[Title] Management of refractory overactive bladder

[Abstract]

Key content

- Overactive bladder does not respond to first-line treatment in over 50% of cases.
- There is no agreed definition of what constitutes refractory overactive bladder.
- Botulinum toxin injection is effective, with a long duration of action but appreciable rates of urinary retention and infection (around 10% and 20%, respectively). There remain some questions about the preferred dose and the schedule of repeat dosing.
- There are few data on cost-effectiveness of botulinum toxin.
- Sacral nerve stimulation is an invasive, complex and expensive procedure.
- Sacral nerve stimulation is effective, but reoperation rates and complications are common.
- Percutaneous tibial nerve stimulation is a less invasive, cheaper alternative to sacral nerve stimulation but long-term efficacy is yet to be confirmed.

Learning objectives

- To understand the available data on the efficacy and safety of botulinum toxin use.
- To be aware of the need for thorough assessment of patients, and the importance of multidisciplinary team review and appropriate detailed counselling.
- To understand the available data on the efficacy and safety of the alternative methods of neuromodulation.

Ethical issues

• The long-term benefits and risks of these treatments are not fully defined. Is it ethical to commence potentially lifelong treatment without robust, high-quality data confirming safety?

Keywords: botulinum toxin / detrusor overactivity / neuromodulation / overactive bladder / sacral nerve / tibial nerve

[Q: Please check the correct level headings have been used throughout]

[Heading 1] Introduction

Overactive bladder (OAB) has been defined by the International Continence Society as a bladder storage problem consisting of 'urgency, with or without urge incontinence, usually with frequency and nocturia'.¹ This condition can negatively impact all aspects of life including social, work-related, sexual, psychological and emotional aspects,² leading to a significant impact not only on the person with the condition but on society in general. Approximately 400 million people experience OAB, with the number predicted to rise to 546 million by 2018.³ Up to 75% of adults may be affected.⁴ OAB costs include pad use, drugs and catheter costs, in addition to hospital visits.⁵ The economic burden is comparable to the cost of breast cancer, osteoporosis and diabetes, with a German study reporting the cost of OAB to be 3.57 billion Euros per year.⁶

The aetiology of OAB is unclear, but it is usually associated with detrusor overactivity.⁷ Detrusor overactivity is a urodynamic diagnosis characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. Most commonly, no cause for this is found (idiopathic detrusor overactivity), but in some cases an underlying neurological cause such as multiple sclerosis or spinal cord injury is present (neurogenic detrusor overactivity).¹

[Heading 1] Treatment

The conservative treatment of OAB includes lifestyle changes covering caffeine reduction, modification of fluid intake, bladder retraining and weight loss in those with a body mass index greater than 30; supervised pelvic floor exercises and antimuscarinics.^{8–10} In line with the National Institute for Health and Care Excellence (NICE) in the UK and the American Urological Association, lifestyle changes and behavioural therapies should be offered as first-line treatments.^{10,11} Antimuscarinic drugs can be used as second-line treatment or in conjunction with behaviour therapies.^{10,11} Anticholinergic drugs act by blocking muscarinic receptors in the bladder smooth muscle, leading to a direct relaxant effect.¹² Common adverse effects such as dry mouth, constipation and dry eyes occur as a result of blockade of these receptors at other sites.¹³ Antimuscarinic drugs are contraindicated in myasthenia gravis, significant bladder outflow obstruction, severe ulcerative colitis, toxic megacolon and in gastrointestinal obstruction or atony. There is a suggestion that M3 receptors present in the afferent pathway of bladder activation play a direct or indirect role in detrusor overactivity, and this is the rationale for the use of newer, receptor-selective drugs.^{14,15} Intravaginal estrogens can also be used to relieve symptoms in postmenopausal women.¹⁶ Mirabegron is a beta-3-adrenoceptor agonist, which acts by enhancing bladder relaxation during the storage phase of micturition. In the UK, it has been recommended by NICE for 'treating the symptoms of overactive bladder for those in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects'.¹⁷ It has been found to be a safe and effective treatment for OAB, in comparison with placebo and tolterodine tartrate.¹⁸ Common adverse effects include tachycardia and urinary tract infections.¹⁷ Uncontrolled hypertension is the main contraindication to its use.

Conservative and medical treatments are effective, but there is poor long-term compliance with medication, and many patients seek alternative treatments.

[Heading 1] Refractory overactive bladder

A treatment period of 8–12 weeks of pharmacotherapy is recommended before considering other options such as intradetrusor botulinum toxin, neuromodulation and surgical treatment.¹⁰ There is no agreed definition of refractory OAB however, and failure of pharmacotherapy is harder to define and encompasses such wide-ranging factors as lack of efficacy, adverse effects, contraindications and patients' perception and expectation of treatment, leading to discrepancies in the definition used in studies in the literature.¹⁹ Approximately 25–40% of patients fail to achieve satisfactory improvement in incontinence with anticholinergics.²⁰ A multidisciplinary team review should be carried out before invasive therapy for urinary incontinence.¹⁰

[Heading 1] Botulinum toxin

Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum*. Botulinum toxin acts presynaptically by cleaving synaptosomal-associated protein 25 (SNAP-25), which is required for fusion of neurotransmitter-containing vesicles, leading to a decrease of acetylcholine release across the neuromuscular junction and muscle paralysis (Figure 1). It has been shown that the mechanism of action is more complicated than simple paralysis of the detrusor. As well as returning the expression of neuronal sensory receptors to normal levels in bladder biopsies taken from patients being effectively treated,²¹ the mechanism of action may also include a complex inhibitory effect on vesicular release of excitatory neurotransmitters and the axonal expression of other proteins. These are thought to be important in mediating the intrinsic or spinal reflexes thought to cause neurogenic detrusor overactivity **[Q: neurogenic detrusor overactivity?]**.²² This suggests that the sensory afferent pathway is involved. The toxin is resistant to proteolysis and persists in the neurons for a long time, giving a clinical effect of between three and six months on average.

Seven botulinum toxin serotypes (A to G) have been identified. Botulinum toxin A is used in urology and urogynaecology practice. Onabotulinum toxin A is marketed as Botox[@] (manufactured by Allergan, California, USA) and is the most commonly studied form of

botulinum toxin A. Fewer studies exist on abobotulinum toxin A, known as Dysport[@] (produced by Ipsen, Paris, France). Schurch et al.²³ first described the use of botulinum toxin A in treating neurogenic OAB in 1999. Onabotulinum toxin A and abobotulinum toxin A are now increasingly being used for the treatment of refractory overactive bladder but at the time of writing, only onabotulinum toxin A has a licence for this indication.

[Heading 2] Patient selection

The most recent NICE guidance gives recommendations on the process to be followed before treating patients with onabotulinum toxin A (Box 1).¹⁰ A multidisciplinary review is recommended and the currently recommended dose is for 200 units of onabotulinum toxin A, based on the published literature available when the guidance was updated. Since then, several papers have been published,^{24–26} and onabotulinum toxin A is now licensed for use at a dose of 100 units.

NICE guidance also advises all women to be trained in intermittent self-catheterisation before treatment, but the cost-effectiveness of this is questionable. Given that only 10– 15% of women **[Q: treated with onabotulinum toxin A?]** will need to perform intermittent self-catheterisation, some clinicians will offer intermittent self-catheterisation to those deemed at higher risk of urinary retention post-treatment, for example, those with poor eyesight or dexterity, or anyone who expresses anxiety about the procedure.

[Heading 2] Administration

Onabotulinum toxin A is administered via cystoscopic injection using either a flexible or rigid cystoscope. Local or general anaesthesia can be used, but the procedure is well tolerated by most patients and can be completed in 20–30 minutes by a skilled practitioner. Thus, local anaesthesia and the use of a flexible cystoscope in an outpatient setting is recommended. In the UK, the current treatment tariff is considerably greater for outpatient treatment. The drug should be diluted in 0.9% normal saline to give ten units onabotulinum toxin A per site in a final injection volume of 0.5 to 1.0 ml per site. The most

common regimen is to give ten units per site in 20 sites across the dome of the bladder, if 200 units of onabotulinum toxin A is given, and five units in 20 sites for 100 units of onabotulinum toxin A (Figure 2). The dilution for abobotulinum toxin A is different, since the units of these two preparations are not equivalent. The recommended dosage for idiopathic detrusor overactivity **[Q: idiopathic detrusor overactivity?]** is 500 units of abobotulinum toxin A, and the conversion rate is thought to be about 2:1. The senior author has no experience of using abobotulinum toxin A.

Many clinicians will give a single dose of antibiotic prophylaxis, but there is no evidence that this prevents urinary tract infection. If antibiotics are to be used, it should be remembered that aminoglycosides can theoretically potentiate the effect of onabotulinum toxin A and should be avoided, and if a patient wishes to have general anaesthesia, the theoretical potentiating effects on muscle relaxants should be remembered (Botulinum Toxin A Summary of Product Characteristics, April 2014 [Q: Is there a reference for this? Please add to the reference list]).

[Heading 2] Evidence

There is now a considerable body of evidence supporting the efficacy and safety of onabotulinum toxin A. The vast majority of published data are on onabotulinum toxin A and these will be the focus of this section of the review. Eight randomised controlled trials using a placebo have now been published **[Q: are these included in the reference list? Please include the citations here]**.²⁴⁻³¹ The trials include a mix of patients with proven detrusor overactivity and those with OAB syndrome without urodynamic confirmation. It appears patient outcomes are similar regardless of whether or not detrusor overactivity is confirmed. The first small study compared 200 units of onabotulinum toxin A with placebo in 34 men and women.²⁷ Large symptomatic improvements were seen, which were maintained for six months and mirrored by significant increases in bladder capacity. A small study (32 women) compared 200 and 300 units of onabotulinum toxin A with placebo.²⁸ At six weeks, all 15 women treated with the active drug showed a 50% reduction in the frequency of incontinence episodes, 24% improvement in nocturia and 12% improvement in voiding frequency. Brubaker et al.²⁹ showed that 72% of the treatment group (28 women) reported a minimum of 75% reduction in incontinence episodes. The five largest trials show consistent data (Table 1).^{24–26,30,31}

Three systematic reviews have been published,^{32–35} with the most recent by Cui et al. in 2013. This included eight publications involving a total of 1320 patients in the analysis, including six randomised controlled trials that compared onabotulinum toxin A with placebo. In this analysis onabotulinum toxin A significantly decreased the mean number of urinary incontinence episodes per day by 2.77 compared with 1.01 after placebo (P<0.00001); and the mean number of micturitions per day: –1.61 versus –0.87 (P<0.00001). A total of 29.2% versus 7.9% of patients became continent (P<0.00001) (Table 1). Safety assessments indicated onabotulinum toxin A was often associated with complications resulting from post-void residuals (P<0.00001), urinary tract infections (UTI) (P<0.00001) and clean intermittent catheterisation (P<0.00001).

It remains unclear what the optimum dose of botulinum toxin A is. Dmochowski et al.³¹ showed that 50 units of onabotulinum toxin A was less effective than all higher doses, and 2012 and 2013 randomised trials have shown that 100 units may be as effective as 200 units but with a lower rate of adverse events, and a lower rate of urinary retention.^{24–26} Whether this is offset by a more rapid return of bothersome symptoms is unclear. Some authors suggest that 150 units may be the ideal dose to balance long-term efficacy with fewer adverse effects.^{31,36} In the UK, current guidance recommends 200 units of onabotulinum toxin A as discussed above, although 100 units may be offered, after discussion about the benefits of the lower risk of retention with this dose. It should be pointed out that UK NICE guidance [Q: what guidance? NICE?] recommends urodynamic confirmation of detrusor overactivity in all cases, whereas the drug licence allows treatment with 100 units for patients with OAB alone.

There is growing evidence that repeated injections are equally effective. Sahai et al.³⁷ analysed data from 34 patients (men and women) with idiopathic detrusor overactivity, treated with 200 units of onabotulinum toxin A, and reported a mean interinjection period of 377, 378 and 256 days before injection numbers 2, 3 and 4. Urinary frequency, urgency and incontinence, and quality of life assessments showed equivalent improvements after each injection. Dowson et al.³⁸ extended this cohort, and analysed data from 100 patients receiving 200 units of onabotulinum toxin A. Fifty-three patients had two injections, with only 20 having three or more. The outcomes after each injection (up to the fifth analysed) showed no difference from each other. Granese et al.³⁹ studied 68 women treated with 100 units of onabotulinum toxin A, of whom 20 received a second injection and reported equivalent effect after each injection. Gousse et al.⁴⁰ compared repeat treatment with either 100 or 150 units of onabotulinum toxin A after randomisation in 60 patients (51 women) and also showed equivalent efficacy in terms of quality of life assessment and global improvement. Repeat treatment can be given without referral back to the multidisciplinary team if the first treatment has been effective.¹⁰

[Heading 1] Sacral nerve stimulation

Sacral nerve stimulation (SNS) with an implantable device is licensed for the treatment of urge incontinence, urinary frequency and urinary retention.

[Heading 2] Mode of action

The mechanism of action of neuromodulation is complex and not fully understood. It works on the principle that activity in one neural pathway can influence activity in another neural pathway. Normal micturition is controlled by pathways in both the peripheral and central nervous systems. The S2–S4 nerve roots of the sacral nerve provide the autonomic (peripheral) and somatic (central) innervation to the pelvic floor, urinary bladder and urethra.^{41,42}

Whether SNS works predominantly in the efferent pathway via the pudendal nerve or the afferent pathway in the spinal cord or higher cortical centres of micturition is a matter of debate, but opinion seems to be shifting to the theory of the sacral neuromodulation **[Q: sacral neuromodulation?]** working on the afferent pathway and modulating reflexes that influence the bladder and pelvic floor response.^{41,42}

[Heading 2] Patient selection

NICE and American Urological Association guidance^{10,11} recommends offering SNS to those who have not responded to conservative management, including drugs, and are unable to perform intermittent self-catheterisation, and to consider SNS if a woman's symptoms have not responded to conservative management and onabotulinum toxin A injections. SNS is contraindicated in patients who have inadequate response to test stimulation.

[Heading 2] Details of procedure

Evaluation of SNS for each patient must be performed prior to implantation of the permanent stimulation device as it is difficult to predict response. There are two techniques of evaluation before permanent implantation: peripheral nerve evaluation or a Stage 1 implanted evaluation. Peripheral nerve evaluation is carried out as an in-office procedure under local anaesthesia, with a temporary electrode. An electrode is inserted through a skin incision a few inches above the coccyx and just off the midline near the S3 sacral foramen, and a smooth temporary electrode is inserted. Correct placement of the electrode is confirmed by levator ani motor response, plantar flexion of the big toe and stimulation of perineal sensation. Basic evaluation can be carried out for up to seven days and a bladder diary is kept to evaluate symptoms pre-procedure and during the test phase. Success is usually taken as an arbitrary minimum of 50% improvement of symptoms compared with baseline.

Basic evaluation is effective for most patients, but in some it does produce a sufficient

response and so recently advanced evaluation has been developed. Evaluation is a day case procedure performed under sedation or general anaesthesia, and the permanent, tined electrode is inserted under fluoroscopic guidance and used for evaulation.

, Stage I evaluation can be done for up to 14 days. A

For patients with successful evaluations, a second procedure under general anaesthetic is required to place a permanent tined electrode and subcutaneous permanent stimulator (or only to attach the implantable stimulator after advanced evaluation) (Figure 3). A review in 2010⁴³ showed that the rate of progression to permanent neurostimulator implantation was 40–50% in peripheral nerve evaluation and 70–90% in advanced evaluation. Bannowsky et al.⁴⁴ showed that bladder capacity was improved to a greater extent with advanced evaluation (55% increase) than with peripheral nerve evaluation (30% increase). Both techniques improved detrusor overactivity by 75%.

[Heading 2] Efficacy of SNS

Two small studies reported significant improvement rates (more than 50% reduction in leakage episodes of 33-59%)^{45,46} (Table 2), with a stable long-term success rate of around 65%.

van Kerrebroeck et al.^{47]} carried out a five-year, prospective multicentre non-randomised study to evaluate the long-term efficacy and safety of SNS on refractory urge incontinence, urgency frequency and retention in 163 patients. They reported that 68% of patients with urge incontinence and 56% with urgency frequency had successful outcomes at five years, with a revision rate of 42% (Table 2).

A systematic review⁴⁸ identified four randomised trials of SNS implantation and 30 reports of uncontrolled cases. Pooled analysis of the data from 120 patients recruited to the four trials demonstrated 80% of participants reported continence or a more than 50% improvement in incontinence symptoms compared with 3% reporting the same in the control group. The case series showed similar results, with 67% achieving continence or more than 50% improvement in symptoms. Incontinence episodes, leakage severity,

voiding frequency and pad use were all reduced significantly. The available longer-term data suggested that the benefits obtained from SNS persisted for up to 3–5 years after implantation.

[Heading 2] Adverse effects

The Brazzelli review⁴⁸ reported an overall reoperation rate of 33% (282 of 855 patients), most often due to pain and infection at the implantation site, or lead migration (causing loss of effect) requiring repositioning. Other problems included wound infections or breakdown, and adverse effects on bowel symptoms. Nine percent of treated patients needed permanent removal of the electrodes.

[Heading 1] Percutaneous posterior tibial nerve stimulation

Percutaneous posterior tibial nerve stimulation (PTNS) is an alternative, less invasive method of neuromodulation, which is therefore considerably cheaper. There are fewer published high-quality data supporting the use of PTNS and so it should only be offered after a multidisciplinary team review in women who have failed conservative therapy, including anticholinergic drug treatment, and who do not want botulinum toxin treatment or SNS.¹⁰ The mode of action of PTNS is unclear. The posterior tibial nerve contains mixed sensory motor fibres and emerges from the same spinal segments as the sacral nerve. Neuromodulation of the sacral nerve plexus via the posterior tibial nerve is thought to produce the effects on bladder symptoms **[Q: any reference/s?]**.

[Heading 2] Description of procedure

PTNS is a minimally invasive procedure easily carried out in the outpatient setting. A fine gauge needle is inserted 4–5 cm superior to the medial malleolus of the ankle with a surface electrode placed on the foot (Figure 4). This is connected to a low-voltage stimulator adjusted to deliver electrical pulses to stimulate the nerve, which can produce a

tingling sensation (sensory) or involuntary plantar flexion or fanning of the toes (motor) response. Initial treatment consists of 12 weekly sessions lasting 30 minutes each.⁴⁹

[Heading 2] Studies on efficacy

Two randomised studies looking at the efficacy of PTNS exist. The first is a randomised, multicentre, controlled study comparing the effects of 12 weeks of weekly PTNS to 4 mg daily extended-release tolterodine.⁵⁰ Subjects in the PTNS arm reported a statistically significant (P=0.01) global improvement compared with tolterodine (Table 3). There were no serious adverse events reported. Subjects who reported an improvement in symptoms in the initial 12-week phase were offered continuing PTNS at treatment intervals designed to alleviate symptoms during the duration of treatment and followed up at six months (n=30) and 12 months (n=25). At six months, frequency improved by 3.2 voids/day, nocturia by 1.2 voids/night, and urge incontinence by 1.6 voids/day. The corresponding values at 12 months were 2.8 voids/day, 0.8 voids/night and 1.6 voids/day. The second study was a randomised, double blind trial involving 220 patients comparing PTNS with sham treatment.⁵¹[Q: this is the same reference as the first study. Is this correct?] The subjects' global response assessment [Q: in full? Is this global response assessment?] showed 54.5% had moderate or markedly improved symptoms in the PTNS arm compared with 20.9% in the sham arm (P<0.001) (Table 3). All reported outcomes were statistically significant at 13 weeks, but not seven weeks, showing that a 12-week course is required to improve OAB symptoms. Those who had received treatment with medication before responded more (62.9%) to treatment compared with those who had not previously received medication (48.5%). During long-term efficacy and safety of patients in this trial [Q: in full? What does this refer to?] participants after three years of PTNS therapy, it was found that 77% (95% CI 64-90%) of 29 patients maintained a moderate to marked improvement in symptoms.⁵²

Thus, there is limited level 1 evidence on the efficacy of PTNS in treatment of OAB disorder, but ideally the findings need to be confirmed by further (larger) randomised

controlled studies and meta-analysis of these findings. Two systematic review articles are published but no meta-analysis has been carried out. PTNS has the potential to be an office-based therapy and first-line treatment option for patients with OAB because it is minimally invasive and does not involve placement of a permanent implant.

[Heading 1] Third-line treatments

For some patients, their OAB symptoms can be refractory to all the treatments outlined above. For these patients the treatment options are limited to major surgical procedures or long-term catheterisation. A detailed consideration of these is beyond the scope of this article, but after appropriate multidisciplinary review and detailed counselling, severely affected patients may be offered urinary diversion into an ileostomy or clam ileocystoplasty. Both are major and complex surgical procedures with significant shortand long-term morbidity and mortality (approximately 1% postoperative mortality rate). Long-term indwelling urinary catheterisation is often overlooked as a simple and effective means of restoring continence. Complications do occur but these are usually symptomatic urinary tract infection and catheter-related complications, including encrustation and bypassing. However, for some patients an indwelling catheter (either urethral or suprapubic) can be an acceptable long-term solution.

[Heading 1] Conclusion

OAB remains a challenging condition to treat. Many women fail to obtain benefit from conservative measures and oral medication. Secondary treatments such as botulinum toxin and nerve stimulation appear to be highly effective, although each procedure carries its own risks and complications, and both are invasive and expensive treatments which require long-term follow-up and investment in the patient by the healthcare team. However, many patients find these secondary interventions effective in restoring quality of life and independence.

Contribution of authorship:

JW performed the literature search, wrote the first draft and contributed to revisions and approved the final paper. DGT revised the draft article and approved the final paper.

Disclosure of interests:

JW has no conflicts of interest. In the last three years DGT has received honoraria for advisory boards (two) from Allergan UK, and has received an honorarium for lecturing, plus travel costs, for attending the UK Continence society on one occasion from Ethicon.

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Box 1. Summary of National Institute for Health and Care Excellence guidance on botulinum toxin A¹⁰

After a multidisciplinary team review, offer botulinum toxin A to women with proven detrusor overactivity that has not responded to conservative management.

Discuss the risks and benefits of treatment:

- 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
- Use 200 units when offering botulinum toxin A.
- 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.

[Figure legends]

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Figure 1. Mode of action of botulinum toxin A.

Figure 2. Injection techniques: (a) suggested pattern with flexible cystoscope (green dots indicate injection

on anterior/dome of bladder; (b) alternative pattern which can be administered via flexible or rigid

cystocscope.

Figure 3. Placement of a permanent subcutaneous sacral nerve stimulator. [Q: figure caption ok?]

Figure 4. Administration of percutaneous posterior tibial nerve stimulation. [Q: figure caption ok?]