Modern management of overactive bladder syndrome

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Abstract

Overactive bladder (OAB) is a term describing a symptom complex characterized by urinary urgency, with or without urgency-associated urinary incontinence and usually with associated urinary frequency and nocturia. Studies report OAB prevalence rates of around 17% in women with a detrimental impact on quality of life.

The NICE guideline on urinary incontinence (UI) outlines recommendations on the assessment and investigation of OAB. It highlights the importance of conservative measures namely lifestyle changes, bladder training and pelvic floor exercises before the prescription of antimuscarinic drugs. Drug use is limited by the side effects of dry eyes, dry mouth and constipation. Symptoms remain refractory in 20% of women. Second line management previously involved surgery either bladder augmentation (such as cystoplasty) or urinary diversion. Modern management however involves posterior tibial nerve stimulation (PTNS), Botulinum toxin or sacral neuromodulation before surgery and it is these therapies that will be the focus of this review.

Keywords antimuscarinics; Botulinum toxin; detrusor overactivity; OAB; urodynamics

Introduction

Overactive bladder (OAB) is defined as urgency with or without incontinence usually along with frequency and nocturia, in the absence of other pathology such as urinary tract infection, calculus or neoplasm. The symptoms extend beyond urgency and incontinence and they can affect the patients' quality of life, confidence, independence and relationships. Studies report OAB prevalence rates of around 17% in women. OAB is subdivided into OAB wet and OAB dry depending on the patient's continence status.

Detrusor contractions are the underlying cause of OAB symptoms. These contractions are either neurogenic or idiopathic in origin. Detrusor overactivity (DO) can be diagnosed using multi-channel filling cystometry. Cystometry is not required or advised before first line conservative management, however it is recommended following failed conservative therapy and in cases of voiding dysfunction.

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In this review, we will discuss the modern management of OAB in terms of second line treatments. Patient assessment and diagnosis and further detail on conservative management will not be discussed, guidance on these has been published by NICE and details can be found in the reading list.

Conservative management of OAB

First line management of OAB should be initiated, and if successful continued, in primary care. This includes lifestyle changes (reducing caffeine and alcohol intake, weight loss), bladder retraining and pelvic floor exercises. If these measures fail drug therapy using antimuscarinics, is the next step in conservative management.

The autonomic nervous system acts on the bladder via the parasympathetic and sympathetic routes. Parasympathetic action is mediated by the release of acetylcholine, which results in detrusor muscle contraction and urethral sphincter relaxation. The sympathetic system is mediated by adrenergic receptors that inhibit detrusor activity and increase urethral pressure. Antimuscarinic drugs work by blocking acetylcholine release, which decreases the parasympathetic action on the bladder and inhibits detrusor contractions and decreases OAB symptoms. There are many antimuscarinics in clinical use, however their use is limited due to the side effects of dry eyes, dry mouth and constipation. Changes in the antimuscarinic preparations and routes of administration have offered some reduction in side effects and improved efficacy.

The newest medication to manage OAB is mirabegron (Betmiga). Launched in the UK in February 2013, mirabegron avoids the side effects of the antimuscarinics drugs by targeting the sympathetic rather than the parasympathetic nervous system. It works by activating Beta 3 receptors located in the bladder wall, which increase the sympathetic nervous system activity and cause detrusor muscle relaxation.

Second line management of OAB

OAB symptoms remain refractory in 20% of women. Referral to secondary care is recommended in such cases when conservative measures and management with antimuscarinics medication has failed, or in cases with voiding dysfunction, or uncertainty about the diagnosis. After review of the patient's signs, symptoms and previous management, a filling cystometry should be undertaken to confirm the diagnosis of detrusor overactivity as the cause of her OAB symptoms.

Following failed conservative management of OAB, the second line management options include posterior tibial nerve stimulation Botulinum toxin injections into the bladder mucosa, sacral nerve modulation or. The main purpose of this article is to discuss these treatments in greater detail, focussing on the mechanisms of action, treatment regimens and the research surrounding them.

Botulinum toxin

Botulinum toxin is a neurotoxin derived from the anaerobic bacterium *Clostridium botulinum*. It has an established clinical role in many areas including torticollis; upper motor neurone syndrome, blepharospasm and strabismus as well as cosmetic use.

Botulinum toxin A is licensed in the management of neurogenic detrusor overactivity, however most preparations do not have UK marketing authorization for this indication. The evidence quoted by NICE is only for the licensed product Botulinum toxin A (BOTOX, Allergan). Its use in idiopathic DO is outwith its UK marketing authorization. There is a growing body of evidence to support the use of Botulinum toxin A idiopathic OAB, indeed it is recommended by NICE in women who have not responded to conservative treatments, and who are willing and able to self-catheterize. There is a lack of long-term data and this should be documented as part of patient counselling and consent. NICE also advice that special arrangements are in place for audit or research. The use of Botulinum type B is not recommended in OAB.

Mechanism of action of Botulinum toxin on the bladder: botox works on many different receptors within the bladder wall. The exact mechanism by which it reduces OAB symptoms is not clear. It is known to inhibit the pre-synaptic release of acetylcholine from the parasympathetic efferent nerves, which leads to the relaxation of the detrusor muscle. It also affects C-fibre afferents that in turn reduce in the sensation of urgency, and inhibits adenosine triphosphate (ATP) and substance P release from the urothelium. All of these actions have been implicated in mediating the intrinsic and spinal reflexes that lead to OAB.

Administration of Botulinum toxin for OAB: Botulinum toxin is injected into the bladder wall under direct vision using either a rigid or flexible cystoscope, under local or general anaesthetic. Several injection techniques have been described, such as omitting the trigone, injection volume and dosage. Evidence suggests injecting the trigone does not affect safety of efficacy of the treatment, however it is avoided due to the theoretical risk of ureterovesical reflux. NICE guidelines recommend the use of 200 IU of botox type A for idiopathic OAB. In cases where the patient wishes to reduce their chances of self-catheterization a reduced dose of 100 IU botox can be considered with the acceptance that this may in turn come with a reduced chance of success. If treatment is successful, follow up should be offered at 6 months, or sooner if symptoms return.

A study funded by Allegan compared 50, 100, 150, 200 and 300 IU injections with placebo. Any dosage of botox was superior to placebo, however the dose response effect appeared to tail off above 150 IU. Other studies have not shown this trend but have demonstrated a longer duration symptom-relief with higher doses. The duration of effect ranges from 3 to 15 months and is patient rather than dose specific.

The RELAX study is a randomised blinded placebo-controlled trial of 240 women, using 200 IU in the treatment arm. As the largest published RCT it has influenced the NICE guidance. Symptoms were assessed at baseline, 6 weeks, 3 months and 6 months. The primary outcome was voiding frequency per 24 hours at 6 months, with secondary outcomes including urgency and incontinence episodes and quality of life data. The results favoured the use of botox; median voiding frequency botox compared with placebo (08.333 v 9.67 ($p = 0.0001$)), urgency episode (3.83 v 6.33 $p < 0.0001$) and leakage episodes (1.67 v 6.00 $p < 0.0001$). 31% of the treatment arm became fully continent. The results of this trial showed urgency and incontinence improved more than frequency, however all three outcomes show significant results favouring botox.

Adverse events reported included urinary tract infection, transient haematuria and the need to perform clean intermittent self-catheterization (CISC) due to high post void residual volumes or voiding difficulties. The RELAX trial quoted risk of UTI as 1 in 3, and CISC as 1 in 6 patients at 6 months. This figure supports the recommendation by NICE that patients undergoing treatment with botox for OAB should be willing and able to undertake CISC for as long as needed. Those not willing or able to undertake CISC are not candidates for botox and other treatments should be considered.

Further research is required on some aspects of the botox treatment such as dosage and injection regimens. However evidence shows that it is an effective treatment in cases of refractory OAB. Repeated treatments are needed but with growing experience in its use, and the development of outpatient treatments, it is an attractive alternative to other second line treatments such as sacral nerve modulation and posterior tibial nerve stimulation.

Posterior tibial nerve stimulation

PTNS was first described in the 1980's by McGuire et al., but was not used clinically for the treatment of OAB until 2000. The exact mechanism of action is unclear but thought to be by retrograde stimulation of the sacral nerve plexus causing neuromodulation. Direct stimulation of the posterior tibial nerve alters the function of the sacral nerve plexus giving an improvement in OAB symptoms. This nerve plexus originates from the same spinal segment as the nerves that supply the bladder and pelvic floor, and this neuromodulation has been shown to reduce OAB symptoms.

Administration of PTNS for OAB: NICE recommends the use of PTNS only in cases where conservative and drug therapies have failed, and the patient does not wish to have treatment with Botulinum toxin or percutaneous sacral nerve stimulation. The patient should be advised there is little evidence to routinely recommend the use of PTNS for OAB. To administer PTNS, the patient sits in a reclining chair with the treatment leg elevated (Figure 1). An electrode needle is passed percutaneously, cephalad to the medial malleolus so as to be near the posterior tibial nerve but not directly touching it. The needle is then connected to a low voltage stimulator to deliver pulsatile energy for the 30 minute treatment. Sensory effects of the treatment include tingling in the foot, ankle and toes, and motor effects of the treatment include fanning of the toes and plantar flexion. Twelve sessions each lasting 30 minutes 1 week apart are advised with further sessions as needed for longer term relief.

The SumiT trial is a multi centre double blind trial looking into the efficacy of PTNS in the treatment of OAB of 220 women and is the only published randomised controlled trial concerning to date. Outcome measures were assessed at baseline and 13 weeks, and included improvements in global response, voiding diary parameters, OAB and quality of life questionnaires. PTNS treatment resulted in a statistically significant improvement in symptoms with a response of 55% compared with 21% in the control arm. Although these results are very encouraging regarding the outcomes for PTNS, the sample size in this RCT was relatively small and follow up time was short. A recent systematic review concluded that there is limited high quality data for the use of PTNS for the treatment of OAB in women, and recommended further trials would be beneficial to draw more solid conclusions.