What can be done for overactive bladder?

Overactive bladder, which is set to become more common as the population ages, can be a distressing and embarrassing condition with a significant impact on quality of life. But the symptoms and management are not always well understood and this can lead to inappropriate or misguided treatment. Mark Thomas and Alistair Rogers summarise the clinical aspects of the condition and its management options, with emphasis on current pharmacotherapy.

The term “overactive bladder” has previously been subject to much controversy. The definition devised by the International Continence Society (ICS) in 2001 describes the condition as a symptom or syndrome suggestive of lower urinary tract dysfunction and, more specifically, as “urgency, with or without urge incontinence, usually with frequency and nocturia”. Urgency describes the complaint of sudden compelling desire to void that is difficult to defer, and urge incontinence is the complaint of any involuntary leakage of urine immediately preceded or accompanied by urgency. (Overactive bladder can also be described as dry, where there is no associated incontinence, and wet, where urge incontinence is a symptom.) The ICS defines frequency as a subject’s perception of urinating too often during the day. A threshold of more than eight voids per day has also been used. Nocturia is accepted as being woken from sleep to pass urine at least once.

Panel 1 (p20) describes bladder anatomy and physiology.

Prevalence, causes and mechanisms

Due to different definitions of overactive bladder over the years, there is little and conflicting data on its prevalence. From recent studies, however, it appears that the overall prevalence is 17 per cent in Europe and 16 per cent in the US. Wet overactive bladder is more common in women than men (9 per cent compared with 3 per cent). Prevalence increases with age — 2 per cent of 18- to 24-year-old women admit to symptoms compared with 19 per cent of 65- to 74-year-olds.

Most cases of overactive bladder are probably due to detrusor muscle overactivity. This can be idiopathic but can also be secondary to conditions such as bladder stones, urinary tract infections and bladder tumours. Causes of symptoms are summarised in Panel 2 (p20) and several of these factors may contribute to poor bladder function in a patient.

Overactivity of the detrusor muscle results when a large proportion of bladder wall contracts outside of volitional control. A number of hypotheses have been suggested to explain idiopathic overactivity. Although detailed description of these is outside the remit of this article it appears that there is a combination of increased excitatory nerve impulses, decreased inhibitory impulses, supersensitivity, increased connectivity of detrusor muscle fibres and loss of cholinesterase (which breaks down acetylcholine). It has been noted that the nerves supplying the bladder in detrusor overactivity can undergo long-term changes. Some drugs can also cause symptoms of overactive bladder or worsen the condition. Examples are given in Panel 3 (p21).

Clinical presentation and symptoms

Overactive bladder can cause disruption to routines and psychological stress. For example, patients will often have to stop activities to pass urine and, in some cases, the condition stops people undertaking normal life activities, such as going to the shops. In cases where overactive bladder is associated with incontinence there is also a need to change underwear or to use incontinence pads. Quality of life instruments, such as the SF-36 health survey (36 questions designed to measure the relative burden of a medical condition and the benefits achieved by treatment), have been devised to assess the impact of the condition.

The natural progression of overactive bladder in an individual can vary and will depend on the underlying cause. In people with idiopathic overactive bladder symptoms can be transient, settling with conservative measures, or permanent, requiring lifelong management.
The physiology of the bladder is characterised by alternating states of filling (and storage) and voiding. Average bladder capacity is between 300 and 600 ml. The bladder wall is lined by transitional cell epithelium (urothelium). The main muscle of the bladder, the detrusor muscle, lies within the wall and comprises smooth muscle cells with interspersed interstitial cells and blood vessels. It is incorporated into the tissue forming the framework of the bladder (stroma), which is made up of collagen and elastin in a matrix.

The bladder is served by parasympathetic, sympathetic and somatic nerves. Excitation of parasympathetic nerves releases acetylcholine. This binds to muscarinic receptors on the surface of smooth muscle cells. Intracellular calcium is subsequently increased (via phospholipase-c) by the activation of cell surface calcium channels and the liberation of calcium from the sarcoplasmic reticulum in the cytoplasm, resulting in contraction.

Five muscarinic receptors have been identified (M1–5) with M2 and M3 predominating in the bladder. Although M2 receptors are more prolific, the M3 receptors are most important for smooth muscle contraction. The role of M2 receptors is still unclear. Aberrations in the normal physiology of the bladder can result in a variety of symptoms.

Beta adrenergic receptor stimulation via sympathetic nerves inhibit detrusor muscle contraction. During bladder filling, sympathetic stimulation is dominant. Parasympathetic stimulation causes bladder emptying. If the bladder has an internal sphincter, which extends into the bladder neck and is normally closed. Like the detrusor muscle, it is controlled by the autonomic nervous system. Stimulation of alpha adrenergic receptors in the bladder neck contributes to urinary continence. An external bladder sphincter is under voluntary control (receiving innervation from the pudendal nerve). During urination, both internal and external sphincters relax, allowing the passage of urine when the detrusor contracts.

In the assessment of patients with overactive bladder it is important that a clear history is taken to elucidate possible causes — details on systemic disease, caffeine and alcohol intake, current medicines, haematuria or urinary tract infections should be sought. The clinician should examine the patient to exclude a palpable bladder (suggestive of chronic retention), abdominal mass, previous operations, genital abnormality and neurological disorders.

Patients with overactive bladder and associated urge incontinence may also have an element of stress incontinence (involuntary loss of urine during physical activity, such as exercise, laughing or coughing) and the pelvic floor muscles should be assessed at examination. A midstream urine sample should be taken to exclude urinary infection. A three-day fluid voiding diary should be kept. This usually takes the form of a chart, which the patient uses to record the times and amounts of oral intake, voided volume, degree of urgency and urine leakage. Other investigations that should be considered, depending on the clinical presentation, include a urinary tract ultrasound, an X-ray of the abdomen (to look for renal stones) and a flexible cystoscopy. To date, the most definitive objective investigation for detailing detrusor overactivity in terms of bladder urodynamics is a cystometrogram (CMG). This entails placing a small catheter, which has a pressure transducer in it, in the bladder. A second pressure catheter is placed in the rectum to measure abdominal pressure. The bladder is filled and the detrusor pressure calculated by subtracting the abdominal pressure from the bladder pressure. Spikes in bladder pressure correspond to involuntary detrusor contractions.

However, diagnosis of overactive bladder is generally symptomatic.

Management
The assessment and management of overactive bladder requires a multidisciplinary approach and can include doctors (GPs, urologists and gynaecologists), continence nurse specialists, physiotherapists, pharmacists and other community healthcare workers.

Not all patients who present with overactive bladder symptoms need referral to secondary care and initial treatment can be started in the community. However it is important to recognise symptoms and signs that might suggest a more sinister underlying disease. For example, transitional cell carcinoma of the bladder can present with similar symptoms to overactive bladder and should be considered especially in the elderly, particularly smokers. Haematuria (on urinalysis) should be investigated appropriately.

Overactive bladder symptoms associated with severe pain may suggest another condition (e.g., painful bladder syndrome, renal colic) and should be investigated further. If symptoms are secondary to another condition, that condition must be treated.

Patients who have no concerning features and start treatment in the community should be referred to secondary care if they do not respond. A good algorithm available to guide initial management is available from the International Continence Society.

Conservative treatments
The National Institute for Health and Clinical Excellence recommends that simple measures are tried for three months before any pharmacological treatment. Reducing excessive fluid intake, especially caffeine or alcohol-containing drinks, can have a dramatic effect on symptoms and is sometimes all that is required. Reducing evening drinks will help with nocturia. Weight loss in those with a body mass index over 30 can also improve urinary symptoms.

Bladder training (or bladder drill), where progressive delay in responding to a desire to void and timed voiding (where patients train themselves to go to the toilet at certain times of day), can be useful in ‘re-educating’ the bladder.

Pelvic floor exercises (sometimes referred to as Kegel exercises) are designed to strengthen pelvic floor musculature and can have a role in improving urge as well as stress incontinence. During these exercises, the patient contracts the muscles that extend from...
Pads or collection devices, in the initial stages recommend containment products, such as education is important if they are to have any six to 12 months. 

Patients should remain on treatment for at least three to six months. NICE recommends that patients prescribed drug treatment for urinary incontinence in women,”6 and 97 an initial dose of 5mg daily, which may be titrated to a maximum of dose of 10mg daily.

• Antimuscarinic drugs used to treat overactive bladder act mainly at M2 and M3 muscarinic receptor subtypes, inhibiting involuntary contractions in the detrusor muscle and increasing bladder capacity. A therapeutic effect is normally observed within two to three weeks of starting treatment. Patients should remain on treatment for at least three to six months. NICE recommends that patients prescribed drug treatment for overactive bladder are reviewed every four to six weeks, in order to assess symptoms, gauge the effectiveness of the treatment and determine if they are experiencing any side effects. Following this initial assessment period, patients should then be reviewed every six to 12 months. 

In addition to NICE clinical guidelines 40 (“Urinary incontinence: the management of urinary incontinence in women”)* and 97 (“Urinary incontinence: the management of urinary incontinence in men”);7 a number of meta-analyses reviewing antimuscarinic drugs have been performed.8 Current evidence shows that there is little significant difference, in terms of efficacy, among these drugs so the major factors influencing treatment choice should be cost-effectiveness, drug tolerability, compliance and ease of dosing.

**Oxybutynin** Immediate release oxybutynin is a well established treatment option. The dose is 5mg twice or three times a day, increasing to a maximum of 5mg four times a day: This should be reduced in the elderly or if the patient develops side effects at the higher doses. 

Extended-release oxybutynin offers an alternative for patients who may be unable to tolerate the side effects associated with immediate release preparations — anecdotal evidence suggests this may offer an improved side effect profile but its place in therapy is not well established at present. Initially patients should be prescribed 5mg daily, increasing by 5mg each week up to a maximum daily dose of 20mg. However, this may not offer the most cost-effective treatment option. A patch that releases 3.9mg of oxybutynin over three to four days (Kerentina) is available. It should be applied to dry, intact skin on the abdomen, hip or buttock. Around 8 per cent of patients have to stop treatment as a result of localised skin reactions. This product can be regarded as a third- or fourth-line option in patients who benefit from oral oxybutynin but cannot tolerate the side effects or who would benefit from using a patch to aid compliance.

**Tolterodine** Tolterodine is a well established second-line treatment option. As stated in the NICE guidelines, there is insufficient evidence to recommend one second-line antimuscarinic as more clinically effective than another, but there is currently a good range of evidence and clinical experience to support use of tolterodine as a cost-effective alternative to oxybutynin. Instant release tolterodine appears to cause more dry mouth than the modified release formulation. The modified release capsule is the more cost-effective preparation. This also appears to have an improved side effect profile compared with instant release oxybutynin and has the additional benefit of not requiring any dose titration.

**Fesoterodine** Fesoterodine (Toviaz ▼) is a relatively new drug. It is a pro-drug that is hydrolysed, after oral administration, to the same active metabolite as tolterodine (5-hydroxyethyl tolterodine). Fesoterodine is prescribed at a starting dose of 4mg daily and may be titrated up to 8mg daily if required. In 2008, the Scottish Medicines Consortium approved restricted second-line use of fesoterodine within NHS Scotland. At the time of writing, there is no such recommendation from NICE in place.

**Antimuscarinic side effects** The main side effects of antimuscarinic drugs are dry mouth, dry eyes, blurred vision, constipation, oesophageal reflux, drowsiness, dizziness and palpitations. These result from action on muscarinic receptors located in parts of the body other than the bladder. For example, dry mouth occurs in 20 to 40 per cent of patients and is caused by antimuscarinic effects on M1 and M3 receptors in the salivary glands.

Although immediate-release oxybutynin is currently the most cost-effective drug treatment available, compliance often proves to be a problem given the high incidence of side effects (mainly dry mouth, dry eyes and a number of non-pharmacological interventions) 

**PANEL 3: DRUGS LINKED WITH SYMPTOMS**

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Increased production of urine</td>
</tr>
<tr>
<td>Alpha agonists</td>
<td>Can induce urinary retention, overflow incontinence and narrowing of urinary sphincter</td>
</tr>
<tr>
<td>Alpha-adrenergic antagonists, outflow</td>
<td>Can induce stress incontinence and relax bladder</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Cough can induce stress incontinence</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Can induce urinary retention and overflow incontinence</td>
</tr>
<tr>
<td>serotonin antagonists</td>
<td>Can induce urinary retention and overflow incontinence</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Can induce urinary retention and overflow incontinence</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Increased production of urine</td>
</tr>
<tr>
<td>Cholinesterase Inhibitors</td>
<td>Can increase bladder contraction</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Increased production of urine</td>
</tr>
<tr>
<td>Opioids</td>
<td>Can induce urinary retention and overflow incontinence</td>
</tr>
<tr>
<td>Sedatives and hypnotics</td>
<td>Can reduce awareness of need to urinate</td>
</tr>
</tbody>
</table>

**Antimuscarinic has M3 subtype receptor selectivity and, as a result, may be less likely to cause the antimuscarinic side effects observed in patients taking less selective oxybutynin preparations (see below). Solifenacin remains a useful second-line alternative to oxybutynin, and is prescribed at an initial dose of 5mg daily, which may be titrated to a maximum of dose of 10mg daily.**
Intravaginal oestrogen for overactive bladder
Advising patients on pharmacological
Propiverine for urinary frequency
Desmopressin if nocturia is troublesome
Prescribing within specialist urology

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constipation) and the three times a day dosing regimen. Up to 30 per cent of patients stop taking oxybutynin for these reasons. Pharmacists have a role in informing patients of potential side effects and advising how the impact of these may be minimised.

Dry mouth Persistant dry mouth can put patients at risk of oral infections and pharmacists can advise on simple measures that can reduce this side effect, such as taking small and frequent sips of cool water (noting cautions to maintain an appropriate fluid balance) and using sugar-free pastilles or sugar-free gum to stimulate residual saliva function. An artificial saliva product can be recommended or prescribed (but note that some are only prescribable on the NHS for dry mouth associated with radiotherapy or sicca syndrome).

Constitution Patients should be advised to maintain a balanced diet, high in fibre, ensuring an appropriate fluid intake within the recommendations of their urologist. If constipation becomes a problem, then pharmacists are well placed to recommend suitable laxative therapy. Given the mechanism of this side effect (the slowing of gut smooth muscle) a stimulant laxative may be preferable, if appropriate.

Dry eyes Artificial tears, in either an eye drop or gel formulation, used up to four times a day, are usually sufficient to treat dry eyes associated with antimuscarinic drugs.

Special considerations
In the case of symptoms of overactive bladder and associated conditions that are resistant to the standard therapies, consideration could be given to the following treatments, under specialist supervision:

• Intravaginal oestrogen for overactive bladder symptoms in postmenopausal women with vaginal atrophy. (Mucosal dryness and atrophy caused by the menopause can affect the urethra leading to urinary symptoms. It can also predispose to urinary tract infection which, in turn, can cause overactive symptoms.)

• Desmopressin if nocturia is troublesome (note that although this drug is licensed for nocturia, using it to treat overactive bladder is not in the UK product licence so any standard informed consent arrangements should be applied).

• Propiverine for urinary frequency

It should be noted that the NICE clinical guidelines state that some treatments that were previously advocated for overactive bladder should not be used. These include flavoxate, imipramine, propantheline, systemic hormone replacement therapy and complementary therapies.

Options for failed drug therapy
Currently there are three main therapies to consider for patients in whom drug therapy has failed: intravesical pharmacotherapy, neuromodulation and surgery.

PRACTICE POINTS
Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist’s CPD portfolio.
1 Ask about continence during medicines use reviews with patients on drugs in Panel 3.
2 Visit www.nhs.uk for further information on pelvic floor exercises. Practise explaining these and bladder training.
3 Make sure your staff know which incontinence pads or collection devices to recommend.

Consider making this activity one of your nine CPD entries this year.

Intravesical pharmacotherapy The past 10 years has seen the emergence of botulinum toxin A as an effective treatment for overactive bladder (unlicensed indication). Multiple aliquots are injected into the detrusor muscle, sparing the bladder trigone (where the ureters enter the bladder). Most urologists require detrusor overactivity to be confirmed on a cystometrogram before considering treatment. Success rates are as high as 80 per cent and the effects last for six to 12 months. Repeated treatments can be given but the long term effects of repeated botulinum toxin A injections are not yet known.

Neuromodulation Electrical stimulation of the bladder nerve supply can be used to suppress reflexes responsible for involuntary bladder muscle contraction and involves surgery to site a nerve stimulator. This treatment tends to be reserved for people who have not responded to intravesical botulinum toxin.

Surgery Surgical options tend to be reserved for highly refractory cases and include cystoplasty, where the bladder size is increased using bowel. Urinary diversion, such as an ileal conduit, can also be used and leaves the patient with a permanent stoma.

Summary Overactive bladder is common, has a varied degree of severity and a wide variety of possible underlying causes. Careful initial assessment is vital if the appropriate patient tailored management strategy is to be employed. In some patients behavioural (conservative) management is all that is required. For others, antimuscarinic drugs can bring marked relief. It is important that pharmacists are aware of the indications for starting medical therapy as well as the potential side effects, NICE guidelines governing appropriate regimens and the possible options for refractory disease. Future work will, no doubt, aim to produce antimuscarinics with greater specificity and longer action, as well as developing further transdermal preparations.

Pharmacists can play a useful role in the management of overactive bladder by:

• Giving lifestyle advice to patients
• Advising patients on pharmacological treatments options
• Advising patients how to deal with side effects from antimuscarinic therapy
• Identifying alarm symptoms for referral
• Promoting cost-effective prescribing
• Prescribing within specialist urology clinics

Further reading

References

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