The management of overactive bladder symptom complex

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Overactive bladder (OAB) is a symptom complex characterised by urinary urgency, with or without urgency incontinence, usually associated with increased daytime frequency and nocturia. This article discusses our current understanding of OAB and its recommended management.

Overactive bladder (OAB) is a common symptom complex that affects men and women with a similar prevalence overall. In male patients, these symptoms are often attributed to benign prostatic disease. Women are more likely to be affected by urgency incontinence than men and approximately a third of women with OAB symptom complex have OAB ‘wet’ (where there is concomitant urgency incontinence).

Guidelines emphasise the importance of conservative treatment modalities including lifestyle advice and careful assessment with a voiding diary. Failure to respond to conservative measures will often lead to consideration of pharmacotherapy. The traditional mainstay of pharmacotherapy has been anticholinergic drug treatment. More recently, a first-in-class beta3 agonist has entered the market, which can be used as a second- or possibly even first-line therapy.

In this review, we provide our current understanding of OAB as well as current best practice and management. We provide practical advice relating to real-life clinical practice at a primary care level, and also provide a brief overview of second- and third-line treatments offered at both district general hospitals and tertiary referral centres.

Definition and incidence
According to the International Continence Society, the definition of OAB is a syndrome characterised by symptoms of urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia. The term OAB can only be used if there is no proven urinary tract infection or other causative pathology. In one of the largest population-based surveys to date, the incidence of OAB was calculated to be 11.8%.1 To put this into perspective, the UK prevalence for diabetes and hypertension has been estimated at 6.2% and 24% respectively.2,3

The prevalence is slightly higher among women below the age of 70 years, but it is higher in men above this age. However, from a practical point of view, the overall prevalence is similar in
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the two genders (female 16.0% vs male 16.9%). One importance difference between the two genders is that the prevalence of urgency urinary incontinence (i.e. OAB ‘wet’) is significantly higher in females (9.3%) than in males (2.6%)..

In both genders, the incidence tends to increase with age and management of OAB in the elderly can be particularly challenging due to multiple factors such as increased prevalence of polypharmacy, susceptibility to pharmacotherapy-related side-effects and higher prevalence of other associated conditions such as stress urinary incontinence, poorly controlled diabetes, peripheral oedema and general decreased ability to self-care.

The hallmark symptom of OAB is urinary urgency, which is defined as the sudden compelling desire to void that is difficult to defer. One should not confuse urgency with urge to void as the former is an abnormal sensation and the latter is a normal physiological sensation that can be easily be suppressed without fear of leaking. Patients may commonly describe urgency with sentences such as: “when I need to go, I have to go”, “if I don’t reach a toilet in time, I feel I’m going to wet myself” or “I dread long-distance driving as I may not find a toilet in time”. As one can imagine, urinary urgency is a very bothersome lower urinary tract symptom (LUTS) with negative effects on one’s quality of life. This is especially true with concomitant urgency urinary incontinence. Like any symptom, the severity of the problem will differ greatly between individuals and hence treatment needs to be tailored accordingly.

In summary, OAB is not a pathological condition but rather a group of symptoms. This has been invaluable for researchers, as they have been able to come up with more objective clinical trial endpoints, which in turn has made comparing results easier, as well as helping pharmaceutical companies to invest in and develop new OAB medications, which can be rigorously tested in randomised trials.

The underlying pathology that leads to OAB symptoms is at present not fully understood and more research is required. So far, models to explain what gives rise to OAB symptoms can be attributed to four different mechanisms:

- Phasic smooth muscle detrusor contractions
- Activation of sensory afferent nerves
- Enhanced excitatory transmission in the central nervous system and/or
- Reduced central nervous system central inhibition.

However, why in the absence of any neurological disease (such as non-neurogenic OAB) some patients get OAB symptoms but some don’t remains a mystery. Contrary to popular belief, our understanding of the lower urinary tract neurological innervation remains incomplete and most of our best theories come from animal models. More research is still required to understand what causes OAB symptoms in the first place in order for us to be able to better tailor treatment in the future.

Types of overactive bladder

Broadly speaking, OAB can be classified into two distinct groups: neurogenic or non-neurogenic (also known as idiopathic) OAB. Patients with a concomitant neurological condition that is known to affect the lower urinary tract (such as multiple sclerosis, Parkinson’s disease or spina bifida) are termed as having neurogenic OAB. It is important to bear in mind that some neurological conditions may initially present with LUTS before the onset of other more obvious or classic neurological symptoms, leading to a delay in diagnosis of the neurological condition. A classic example of this is multiple sclerosis, in which up to a third of patients have LUTS as part of their initial presenting symptoms. Fortunately, most patients will have non-neurogenic OAB.

Overactive bladder vs detrusor overactivity

It is commonly thought among many medical professionals that urgency symptoms arise from ‘bladder spasms’. Unfortunately, this is not necessarily the case. When real-time bladder pressures are measured in invasive pressure-flow urodynamic studies, patients may or may not have a rise in bladder pressure during the filling phase of the bladder. If a rise in bladder pressure is detected, then it is termed detrusor overactivity rather than OAB. To make matters even more confusing, patients may even have asymptomatic detrusor overactivity, and up to 50% of control patients in clinical trials with no OAB symptoms are found to have detrusor overactivity during urodynamic studies. The relationship between OAB and detrusor overactivity is illustrated in Table 1.

Although pressure-flow urodynamic studies are extremely helpful, they are labour intensive, costly, invasive and potentially embarrassing to the patient. Hence, patients with OAB symptoms are initially treated empirically and pressure-flow urodynamic studies are reserved for patients who fail to improve with conservative management and/or pharmacotherapy and who require second or third-line treatments under the care of a urologist.

Investigations

The general aim is to exclude other diagnoses that could also present with urinary urgency, frequency or nocturia. A careful history, examination and some basic investigations will help to exclude other urological conditions such as urinary tract infections, bladder stones, bladder cancer, bladder outlet obstruction (e.g. due to benign prostatic hyperplasia) and diabetes mellitus-related polyuria.

Frequency/volume chart

A frequency/volume chart is an inexpensive and very useful test that gives invaluable objective parameters such as daytime urinary frequency, voided volumes during each void, maximum functional bladder capacity, total daily urine output and number

<table>
<thead>
<tr>
<th>Rise in intravesical pressure detected during filling phase of urodynamic studies?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAB symptoms present?</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>Yes</td>
<td>OAB</td>
<td>Detrusor overactivity</td>
</tr>
</tbody>
</table>

Table 1. The relationship between overactive bladder (OAB) and detrusor overactivity
of nocturia episodes. The patient is provided with a measuring jug and a printed chart to fill in and is asked to measure and record each void over a three-day period (see Figure 1). The patient is also required to make a note the next day of the time that he/she fell asleep as well as any urinary leakage episodes. It is only with a well-recorded frequency/volume chart that one can calculate the presence or absence of nocturnal polyuria. Nocturnal polyuria is defined as the production of more than a third of the total 24-hour urine output during sleep.

Although it is beyond the scope of this article to go into the mechanisms of the many causes of nocturnal polyuria, it can be broadly divided into either: third-space fluid retention in the lower limbs that gets redistributed intravascularly while lying flat at night leading to increased renal perfusion and increased urine production (eg lower limb oedema in congestive cardiac failure); or obstructive sleep apnoea (OSA)-related hypoxaemia causing transient pulmonary hypertension leading to the excessive release of atrial natriuretic peptide (ANP) hormone, which causes excessive renal excretion of sodium and water.6

Dipstick urine
The following dipstick urine tests should be carried out:
• Leucocytes, blood and nitrites – can help to exclude urinary tract infections
• Blood – a non-specific finding in conditions such as urinary tract malignancy and stones
• Glucose – metabolic causes such as undiagnosed or poorly controlled diabetes mellitus can result in polyuria leading to urgency, frequency and nocturia.

Blood tests
Recommended blood tests include:
• Urea and electrolytes – primarily to ensure normal serum creatinine and hence, indirectly, renal function
• HbA1c – if diabetes is suspected
• Serum-corrected calcium – although it is uncommon, if polyuria is present in the frequency/volume chart, it is important to ensure that there is no hypercalcaemia-related polyuria.

Ultrasound of the kidneys and bladder
Ultrasound is an inexpensive and safe radiological test to exclude any renal tract masses, hydronephrosis and, to a certain extent, benign prostatic enlargement. In young patients with no other risk factors, ultrasound may not be required. Another advantage is that most sonographers will perform a pre-void and post-void ultrasound of the bladder to assess for any post-void retention of urine (note that this will be omitted if ultrasound of the abdomen is ordered instead). This is a useful way of ascertaining post-void residual volume in a busy GP clinic where a bladder scan machine is not available or if the patient is obese, which makes palpation of a full bladder more difficult.

Once other pathological conditions have been excluded, then the patient can be said to have idiopathic or non-neurogenic OAB. Due to its invasive nature, a pressure-flow urodynamic study is not necessary on initial presentation and one can start conservative management with or without pharmacotherapy. However, if a more invasive procedure such as intravesical botulinum toxin injection or sacral neuromodulation is required, then urodynamic studies will be warranted.

Management
Like many chronic diseases, OAB is a very challenging condition to manage well. We believe that empowering patients to take charge of their own health is a very important step. Helping a patient to understand their condition and manage their expectations will go a long way towards improving treatment compliance and confidence in the healthcare system. Patients may come with myriad anxieties such as fear of having an undiagnosed urinary malignancy or serious ‘kidney and/or bladder problems’ and we feel that the speedy exclusion of significant pathology will be invaluable in helping to reassure the patient. Never forget to remind the patient that non-neurogenic OAB in itself is not a life-threatening condition, but this should not be used as an excuse to disregard the patient’s worries as any less serious.

OAB management has to be seen as a long journey and healthcare providers must help patients to navigate it. Early on, it will be beneficial to make the patient aware that it may
take a considerable time to find the ‘right’ or ‘better-suited’ treatment(s) to achieve an acceptable balance between efficacy and side-effects. Too often, patients lose faith in healthcare providers after being given some anticholinergic medications with little explanation or reassurance about their condition. If this initial treatment fails to meet the patient’s expectations, it can lead to ‘doctor hopping’ or not turning up for follow-up appointments, which inevitably will lead to patients being disillusioned and frustrated, and some will sadly just decide to carry on living with their OAB symptoms indefinitely. We understand that in an ever-underfunded and time-restrained primary healthcare system it is extremely difficult and challenging to achieve this, but we feel that it will be time well spent in the long term.7

Conservative management
Lifestyle changes include smoking cessation, weight loss and avoiding/minimising intake of caffeinated and/or carbonated drinks. It is important to note that the caffeine content of coffee and tea are similar, and decaffeinated versions (which still have caffeine but at much lower doses) may be helpful for some. It is not too uncommon in routine clinical practice to see office-based workers in air-conditioned environments drinking four to eight cups of coffee by lunchtime. Fluid volume management is also crucial. Patients may have conflicting healthcare advice from health and beauty magazines advocating good hydration, and some patients may take this advice to an unhealthy extreme.

Although most patients will be sensible with their fluid intake, some patients may inadvertently drink excessive fluid volumes during the daytime, leading to fluid intakes of well over three or four litres per day. Apart from a small amount of water loss through perspiration, respiration and faeces, most fluid intake will be excreted renally (what goes in, must come out) and once again, an accurately completed frequency/volume chart will be very helpful to guide patients in managing their own fluid intake. Typical sensible fluid intake will be approximately 20ml/kg per day, which usually equates to 1.5–2 litres per day. Of course, fluid requirements will vary depending on the nature of the patient’s profession or physical exercise regimen. We feel that empowering patients to take charge of their condition is paramount for a better outcome.

Other conservative management options include bladder retraining (where the patient is taught to gradually delay voiding in order to suppress the urgency episodes) as well as pelvic floor exercises (most useful in mixed urinary incontinence patients). Recruiting nurses who have the training and expertise in this (eg continence nurse-led services) will be invaluable in this context. However, the literature on the effectiveness of conservative management alone in the treatment of OAB is not very robust, and conservative management has been mostly shown to be more effective when combined with pharmacological therapy.

Pharmacological therapy
Anticholinergic medication
Anticholinergic medication (also known as antimuscarinic medication) such as oxybutynin, tolterodine and solifenacin are still the mainstay of pharmacological treatment for OAB. They are usually relatively inexpensive (for the older out-of-patent medications) with a predictable side-effect profile. The main therapeutic target is the muscarinic receptors in the bladder urothelium. There are currently five known muscarinic subtypes (M1 to M5). M2 receptors are the most abundant in the human bladder, but the less abundant M3 receptor plays the most important role. Classically, it is taught that these medicines work by preventing detrusor contractions in the bladder; however, competing and emerging evidence suggests that they work at the urothelium level, preventing abnormal afferent parasympathetic signals reaching the spine/brain that are interpreted as urinary urgency.

Regardless of their actual mechanism of action, anticholinergic medications have been shown to be superior to placebo in multiple randomised controlled trials and meta-analyses (see Table 2). The effectiveness and side-effect profiles of the different anticholinergic medicines are comparable with each other. Notwithstanding, it is important to note that the placebo effect is quite substantial in these studies.8 Furthermore, non-compliance rates are rather high due to the inability of patients to tolerate the anticholinergic side-effects associated with this class of medication. Dry mouth, constipation and lethargy are some of the commonest side-effects. In one study in men and women with urinary incontinence, an increasing anticholinergic drug discontinuation rate was observed in years 1, 2, and 3 of 74.8%, 77.6% and 87% respectively.9 In another study in women with lower urinary tract symptoms, the median time for overall anticholinergic drug discontinuation was 4.76 months. The six-month unadjusted cumulative incidence of discontinuation was 58.8% and the proportion of episodes in which women switched to another medication was 15.8%. At six months, the adjusted cumulative incidence of discontinuation with different anticholinergic medicines was as follows: oxybutynin 71%, tolterodine tartrate 61%, extended-release oxybutynin 57%, and extended-release tolterodine tartrate 54%.10

The advent of extended-release formulations may help towards improved compliance as they reduce the dosage to only once a day (eg tolterodine SR or solifenacin). As effectiveness of different anticholinergic medications is similar and predicting side-effect occurrence at an individual level is difficult, it is hard to recommend one anticholinergic medication above another. Other variables such as cost and ease of administration may ultimately play an important role in the decision. There is evidence to suggest that cycling through more than two types of anticholinergic medication may not provide additional benefit, resulting in suboptimal care. We recommend referral to a urologist without delay if pharmacotherapy fails to improve symptoms adequately rather than cycling through every anticholinergic medication available. The use of transcutaneous anticholinergic patches is no longer popular due to possible skin reactions and/or discomfort, and possible variable absorption affecting efficacy.11

Beta2 agonist treatment
The latest class of medication in the management of OAB is mirabegron (Betmiga), which is a first-in-class beta2 agonist. It works via the sympathetic nerve pathway by stimulating beta2
Although one would expect combination therapy with mirabegron and any anticholinergic medication to give similar results, at present the only anticholinergic medication that has been studied in combination therapy is solifenacin. Therefore, if combination therapy is eventually needed, solifenacin is the recommended initial or second-choice anticholinergic medication.

### Intradetrusor botulinum toxin injection

The use of intradetrusor botulinum toxin type A injection (Botox or Dysport) is now a well-established treatment modality for refractory OAB with good level 1 evidence showing superiority compared to both placebo and anticholinergic medications. Clinically, botulinum toxin is now widely available in most urology departments across the NHS and treatment is usually a relatively simple procedure that is performed under lignocaine urethral gel instillation. A flexible cystoscope of <18Fr is inserted via the urethra (or suprapubic tract if already available) and intradetrusor botulinum toxin is given in divided doses through a fine needle throughout the urinary bladder.

The usual dose of Botox (which is the more popular brand of the two) is 100 units usually sparing the bladder trigone and this can be repeated every 3–12 months depending on the individual patient's response. Depending on the initial response, the subsequent session's dose can be increased to 200 units and up to a maximum of 300 units, although such high doses are rarely given for patients with non-neurogenic OAB. Risk of infection is low and the procedure is usually covered with oral antibiotics. It is paramount at the time of counselling that the patient is taught how to perform intermittent self-catheterisation as one in 10 patients undergoing intradetrusor botulinum toxin injection may develop transient retention of urine. Any patient unwilling to self-catherise or let a caregiver catheterise them should not be offered intradetrusor botulinum toxin injection.

After the first intradetrusor botulinum toxin injection session, the patient is usually assessed at an outpatient clinic a few weeks later and subsequently monitored to see how long the effects will last. This period may differ significantly between individuals but it tends to average six to nine months before a repeat session is required. Botulinum toxin is otherwise con-
Considered very safe and histological studies have failed to show any long-term adverse effects on the bladder such as tissue fibrosis.\(^{16}\)

In the largest randomised trial to date, Botox 100 units significantly decreased the number of urinary incontinence episodes per day at 12 weeks, with a mean decrease from baseline of 2.95 and 1.03 in the Botox and placebo groups respectively (\(p<0.001\)). Significant reductions from baseline compared with placebo in all other OAB symptoms were also observed at week 12 following Botox treatment. The proportion of patients with a positive response at week 12 was significantly greater with Botox than placebo (62.8\% vs 26.8\%; \(p<0.001\)).\(^{17}\)

**Sacral nerve stimulation**

Another well-established option for the treatment of OAB refractory to pharmacotherapy is sacral nerve stimulation (SNS), which has been in use for over 30 years now. The precise mechanism of action of SNS is still unknown and careful patient selection is paramount to improve its success rate. In carefully selected patients, success rates have been reported to range between 50–90\%. Based on animal studies, SNS induces either excitatory or inhibitory reflexes to the bladder, which can be potentially modulated depending on the frequency and intensity of electrical stimulation delivered to the S3 nerve root.\(^{18}\)

In the UK, funding is carefully regulated and there are stringent inclusion and exclusion criteria for its use in specialised urological centres. For example, patients must have failed both conservative treatment and pharmacotherapy or had to discontinue pharmacotherapy due to intolerable side-effects. All patients considering SNS have to undergo pressure-flow urodynamic studies and unlike intradetrusor botulinum toxin injection, only patients with proven detrusor overactivity are eligible to apply for funding for SNS insertion on the NHS.

The SNS device insertion is performed in two separate stages. In the first stage, a long thin wire electrode (usually barbed to avoid displacement) is percutaneously inserted into the S3 foramina under fluoroscopic guidance either under general anaesthesia or local anaesthesia with sedation. The electrode is then attached to a portable external SNS electrical device. Patients are usually discharged on the same day and closely followed up for the next few weeks when the frequency and intensity of the electrical stimulation can be adjusted accordingly. A frequency/volume chart before and after the procedure is mandatory and only those who have a 50% improvement in symptoms will be eligible to undergo the second stage, where the external device is replaced with a permanent internal one with a battery life of 5–10 years. The device is similar in size to a cardiac pacemaker but replacing the battery is usually a technically simpler procedure. Although relatively safe, there is always the risk of infection, bleeding, mechanical failure or loss of efficacy for many reasons, including the internal displacement of the electrode wire. Permanent nerve injury or solid organ injuries are extremely rare.

In a small three-year follow-up study of 41 patients with urinary urgency incontinence, 59\% of patients showed greater than 50\% reduction in leaking episodes per day, with 46\% of patients being completely dry following SNS device insertion. After two years, 56\% of patients with urgency-frequency showed a greater than 50\% reduction in voids per day.\(^{19}\)

**Posterior tibial nerve stimulation**

Posterior tibial nerve stimulation (PTNS) is a minimally invasive procedure in which a trained healthcare professional inserts a needle electrode percutaneously close to but separate to the posterior tibial nerve just above the ankle. A second surface electrode sticker is placed to the medial aspect of the ipsilateral calcaneus. Both electrodes are connected to a small electrical stimulator device. After electrode placement, each treatment session consists of 30 minutes of stimulation. The patient is required to attend once a week for 12 weeks and if the response is favourable, the patient will need maintenance treatment once a month thereafter.

A randomised, double-blind, sham-controlled study in 220 patients with OAB reported moderate or marked improvement in bladder symptoms in patients receiving PTNS compared with the sham group (54.5\% vs 20.9\%; \(p<0.001\)). In addition, PTNS

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**KEY POINTS**

- Overactive bladder (OAB) is a group of symptoms (symptom complex) characterised by urinary urgency with or without urgency urinary incontinence, usually associated with increased daytime frequency and nocturia.
- The underlying pathology that leads to OAB symptoms is not fully understood, but is likely to be multifactorial and in many cases is related to the ageing process.
- Although idiopathic OAB is not in itself life threatening, it is detrimental to quality of life, especially when urgency urinary incontinence is present (ie OAB wet).
- The physician’s initial aim is to exclude other pathologies that may also present with similar symptoms.
- An accurately completed frequency/volume chart for three consecutive days is an inexpensive and important investigation.
- Pharmacotherapy with anticholinergic medication is effective but compliance can be low due to potential anticholinergic side-effects such as dry mouth or constipation.
- Anticholinergic medications are contraindicated in patients with untreated narrow angle-glaucoma, untreated urinary retention or severe decreased gastrointestinal motility conditions (such as moderate/severe constipation).
- Mirabegron, a beta\(_2\) agonist, has similar efficacy to anticholinergic medications without their anticholinergic side-effects; caution is advised in patients with uncontrolled hypertension.
- Posterior tibial nerve stimulation has limited data on long-term efficacy and can be time consuming and costly when used percutaneously.
- Referral to a urologist should be considered (as per local guidelines) if there is failure to respond to pharmacotherapy so that patients may benefit from specialist evaluation and other treatment modalities such as intradetrusor botulinum toxin injection or sacral nerve stimulation.
overactive bladder: a randomised, multicentre phase 3 study (SYNERGY)
monotherapy: a randomised double-blind

References

Declaration of interests
Professor Chapple is an author for Allergan; consultant/advisor for Astellas Pharma, Bayer Schering Pharma AG, Ferring, Galvani Bioelectronics (GSK), Pierre Fabre, Symimetics, Taris Biomedical and Urovant Sciences; Researcher for Astellas Pharma and Ipsen; and a meeting speaker for Astellas Pharma and Pfizer.

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