pre-treatment level.

Treatment outcomes

	50 units of injection % (n=33)	**100 units of injection % (n=33)**
Excellent (QOL index improved by >2 and 50% reduction in PVR and ≥ 25% reduction in MUCP)	69.7 (23/33)	60.6 (20/33)
Improved (QOL index improved by 1 and improvement of VUD parameters by either a ≥ 50% reduction in PVR or a ≥ 25% reduction in MUCP)	15.2 (5/33)	30.3 (10/33)
Failed (no improvement in QOL regardless of urodynamic improvement)	15.2 (5/33)	9 (3/33)
Overall rate of success	84.9 (28/33)	90.9 (30/33) p=0.452

Treatment outcomes in patients with different aetiologies

	Excellent %(n)	**Improved % (n)**	**Failed % (n)**	**p value**
Poor relaxation of urethral sphincter (n=11)				**0.182**
50 units (n=5)	60 (3/5)	40 (2/5)	0	
100 units (n=6)	100 (6/6)	0	0	
DU (n=28)				**0.066**
50 units (n=19)	68.4 (13/19)	10.5 (2/19)	21.1 (4/19)	
100 units (n=9)	33.3 (3/9)	55.6 (5/9)	11.1 (1/9)	
DV (n=21)				**0.399**
50 units (n=6)	83.3 (5/6)	16.7 (1/6)	0	
100 units (n=15)	53.3 (8/15)	33.3 (5/15)	13.3 (2/15)	

Data on 6 DSD patients are not presented here as this indication is out of the scope of this assessment.

Key safety findings

None reported

Study 4 Jiang (2021)

Study details

Study type	Retrospective case series
Country	Taiwan
Recruitment period	2016
Study population and number	N= 81 women with non-neurogenic DV
Age	Age not reported; 100% women
Patient selection criteria	Inclusion criteria: all women with DV (confirmed on VUD studies) refractory to medical treatment who had urethral botulinum 100 units, evidence of radiographic obstruction at the middle urethra with an open bladder neck and urodynamic findings, with baseline and postoperative urodynamic data were included. Exclusion criteria: no urethral stricture or anatomic bladder outlet obstruction.
Technique	Urethral botulinum injections were done under light intravenous general anaesthesia 100 units reconstituted to 4 ml with normal saline to create a solution equivalent to 25 U/ml. botulinum was injected into the urethral sphincter along the urethral lumen at the 2, 5, 7, 9, and 12 o'clock positions.
Follow up	3 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: short follow-up period.

Study design issues: retrospective analysis; DV was classified into 3 groups according to the site of obstruction. Successful treatment outcome was defined as an improvement of VE by 10% and reported global response assessment by ≥1. global response assessment was reported as excellent (+3), markedly improved (+2), mildly improved (+1), no change (0) or worsened (−1), according to their perception of voiding after the botulinum injection. Changes in urodynamic parameters between the treatment success and failure groups and among three DV subgroups were assessed.

Key efficacy findings

- Number of patients analysed: 81

Changes in urodynamic parameters between the treatment success and failure groups

	Treatment successful^ % (n)		**Treatment failure % (n)**		
	67.9 (55/81)		32.1 (26/81)		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**P value**
First sensation filling (ml)	152.3 ± 79.5	150.4 ± 94.3	119.2 ± 52.4	131.7 ± 105.6	0.652
Full sensation (ml)	225.2 ± 97.0	206.9 ± 102.8	195.4 ± 67.7	173.1 ± 125.9	0.910
Urge sensation (ml)	257.8 ± 107.6	232.1 ± 119.9	226.0 ± 82.6	192.8 ± 136.3	0.839
Pdet (cmH_2O)	59.9 ± 38.8	44.4 ± 33.6*	51.2 ± 36.0	36.2 ± 35.7	0.959
Compliance	60.9 ± 52.8	64.2 ± 63.8	69.6 ± 84.7	57.3 ± 61.2	0.526
Qmax (mL/s)	8.51 ± 6.21	8.83 ± 8.19	7.53 ± 4.72	4.85 ± 4.33	0.254
Volume (ml)	146.2 ± 108.2	160.1 ± 140.7	126.5 ± 87.1	82.9 ± 73.4	0.185
PVR (mL)	206.0 ± 137.5	132.6 ± 156.1*	195.3 ± 101.6	243.3 ± 239.2	0.032
CBC (ml)	352.2 ± 145.2	292.6 ± 136.9 *	321.9 ± 116.6	326.2 ± 215.4	0.185
VE	42.7 ± 28.3	58.2 ± 36.8 *	40.3 ± 27.4	34.3 ± 32.4	0.057
BOOI	42.9 ± 41.8	26.7 ± 39.5 *	36.1 ± 37.4	26.5 ± 32.8	0.630

Data are presented as mean±SD; * statistically significant difference between baseline and follow up.

^defined as an improvement of VE by 10% and reported global response assessment by ≥1.

Lower urinary tract symptoms before and after treatment among the 3 DV subgroups

Lower urinary tract symptoms	**Total % (n=81)^^**		**Bladder neck dysfunction and DV 8.6% (7/81)**		**Midurethral DV 67.9% (55/81)**		**Distal urethral DV 23.5% (19/81)**	
	Baseline	**Follow-up^^**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Storage symptoms	70.4 (57/81)	50.6 (41/81)	71.4 (5/7)	42.9 (3/7)	72.7 (40/55)	54.5 (30/55)	63.2 (12/19)	42.1 (8/19)
Frequency/urgency/nocturia	19	17	1	1	10	10	8	6
Urge incontinence	38	24	4	2	30	20	4	2
Voiding symptoms	87.7 (71/81)	42 (34/81)	85.7 (6/7)	28.6 (2/7)	87.3 (48/55)	38.2 (21/55)	89.5 (17/19)	57.9 (11/19)
Difficulty urination	67	34	5	2	45	21	17	11
Urinary retention	4	0	1	0	3	0	0	0
Painful symptoms	13.6 (11/81)	4.9 (4/81)	14.3 (1/7)	0	9.1 (5/55)	3.6 (2/55)	0	0
Bladder pain	6	2	1	0	5	2	0	0
Micturition pain	5	2	2	1	3	1	0	0

^^ between 1 to 3 months after injection.

Key safety findings

	% (n)
Haematuria (mild, resolved in 3 days)	6.2 (5/81)
Difficulty in urination (mild resolved in 3 days after treatment)	8.6 (7/81)

Study 5 Panicker JN (2016)

Study details

Study type	Case series
Country	UK
Recruitment period	2009-2012
Study population and number	N= 10 women with a primary disorder of urethral sphincter relaxation (Fowler's syndrome) with impaired voiding (n=5) or complete urinary retention (n=5)
Age	mean age 40 (25–65) years, all women
Patient selection criteria	Inclusion criteria: patients with a diagnosis of Fowler's syndrome (elevated UPP, sphincter volume, and abnormal EMG) Exclusion criteria: urological and neurological causes for voiding dysfunction; a history of previous urethral surgery, neurological disease, pregnancy, current UTI, and those taking anticoagulants.
Technique	After 2% lidocaine injection, 100 units of botulinum (dissolved in 2ml saline) was injected into the external urethral sphincter on either side under EMG guidance. This was done as an outpatient procedure.
Follow up	10 weeks
Conflict of interest/source of funding	No conflicts of interest. Study partly funded from National Institute for Health Research (NIHR), Urology foundation, and In Comb project. Allergan provided botulinum injections.

Analysis

Follow-up issues: short follow-up period; patients were reviewed at 1, 4 and 10 weeks.

Study design issues: small pilot study in one centre. Baseline symptoms were assessed using the IPSS questionnaire, and Qmax and PVR were measured. The primary outcome was restoration of voiding for women with urinary retention and ≥50% improvement in Qmax in women with impaired voiding, at 10 weeks. The secondary outcomes measured were improvements in PVR and IPSS at 10 weeks.

Key efficacy findings

- Number of patients analysed: 10

Patient reported symptom scores and VUD parameters

	Baseline	**10 weeks**
Mean IPSS score	25.6	14.1
Mean 'bother' score on IPSS	6.1	3.5
Mean Qmax (mL/s) in people who could void	8.12	15.8
Mean Qmax in people with complete retention who could void spontaneously		14.3
Mean PVR (mL)	260	89
Mean static UPP (cmH_2O)	113	90 (p=0.037)

7 women chose to return for repeat injections.

Key safety findings

Unable to void (at week 10, continued with CSIC)	1
UTI (in those with history of recurrent UTI)	3

Study 6 Ou Y-C (2021)

Study details

Study type	Case series
Country	Taiwan
Recruitment period	2002-2019
Study population and number	N= 106 women having sphincteric botulinum-A injections for refractory EUS dysfunction. Indications: N=56 idiopathic EUS dysfunction (23 DV and 33 PRES) N=50 neurogenic EUS dysfunction (20 DSD, and 30 PRES)
Age	mean age 61.8 ± 19.7 years; all women
Patient selection criteria	Inclusion criteria: women who had had urethral sphincteric botulinum injections due to refractory voiding dysfunction caused by EUS dysfunction (diagnosed using image characteristics of VUDS during voiding phase) were retrospectively reviewed. Exclusion criteria: patients with complicated clinical conditions such as a history of lower urinary tract reconstruction or urethra stenosis were excluded.
Technique	botulinum-A injection (100 units) diluted in 5 mL of normal saline was injected into the urethral sphincter (5 injections were done circumferentially via a perineal route under general anaesthesia).
Follow up	1 month
Conflict of interest/source of funding	No conflicts of interest. Study was supported by grants from the National Cheng Kung University Hospital.

Analysis

Follow-up issues: short follow-up period; patients were reviewed at 1, 4 and 10 weeks.

Study design issues: retrospective analysis with small number of patients; urinary function assessments such as uroflowmetry, and VUDs were done according to the International Continence Society recommendations. Baseline and post treatment urinary parameters were assessed and subjective and objective outcomes were assessed 1 month after the injections. Subjective outcomes reported in the medical records were graded as “good” or “poor” according to the patient’s perceptions of improvement (no validated questionnaires were used). Objective outcomes were graded as “good” if there was a 50% improvement in the Qmax or PVR after the injection. Other issues: data on patients with neurogenic EUS dysfunction (n=50) and mixed data on outcome predictors for both neurogenic and idiopathic sphincter dysfunction has not been presented here as it is out of the remit of this overview.

Key efficacy findings

- Number of patients analysed: 106

Therapeutic outcomes and VUD parameters -idiopathic voiding dysfunction

		DV % (n=23)	PRES % (n=33)	P value
Good subjective outcome		65 (15/23)	64 (21/33)	0.903
Good objective outcome		74 (17/23)	67 (22/33)	0.562
Urinary flow parameters				
Qmax	Baseline	7.3±3.2	7.4±5.4	0.980
	Follow-up	10.2 ** ±5.7	10.2 * ±7.7	
VV	Baseline	139.7 ±94.3	130.5 ±125.6	0.559
	Follow-up	174.7 ±104.7	190.9 ±124.6	
PVR	Baseline	160.8 ±98.5	188.1 ±147.5	0.657
	Follow-up	134.1 ±99.4	171.0 ±221.8	
CBC	Baseline	300.4 ±135.4	318.7 ±127.8	0.328
	Follow-up	308.8 ±118.9	360.4 ±203.5	
VE	Baseline	0.47 ±0.23	0.43 ±0.32	0.616
	Follow-up	0.59 ** ±0.30	0.60 ** ±0.32	
VUDs parameters				
First sensation of filling	Baseline	117.7 ±89.6	164.4 ±74.3	0.086
	Follow-up	110.4 ±69.8	151.8 ± 72.4	
Full sensation	Baseline	191.7 ±90.9	250.3 ± 108.3	0.023
	Follow-up	163.3 ±77.4	251.7 ± 109.8	
Urge sensation	Baseline	228.9 ±111.9	286.3 ± 127.0	0.004
	Follow-up	180.3 ±83.4	293.8 ±114.1	
Compliance	Baseline	92.4 ±125.4	74.4 ±87.5	0.194
	Follow-up	44.5 ±35.6	65.5 ±66.4	
Pdet	Baseline	53.6 ±29.0	13.0 ±11.9	0.136
	Follow-up	51.1 ±31.2	11.9 ±15.4	
Qmax	Baseline	5.8 ±2.5	4.2 ±5.4	0.334
	Follow-up	6.3 ±4.3 6.7 ±6.6	6.7 ±6.6	
BOOI	Baseline	41.9 ±30.8	4.6 ±11.3	0.116
	Follow-up	38.5 ±33.0	-1.5 ±15.9	
PVR	Baseline	217.2 ±128.2	314.3 ±248.6	0.118
	Follow-up	174.4 ±135.9	305.2 ±263.1	
CBC	Baseline	340.5 ±126.7	402.8 ±237.1	0.044
	Follow-up	303.9 ±141.6	430.0 ±198.3	

VE	Baseline	0.40 ±0.22	0.22 ±0.27	0.769
	Follow-up	0.47 ±0.33	0.39 ±0.38	

*p <0.05 within group differences in changes after treatment.

**<0.01 within group differences in changes after treatment.

Study 7 Nadeem M (2022)

Study details

Study type	Case series (retrospective)
Country	UK
Recruitment period	2015–2019
Study population and number	N= 35 women having EUS botulinum-A injections for nonneurogenic non-relaxing sphincter causing voiding dysfunction. Women were classified before treatment into 3 groups: Group 1—those who were able to void spontaneously (n=7), Group 2—those who did CIC (n=25), and Group 3—those with an indwelling SPC (n=3).
Age	mean age 37.5±15 years (range 18 to 72 years); all women
Patient selection criteria	Inclusion criteria: all patients with a urodynamic diagnosis of non-relaxing sphincter having their first treatment with cystoscopy trans urethral EUS injection of BTX-A were retrospectively reviewed. Exclusion criteria: patients aged less than 18 years and those with neurogenic bladder were excluded.
Technique	Cystoscopy trans EUS botulinum-A injection (100 units) diluted in 2 ml of normal saline was injected into the urethral sphincter (4 0.5 ml injections were done circumferentially via a perineal route under general anaesthesia in a day care setting).
Follow up	mean 20 ± 13 months (range 8 months to 60 months)
Conflict of interest/source of funding	Authors declare no conflict of interest.

Analysis

Follow-up issues: long-term follow-up period; patients were reviewed at 6 weeks and every 3 months.

Study design issues: retrospective analysis with small number of patients; urinary function assessments such as uroflowmetry, and VUDS were done according to the International Continence Society recommendations both before and after-injections. All women were assessed with Qmax, PVR, and the 5-point patient global impression of improvement questionnaire at 6 weeks and then at 3 monthly intervals. QOL was assessed

using the International Prostate Symptom Score QOL question on a scale of 0 (delighted) to 6 (terrible), 0–2 was marked as good, 3–4 was moderate, and 5–6 was marked as poor QOL.

The subgroups were small with different patient numbers.

Population issues: more than 50% patients had a history of prior surgical interventions including urethral dilatations in 16, failed sacral neuromodulation in 15, and pelvic surgery in 4.

Key efficacy findings

Number of patients analysed: 35

Outcomes before and after injection

	Before injection (N=35)	**After injection (N=35)**	**P value**
Able to void	7	21	0.025
CIC dependent	25	12	
SPC	3	2	
Qmax ml/s (mean)	8.8	11	
PVR ml/s (mean)	200	149	<0.05

Multivariate analysis identified high preoperative PVR, high preoperative actual MUCP, and previous surgical intervention (urethral dilatation, sacral neuromodulation, and pelvic surgery) as predictors of successful voiding restoration.

Subgroup analysis based on initial voiding status

	Group 1 (n=7)	**Group 2 with CIC (n=25)**	**Group 3 with SPC (n=3)**	**P value**
Qmax ml/s (mean)	8.82	-	-	-
PVR ml/s (mean)	200	216	400	0.002
Pdet at Qmax-cmH20 (mean)	62.5	39	9	0.16
MUCP expected-cmH20 (mean)	95	109	93	0.05
MUCP actual-cmH20 (mean)	58	56	51	0.04

5-point Patient global impression **score:** (where 1 = good improvement, 3 = no improvement, and 5 = much worse).

Good improvement (score 1)	37% (13/35)
Some improvement (score 2)	34% (12/35)
No improvement (score 3)	29% (10/35)
Mean score	1.9 (range 1-3)

Patient global impression of improvement score was higher in Group 2 compared to the other two groups (p = 0.02).

Response to treatment (assessed with PVR volume measurement)

The mean duration of response was 4.7 months (range 0-18 months), 46% (16/35) of patients requested repeat injection, and 29% (10/35) were established on maintenance injections (had more than 2 injections).

Some discontinued and the reasons for discontinuation of treatment were relatively short duration of effect and the need for repeat treatments.

QOL improved in 60% of patients after injection compared to only 17.5% preoperatively rating themselves as having a good QOL.

Safety

2 patients had transient stress urinary incontinence for <6 weeks. This resolved with pelvic floor muscle training.

Study 8 Kao YL (2022)

Study details

Study type	Case series (retrospective)
Country	Taiwan
Recruitment period	2010-2019
Study population and number	N= 103 patients having EUS botulinum-A injections for refractory functional non-neurogenic voiding dysfunction due to urethral sphincter dysfunction.
Age	Mean age 59.7 years in women and 67.3 years in men, 77 women, 26 men.

Patient selection criteria	Inclusion criteria: patients who had urethral sphincter botulinum toxininjection for refractory voiding dysfunction due to DU or urethral sphincter dysfunction were retrospectively reviewed. All patients available for baseline and follow-up VUDS data were included. Exclusion criteria: patients with anatomical urethral conditions including uncorrected benign prostrate obstruction and high-grade pelvic organ prolapse, history of lower urinary tract reconstruction, urethral stenosis and urethral tumour, uncorrected bladder neck dysfunction, neurogenic abnormality related detrusor sphincter dyssynergia, cauda equina syndrome or peripheral neuropathy were excluded.
Technique	Cystoscopy EUS botulinum-A injection (100 units) was injected into the external urethral sphincter under light general anaesthesia. It was done periurethrally in women and transurethrally in men with 4 to 8 injections circumferentially into the external urethral sphincter at a depth of 1.5 cm along the longitudinal direction of the urethral lumen.
Follow up	Not reported
Conflict of interest/source of funding	Authors declare no conflict of interest. The work was supported by grants from a National university hospital and Buddhist medical foundation.

Analysis

Study design issues: retrospective analysis; VUDS and EMG were done according to the International Continence Society recommendations both before and after-injections. The external urethral sphincter dysfunction was subclassified into DV or PRES according to the features of VUDS and EMG. Major comorbidities were collected from medical records. Changes in urodynamic parameters were assessed by VUDS follow-up. Subjective outcomes were measured by global response assessment scored as excellent (+3), markedly improved (+2), mildly improved (+1) or no change (0), according to the patients' perception of the voiding condition after the injections.

Population issues: more than 50% patients had a history of prior surgical interventions including urethral dilatations in 16, failed sacral neuromodulation in 15, and pelvic surgery in 4.

Other issues: results of patients with detrusor activity (n=61) are not reported here as this is out of the remit of this guidance.

Key efficacy findings

Number of patients analysed: 77 women with urethral sphincter dysfunction.

Outcomes before and after injection

	Women (n=77)	**Men (n=26)**

	Before injection (N=77)	After injection (N=77)	P value	Before injection (N=26)	After injection (N=26)	P value
VUDS parameters						
First sensation of filling (ml)	103.6 ±60.5	125.3 ±74.6	0.034	146.2 ±89.6	150.8 ±68.3	0.818
Full sensation (ml)	170.3 ±78.8	193.2 ±98.1	0.059	248.8 ±116.6	251.6 ±134.0	0.919
Urge sensation (ml)	204.5 ±98.3	219.9 ±109.5	0.242	283.9 ±124.3	281.5 ±142.1	0.934
Compliance (ml/cm2 H20)	46.3 ±62.2	56.3 ±64.6	0.258	44.5 ±44.6	56.4 ±50.7	0.424
Detrusor overactivity	66% (51/77)	55% (42/77)	0.083	35% (9/26)	50% (13/26)	0.103
Maximal detrusor pressure Pdet (cm/H20)	54.7 ±36.0	45.5 ±33.9	0.009	24.2 ±17.5	23.5 ±17.3	0.791
Qmax: maximal uroflow rate (ml/s)	6.5 ±4.9	6.9 ±5.5	0.430	5.5 ±5.3	6.8 ±6.0	0.271
BOOI	41.8 ±37.5	31.6 ±35.9	0.010	13.3 ±16.5	10.0 ±15.1	0.405
VV (ml)	124.2 ±102.5	138.8 ±124.0	0.337	138.5 ±137.0	138.6 ±150.8	0.997
PVR (ml)	187.4 ±142.8	200.9 ±159.0	0.480	237.4 ±176.5	231.1 ±191.8	0.831
Bladder voiding efficiency (%)	42.4 ±31.9	45.1 ±35.8	0.540	40.1 ±35.2	44.1 ±39.0	0.552

Global response assessment						
Excellent		26% (20/77)				
Markedly improved		48% (37/77)			72% (7/26)	
Mildly improved		6% (5/77)			46% (12/26)	
No change		18% (14/77)			4% (1/26)	
Missing		1			23% (6/26)	
Successful outcome*		74% (57/77)			73% (19/26)	

*defined as a global response assessment equal to or greater than 2.

Outcomes between different subtypes of urethral sphincter dysfunction including DV and PRES

Women (n=77)						**Men (n=26)**				
	DV		**PRES**			**DV**		**PRES**		
	Before injection (N=70)	**After injection (N=70)**	**Before injection (n=7)**	**After injection (n=7)**	**P**	**Before injection (N=13)**	**After injection (N=13)**	**Before injection (N=13)**	**After injection (N=13)**	**p**
VUDS parameters										
First sensation of filling (ml)	104.6 ±62.4	123.6 ±75.2	93.9 ±39.5	142.7 ±70.4	0.518	119.5 ±52.7	123.0 ±66.4	172.8 ±111.4	178.5 ±60.3	0.038
Full sensation (ml)	171.6 ±80.8	193.2 ±99.4	156.9 ±57.8	192.7 ±90.8	0.990	208.6 ±103.9	203.2 ±140.1	289.0 ±118.4	300.0 ±112.7	0.059
Urge sensation (ml)	205.9 ±100.2	219.0 ±111.0	190.4 ±80.8	229.6 ±101.2	0.794	234.4 ±119.2	203.8 ±132.3	333.4 ±112.5	359.3 ±107.1	0.003
Compliance (ml/cm2 H20)	41.6 ±56.6	57.3 ±67.4	92.5 ±96.8	46.8 ±23.4	0.675	45.5 ±60.5	67.3 ±68.6	43.5 ±22.0	45.6 ±19.8	0.281

Detrusor overactivity	69% (48/70)	59% (41/70)	43% (3/7)	14% (1/7)	0.081	62% (8/13)	85% (11/13)	8% (1/13)	15% (2/13)	0.016
Maximal detrusor pressure Pdet (cm/H20)	56.0 ±33.0	48.2 ±34.3	41.3 ±60.7	18.1 ±9.6 *	0.001	34.7 ±14.5	31.8 ±17.5	13.8 ±13.7	15.2 ±12.9	0.003
Qmax: maximal uroflow rate (ml/s)	6.0 ±4.4	6.4 ±5.1	10.9 ±7.0	12.3 ±6.5	0.003	6.5 ±6.1	9.0 ±6.2	4.4 ±4.4	4.5 ±5.0	0.040
BOOI	44.0 ±33.3	35.4 ±35.3	19.6 ±66.4	−6.4 ±13.4	<0.001	21.6 ±16.0	13.8 ±15.9	5.0 ±12.7	6.2 ±13.7	0.208
VV (ml)	119.7 ±103.0	122.9 ±112.6	168.9 ±91.8	298.4 ±127.1	<0.001	148.3 ±132.0	163.2 ±136.0	128.6 ±146.6	113.9 ±166.0	0.345
PVR (ml)	188.6 ±142.8	211.1 ±156.9	175.7 ±153.2	100.0 ±155.5	0.070	207.8 ±184.5	181.2 ±206.7	266.9 ±170.2	281.1 ±168.9	0.090
Bladder voiding efficiency (%)	41.2 ±31.8	41.4 ±34.5	54.1 ±33.6	82.4 ±26.5	0.002	46.3 ±31.00	59.2 ±39.0	33.8 ±39.2	29.1 ±34.2	0.022
Global response assessment										
Excellent		27% (19)		14% (1)			23% (3)		31% (4)	

Markedly improved^		47% (33)		57% (4)			54% (7)		38% (5)	
Mildly improved		7% (5)		0			8% (1)		0	
No change		17% (12)		29% (2)			15% (2)		31% (4)	
Missing				0			0		0	
Successful outcome*		74% (52)		71% (5)	1.000		77% (10)		69% (9)	1.000

*defined as a global response assessment equal to or greater than 2. ^still need CIC occasionally.

No difference in treatment response rate after urethral sphincter botulinum toxin injection was found among different subtypes of urethral sphincter dysfunction.

Multivariate analysis identified recurrent UTI and bladder voiding efficiency as positive predictors for a successful outcome, and DU was a negative predictor.

Validity and generalisability of the studies

- Studies were limited with small number of patients and short period of follow-up. There was only 1 RCT comparing botulinum with placebo treatment.
- Patients whose condition is refractory to conventional treatments and with heterogeneous non-neurogenic sphincter functions/causes (DV, DU, and PRES, Fowler's syndrome) were included in the studies.
- There is no standardised treatment protocol. botulinum injections were diluted with saline but the dose, number of injections, sites and depth of injection given varied across studies and in some studies repeat urethral injections were given.
- Most of the included studies were conducted by a research group in Taiwan and only 1 small study was from the UK.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention. NICE interventional procedures guidance 536 (2015). Available from http://www.nice.org.uk/guidance/IPG536

NICE guidelines

- Lower urinary tract symptoms in men: management. NICE clinical guideline CG97 (2010). Available from http://www.nice.org.uk/guidance/CG97

- Urinary incontinence in neurological disease: assessment and management. NICE guideline CG148 (2012). Available from http://www.nice.org.uk/guidance/CG148
- Urinary incontinence and pelvic organ prolapse in women: management
- NICE guideline NG 123 (2019) Available from http://www.nice.org.uk/guidance/NG123

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three professional expert questionnaires for botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention were submitted and can be found on the NICE website.

Patient commentators' opinions

Four commentaries from patients who had experience of this procedure were received as part of public consultation, which were discussed by the committee.

Company engagement

There is no specific device used for this procedure. Therefore, no structured information requests were sent to companies.

Issues for consideration by IPAC

- Botulinum injections into the EUS for idiopathic chronic non-obstructive urinary retention is currently done on an off-label basis.

References

1. Jiang Y.-H, Wang C-C, Kuo H-C. (2016) OnabotulinumtoxinA urethral sphincter injection as treatment for non-neurogenic voiding dysfunction – A randomized, double-blind, placebo-controlled study. Sci. Rep. 6, 38905; doi: 10.1038/srep38905.
2. Kuo H-K (2007) Recovery of detrusor function after urethral botulinum A toxin injection in patients with idiopathic low detrusor contractility and voiding dysfunction. Urology, 69: 57-62.
3. Kuo H-K (2007) Comparison of the therapeutic effects of urethral injections of 50 and 100 units of botulinum A toxin for voiding dysfunction. Tzu Chi Medical Journal. 19, 3, 134-138.
4. Jiang Y-H, Lee C-L, Chen S-F et al. (2021) Therapeutic effects of urethral sphincter botulinum toxin A injection on dysfunctional voiding with different videourodynamic characteristics in non-neurogenic women. Toxins, 13, 362, 1-10.
5. Panicker JN, Seth JH, Khan S et al. (2016) Open-label study evaluating outpatient urethral sphincter injections of onabotulinumtoxinA to treat women with urinary retention due to a primary disorder of sphincter relaxation (Fowler's syndrome). BJU Int. 117, 809–813.
6. Ou Y-C, Huang K-H, Jan H-C et al. (2021) Therapeutic efficacy of urethral sphincteric botulinum toxin injections for female sphincter dysfunctions and a search for predictive factors. Toxins, 13, 398, 1-10.
7. Nadeem M, Lindsay J, Pakzad M, et al. (2022) Botulinum toxin A injection to the external urethral sphincter for voiding dysfunction in females: a tertiary center experience. Neurourol Urodyn. 41:1793-1799. doi:10.1002/nau.2502
8. Kao Y-L; Ou Y-C; Tsai K-J; Kuo, H.-C. (2022) Predictive factors for a successful treatment outcome in patients with different voiding dysfunction subtypes who received urethral sphincter botulinum injection. Toxins, 14, 877. https://doi.org/10.3390/toxins14120877

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/01/2023	Issue 1 of 12, January 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/01/2023	Issue 12 of 12, December 2022
International HTA database (INAHTA)	04/01/2023	-
MEDLINE (Ovid)	05/01/2023	1946 to January 04, 2023
MEDLINE In-Process (Ovid)	05/01/2023	1946 to January 04, 2023
MEDLINE Epubs ahead of print (Ovid)	05/01/2023	January 04, 2023
EMBASE (Ovid)	04/01/2023	1974 to December 30, 2022
EMBASE Conference (Ovid)	04/01/2023	1974 to December 30, 2022

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

Ovid MEDLINE(R) <1946 to January 04, 2023>

1 exp botulinum toxins/ 18253
2 (botox or botulinum toxin* or botulinum neurotoxin* or clostridium botulinum or e211kpy694 or meditoxin or neuronox or neurotoxin or oculinum or onabotulinumtoxin a or onabotulinumtoxina or vistabel or vistabex or Bocouture or Xeomin or Dysport or azzalure or BTX-A or BoNT-A).tw. 30063
3 1 or 2 33077
4 Urinary retention/ 5080
5 ((non-obstruct* or nonobstruct* or "non obstruct*") adj4 (urin* or bladder*)).tw. 264
6 ischuria*.tw. 37
7 (Fowler* adj4 syndrome*).tw. 69
8 (Neuropathic* adj4 bladder* adj4 dysfunction*).tw. 124
9 (Neurogenic* adj4 bladder*).tw. 4732
10 (voiding adj4 (dysfunction* or difficult* or problem* or disorder*)).tw. 4197
11 (urethral sphincter adj4 (relax* or fail* or dysfunct* or difficult* or disorder*)).tw. 146
12 Urethra/ and (relax* or fail* or dysfunct* or difficult* or disorder*).tw. 4200
13 or/4-12 17266
14 3 and 13 417
15 animals/ not humans/ 5044488

16 14 not 15 408
17 limit 16 to ed=20211013-20230105 35

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
DasGupta R. Fowler CJ. (2003) The management of female voiding dysfunction: Fowler's syndrome - a contemporary update. Current opinion in urology. 13 (4):293–299.	Review	botulinum toxin injection, sacral nerve simulation has shown some efficacy in the treatment of young women with urinary retention. Although how it works is still not fully understood but is being addressed by ongoing research.	Review
Fenner A (2015) Botox injections are effective for Fowler's syndrome. Nature Reviews Urology 12, 653;	Research highlights of a pilot study	On botulinum improves patient-reported lower urinary tract symptoms and objective measures of bladder function in women with Fowler's syndrome, according to data published.	Review
Gasimov K, Jafarov R, Tatanis V, Bozacı AC, Ceyhan E, Mammadaliyev T, Doğan HS, Tekgül S. Children with Non-Neurogenic Lower Urinary	Retrospective study. 80 paediatric patients (neurogenic	This study showed that botulinum toxin injection is an effective and safe	Paediatric patients Lower urinary tract

Tract Dysfunction Require Less Frequent and Number of Botulinum Toxin Injections Than Neurogenic Ones. J Urol Surg, 2022;9(4):293-299.	bladder) and lower urinary tract dysfunction groups) had treatment with intradetrusor (n=48) n or intrasphincteric (n=32) BTx injection.	treatment in paediatric patients with neurogenic bladder and lower urinary tract dysfunction. For sphincter botulinum toxin injections (neurogenic bladder: 13 patients; lower urinary tract dysfunction: 19 patients) clinical improvement was found in 75% (n=24) n of the patients. There was no significant difference between the neurogenic bladder and lower urinary tract dysfunction groups. QOL questionnaires showed substantial decrease in the lower urinary tract dysfunction groups after bladder and sphincter injections.	dysfunction (voiding pattern and pelvic floor activity, incontinence and urinary tract infections) includes a spectrum of conditions from detrusor instability to serious cases affecting urinary tract without any known neurologic cause.
Jiang YH, Chen SF, Jhang JF et al. (2018) Therapeutic effect of urethral sphincter on a botulinum toxin A injection for urethral sphincter hyperactivity. Neuro-urology and Urodynamics. 37:2651–2657.	Retrospective case series N=95 patients with voiding dysfunction (idiopathic voiding dysfunction n=38) due to urethral sphincter hyperactivity	Satisfactory outcomes were reported in 58 (61.1%) patients, of these 20 were with idiopathic voiding dysfunction. Patients with non-neurogenic voiding dysfunction had a	Outcomes not reported separately for idiopathic voiding dysfunction.

	and who had treatment with injections of 100 U on a botulinum toxin A into the urethral sphincter. 1 month follow-up.	statistically significantly longer therapeutic duration than those with neurogenic voiding dysfunction (9.55 ± 4.18 versus 7.44 ± 2.91 months, P = 0.033). Increased urinary incontinence was reported in 18 patients, including 6 with stress urinary incontinence and 12 with urgency urinary incontinence.	
Jiang YH, Jhang JF, Chen SF et al. (2019) Videourodynamic factors predictive of successful on a botulinum toxin A urethral sphincter injection for neurogenic or non-neurogenic detrusor underactivity. Lower Urinary Tract Symptoms.11:66–71.	N=60 patients (27 with non-neurogenic and 33 with neurogenic DU) refractory to medical treatment had on botulinum injections into the urethral sphincter. Follow-up 1 month	Treatment outcome was statistically significantly better in patients with non-neurogenic than neurogenic DU (p=0.039). The duration of the therapeutic effect was similar between patients with non-neurogenic and neurogenic DU (mean 7.37 versus. 7.69 months, respectively; P = 0.788). In all, 12 patients reported de novo urinary incontinence after urethral botulinum injection, 4 of whom developed stress urinary incontinence and	Outcomes no reported separately for idiopathic aetiology (n=10)

		8 who had exacerbated urgency urinary incontinence. Urethral sphincter injection of on botulinum is effective in 60% of patients with DU. Careful video urodynamic interpretation of bladder neck opening enables urologists to select appropriate candidates for on botulinum treatment.	
Kuo H-K. (2003) Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. The Journal of Urology. Vol. 170, 1908–1912.	Prospective case series N=103 patients had botulinum for various types of lower urinary tract dysfunction (DSD in 29, DV in 20, nonrelaxing urethral sphincter in 19, cauda equina lesion in 8, peripheral neuropathy in 14 and idiopathic DU in 13) Botulinum 50 units in 48 patients and 100 units in 55 patients. Follow-up 1 month.	40 (39%) patients had an excellent result and 47 (46%) had statistically significant improvement. The total success rate was 84.5%. Among these patients mean maximum voiding pressure, MUCP and post-void residual decreased statistically significantly at 2 to 4 weeks after treatment. Among 45 patients with urinary retention the indwelling catheters were removed or clean intermittent catheterization was discontinued in 39 (87%).	Different aetiologies were included and overall therapeutic results were presented. These patients might have been included in the studies (Kuo 2007a) added to the summary of evidence.

Kuo HC. Effectiveness of urethral injection of botulinum A toxin in the treatment of voiding dysfunction after radical hysterectomy. Urol Int 2005; 75: 247–51	N=30 patients with difficult urination after radical hysterectomy due to cervical cancer had urethral injection of 100 units of botulinum (n = 20) or medical treatment (n = 10)	Urethral injection of botulinum can be effectively used to treat patients with DU and non-relaxing urethral sphincter after radical hysterectomy with few adverse effects.	Not sure if this is idiopathic as occurred after hysterectomy.
Kao Y-L, Huang K-H, Kuo H-C et al. (2019) The therapeutic effects and pathophysiology of botulinum toxin A on voiding dysfunction due to urethral sphincter dysfunction. Toxins, 11, 728, 1-17.	Review	Botulinum has been applied to various causes of USD, including DV, Fowler's syndrome, and poor relaxation of the external urethral sphincter. A large proportion of patients with different causes of USD report statistically significant improvement in voiding after sphincteric botulinum injections. Botulinum is still a reasonable option for refractory voiding function. To date, studies focusing on urethral sphincter botulinum injections have been limited to the heterogeneous aetiologies of USD.	Review
Lee, CL., Chen, SF., Jiang, YH. *et al.* Effect of	Retrospective study	Women with DV have different	Different treatment

videourodynamic subtypes on treatment outcomes of female dysfunctional voiding. Int Urogynecol J **33**, 1283–1291 (2022). https://doi.org/10.1007/s00192-022-05154-0	Women with VUDS proven DV (n=302) had biofeedback pelvic floor muscle training and medications; urethral sphincter botulinum toxin A injection was administered after treatment failure.	VUDS characteristics resulting from different pathophysiological mechanisms and treatment results. The VUDS characteristics may help predict treatment outcomes of female DV.	modalities assessed. Urethral botulinum toxin injection results already reported in another study (Jiang 2021) added to the overview of evidence.
Osman NI. & Chapple CR (2014) Fowler's syndrome—a cause of unexplained urinary retention in young women? Nature Reviews. Urology. 11, 87–98.	Review	Most studies of Fowler's syndrome are limited due to small cohorts with no control group and a lack of video urodynamic data. Whether Fowler's syndrome represents a distinct cause of urinary retention or results from a maladaptive behaviour and is similar to DV is unclear. Application of sacral neuromodulation in patients diagnosed with Fowler's syndrome can restore normal voiding, in the absence of any effective pharmacotherapy or surgical treatment.	Review

Smith CP, Nishiguchi J, O'Leary M, Yoshimura N, Chancellor MB. Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. Urology 2005; 65: 37–41	N=110 had injections of BTX-A into the bladder (n = 42) or urethra (n = 68) for a variety of lower urinary tract disorders (included neurogenic detrusor overactivity and/or DSD, overactive bladder, bladder neck obstruction, and interstitial cystitis) that was treated with either 100 to 200 U of BTX-A IN external sphincter or by injection into the bladder base using 100 to 300 U of BTX-A diluted in about 10 to 30 mL of sterile saline.	TX-A is equally effective in women as it is in men. When injected into the sphincter, the risk of stress incontinence is low. Bladder injections with BTX-A are effective for not only neurogenic detrusor overactivity, but also overactive bladder. BTX-A can even be considered for interstitial cystitis	Various aetiologies (neurogenic and non-neurogenic) included.