An awfully overactive bladder

By Katie Hayes

Learning objectives

After reading this article you should be able to:
• Identify signs and symptoms of overactive bladder syndrome
• Describe the pharmacological and non-pharmacological treatment options available for overactive bladder syndrome
• Revise doses and identify potential adverse effects of treatments indicated for overactive bladder syndrome.

Case details

Mrs MH is a 54-year-old customer who lives with her daughter and grandson. She has a past medical history including:
• depression
• chronic pain
• migraine
• irritable bowel syndrome
• insomnia
• hypertension
• metabolic syndrome
• hypertriglyceridemia
• overactive (irritable) bladder syndrome
• bladder prolapse (mild)
• chronic cystitis
• osteoarthritis
• dermatitis
• BMI is approximately 30.

The referring GP specifically requested in the referral for a home medication review that a reduction in polypharmacy and minimisation of medication adverse effects was desirable.

Mrs MH’s current medications are:
• lercanidipine 10 mg daily
• fenofibrate 145 mg daily
• imipramine 25 mg – 2 tablets at night
• diazepam 5 mg daily when required
• paracetamol 665 mg – 2 tablets three times daily
• Panadeine Forte – 1 tablet twice daily
• oxycodone SR 20 mg – 1 tablet three times daily
• baclofen 10 mg – 1 tablet four times daily
• prazosin 1 mg – 1 tablet twice daily
• oxybutynin 5 mg – 1 tablet twice daily
• oestradiol cream 1 mg/g – 1 application twice weekly
• hexamine hippurate 1 g – 1 tablet twice daily
• Advantan fatty ointment 0.1% – applied at night when required
• zolpidem CR 12.5 mg at night.

Mrs MH says her quality of life is poor as she has a low mood and frequent tearfulness. She attributes her recent
weight loss (approximately three kilograms in four weeks) to a lack of appetite from her mood and her dry mouth. She does not leave the house often as she is restricted by urinary incontinence and pain which she attributes to osteoarthritis. She describes the pain as constant severe aching with frequent shooting and stabbing pain as well. Her bladder symptoms continue to be a problem and she had to toilet three times in the 90 minute HMR interview. She has urinary incontinence with symptoms of urgency, frequency and nocturia. She also experiences leakage on sneezing and coughing. She would like to exercise and walk her dog to lose more weight, but this has become difficult. Mrs MH currently has well-controlled blood pressure with the use of prazosin. When asked if this was the first antihypertensive she had tried, Mrs MH said some other medications had been tried but she could not tolerate them. Prazosin was prescribed because it may help with her urinary problems. Mrs MH is currently experiencing dry mouth, and she wondered if it could be medication-related.

### Bladder anatomy and function

Normal bladder functioning occurs through interaction between musculoskeletal, neurological and psychological functions. Normal bladder functioning consists of the filling (or storage) and emptying phases. To remain continent, coordination of relaxation of the detrusor muscles and contraction of bladder neck and pelvic floor muscles must occur. During storage, the bladder has low pressure while the urinary sphincter keeps the bladder closed by maintaining high resistance to urinary flow. Bladder filling is said to be passive as it depends on parasympathetic nerve inhibition as well as the properties of the bladder itself. The sympathetic nervous system is also involved in that it inhibits parasympathetic bladder contractions, relaxes and expands the detrusor muscle and constricts the internal urethral sphincter, closing the bladder neck. The pudendal nerve becomes excited during bladder filling which leads to contraction of the external sphincter and therefore assists in maintaining high enough pressure to resist urinary flow. Bladder emptying is voluntary or involuntary. When the bladder is full, afferent stimulation signals to the bladder to empty. The process involved is activation of stretch receptors in the bladder, signalling the sacral cord, which in turn causes the pudendal nerve to cause pelvic floor relaxation and signalling the external sphincter to open. The internal sphincter is also signalled to open by sympathetic innervation. The relaxation of these sphincters causes parasympathetic contraction of the detrusor resulting in appropriate conditions for urination. Control over voiding in a healthy person is controlled by the brain and when the individual decides to delay bladder emptying, inhibitory signals are sent to the pontine micturition centre which stop detrusor contractions and the individual may also contract muscles to keep the external sphincter closed. In infants, involuntary reflex voiding occurs and therefore as the volume of urine in the bladder exceeds the voiding threshold, urination occurs and the pontine micturition centre has no control over this. As the infant ages, the pontine micturition centre matures and control over voiding is gained.

There is a predominance of muscarinic M3 and M2 receptors in the bladder. The M3 receptor is inhibitory and the M2 receptor is excitatory. During the storage phase, it is assumed that there is ongoing release of acetylcholine where it causes initiation of the micturition reflex or enhances the myogenic contractive activity of the detrusor. The bladder also has alpha, and beta receptors. The alpha, receptors are more densely populated in the bladder neck, whereas the beta receptors more highly concentrated in the body of the bladder (trigone). During the storage phase, beta-receptors are responsible for relaxation of the detrusor and alpha receptors are stimulated which cause contraction of the bladder neck.

### Overactive bladder

Patients with overactive bladder (OAB) experience urinary urgency, generally have frequency (where the patient voids more than eight times in 24 hours) and nocturia, and may have urge incontinence without other pathological causes or infection. Around one third of patients with OAB have incontinence. Patients with OAB may also have a urinary tract infection, depression and social isolation.

Patients with OAB have detrusor overactivity where the detrusor muscle involuntarily contracts during the bladder filling stage, where it would ordinarily be relaxed. The exact mechanism behind these contractions is unknown but several theories have been proposed including; the myogenic theory and the neurogenic theory. The myogenic theory proposes that the increase in contractions is due to partial denervation of the detrusor muscle, leading to changes in the muscle cells causing excitation of the muscle and therefore an increase in pressure. In the neurogenic theory, primitive voiding reflexes occur (e.g. as in infants), due to damage to the central inhibitory pathways or sensitisation of peripheral afferent terminals within the bladder where impulses to the CNS are impaired. Acetylcholine binds to muscarinic receptors in normal voiding and it is likely to be increased in the abnormal contractions in OAB. The NOBLE Study reported the incidence of OAB to be 16.5% with 16.9% reported in women and 16.0% in men. The incidence of OAB increases with increasing age, with an incidence of 20% over 70 years of age and 30% at 75 years of age.
Several risk factors are associated with the development of overactive bladder (see Table 1).

Treatment should be initiated with lifestyle modification with or without drug treatment including diet and exercise, pelvic floor exercise and voiding regimens. Caffeine and alcohol should be removed from the diet. Restriction of fluid intake has not been assessed in randomised controlled trials so this may not be helpful, however, timing of fluid intake may be. For example, if a patient has nocturia, they should trial not drinking after 6 pm and voiding before going to bed. Patients with OAB can undergo bladder training, which assists in regaining bladder control by suppressing detrusor contractions through feedback inhibition. Patients initially void at one or two hour intervals and slowly increase the interval between voiding. For instance, a patient can be told to void every 60 minutes and then increase this interval by 15 minutes every week until a comfortable voiding interval has been established.

Pelvic floor exercises can assist in inhibiting contractions of the bladder. With pelvic floor exercises, the patient learns to tighten their pelvic floor when an involuntary contraction occurs and also when sitting up from lying down and standing up from sitting down, which is frequently when patients with OAB have involuntary contractions leading to urgency.

A combination of both behavioural treatment and drug treatment appears to be most effective, with one study showing women over 55 years of age who added drug therapy to behavioural treatment had a reduction in incontinence episodes of 58–89%. Those who added behavioural therapy to drug treatment were found to have a reduction in incontinence episodes of 73–84%.

Drug treatments for overactive bladder

Anticholinergics

Anticholinergic medications are the treatment of choice in overactive bladder syndrome as these are the receptors that initiate bladder contraction. These medications reduces frequency and incontinence, increase bladder capacity and improve volume voided per toilet visit. In clinical trials, these agents have been found to significantly decrease incontinence rates and reduce the number of voiding episodes in patients with OAB compared to placebo. The most common side-effect from antimuscarinic treatment is mild dry mouth. Patients may also experience blurred vision, constipation, fatigue and urinary retention.

Oxybutynin has a direct muscle-relaxant effect. Its benefit is likely to be in part due to the antispasmodic effects of the drug on the bladder wall. Subjective improvement in symptoms of OAB has been reported as 50–80%. It commonly causes dry mouth and this is the major reason patients discontinue its use. It may be more likely to cross the blood brain barrier than other anti-muscarinics for OAB and therefore cause more central nervous system (CNS) adverse effects such as drowsiness, confusion and memory impairment. The usual dosage range for oxybutynin is 2.5–5 mg two to three times daily up to a maximum of 20 mg daily. Elderly patients should be initiated at 2.5 mg at night and carefully increased if required. Oxybutynin has been found to improve volume voided at a dose of 15 mg daily (in divided doses) compared to tolterodine 4 mg daily.

Tolterodine reduces the number of urgency episodes in a day. It has decreased salivary gland activity compared to oxybutynin and therefore is less likely to cause dry mouth. This has been shown in a clinical trial where tolterodine 4 mg had a reduced rate of withdrawal compared to oxybutynin 7.5–10 mg daily. The recommended dose is 2 mg twice daily, decreased to 1 mg twice daily if adverse effects are not tolerable. Tolterodine is not PBS listed and the cost of this medication may be a barrier to its use for some patients.

Solifenacin is a newer anticholinergic drug used for the treatment of overactive bladder and urinary incontinence. It is a bladder selective muscarinic drug and therefore is less likely to cause dry mouth in patients. In trials, withdrawal rates for solifenacin were similar to placebo. It has been shown to reduce the number of urgency episodes per day. Solifenacin should be initiated at 5 mg daily and increased to 10 mg daily if required. A 10 mg daily dose was also found to provide better improvements in volume voided in a day than tolterodine 4 mg daily. This medication is not PBS-listed and price may have a bearing on choice of therapy.

Darifenacin is another of the newer anticholinergics which is a competitive antagonist at the muscarinic receptor and reduces contractions in the smooth muscle of the bladder. It should be initiated at a dose of 7.5 mg once daily and increased after a minimum of two weeks to 15 mg once daily if necessary. In studies reporting health-related quality of life, those patients administered darifenacin had statistically significant improvements compared to placebo. It also reduces the number of incontinence episodes in a week, the number of voiding episodes, and nocturnal awakenings. There are few comparative trials of darifenacin and other anticholinergic medications for OAB. A small study of 76 patients was conducted to compare the efficacy and tolerability of darifenacin compared to oxybutynin. Each patient received two weeks of each treatment with 10 day intervals between each. The treatments used were darifenacin 15 mg daily, darifenacin 30 mg daily, oxybutynin 5 mg three times daily and placebo. Compared with oxybutynin 5 mg three times daily, darifenacin 15 mg once daily was shown to have comparable efficacy and better tolerability in OAB. Symptom improvement with darifenacin was dose dependent, with the higher dose found to cause a significant reduction in micturition frequency, but this may be offset by the higher rate of adverse effects. Darifenacin is not PBS-listed.

Tricyclic antidepressants

Some tricyclic antidepressants (TCAs) can be used as second line agents in OAB due to properties that cause them to relax the dome of the bladder through an effect on beta3 receptors. Imipramine also decreases bladder contractility through its anticholinergic effects. The dosage of imipramine used in the treatment of OAB is 10–25 mg up to three times a day although, as the drug has a half-life of around 20 hours, three times daily dosing is likely to be unnecessary except in patients who experience intolerable adverse effects, e.g. drowsiness, from taking larger doses less frequently.
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Case discussion

Mrs MH has several intertwined conditions. The benefits of improving one of these conditions are likely to be beneficial to the other conditions. Mrs MH’s poor quality of life is particularly concerning. She is still in her 50s but is unable to leave the house for any extended period of time due to bladder problems and pain. Mrs MH is keen to lose weight and is aware of the benefits it can have for pain, depression and sleeping. She is using several medications to treat overactive bladder, bladder prolapse and chronic urinary tract infection, yet is still having severe OAB symptoms. Her bladder prolapse may be causing the symptoms of stress incontinence and complicating therapy.

Mrs MH’s depression is not well controlled. She has trialled many antidepressants in the past and ceased taking them due to lack of efficacy and/or adverse effects. She is currently taking imipramine which she tolerates reasonably well (the dry mouth she is experiencing may be in part due to this medication) but her dose may be insufficient for her depression.

Mrs MH feels that the incontinence and depression she is experiencing has more of an impact on her quality of life than pain does. She feels that if these were better controlled, than the pain would be even more tolerable.

Actions and recommendations

The addition of oxybutynin to Mrs MH’s medication regime three months ago has resulted in no reduction to her bladder symptoms, and she is experiencing dry mouth which causes her to drink more and exacerbate her overactive bladder syndrome. She had previously been resistant to increasing the dose of oxybutynin when consulting with her GP due to what she perceived as lack of efficacy and concerns about exacerbating her already dry mouth. The oxybutynin patch was considered as it has a lower incidence of dry mouth than the tablets.

However, this was not recommended due to the high rate (greater than 10%) of skin reactions at the application site. Given Mrs MH’s history of dermatitis, it was decided that other strategies were likely to be more suitable initially. Of potential benefit to Mrs MH may be cessation of prazosin, substitution of oxybutynin for a more selective anticholinergic agent such as solifenacin, and increasing imipramine dosage.

It was recommended that prazosin should be ceased. Prazosin may be worsening Mrs MH’s urinary incontinence as it blocks alpha receptors in the bladder neck, decreasing resistance to urinary flow.21 Many other antihypertensives are available. It is important to obtain a complete list of the antihypertensives previously tried and why they were not tolerated. An ACE inhibitor, such as perindopril erbumine 2 mg once daily, would be an appropriate option with titration to an appropriate response if it was not on the “not tolerated” list.

Referral back to the genitourinary surgeon was recommended as any medication changes were likely to provide only a small benefit to Mrs MH’s urinary symptoms. Referral to a continence clinic was also recommended as certain strategies and training may be beneficial, e.g. appropriate fluid intake, timed voiding, pelvic floor exercises.

If further medication was to be trialled for OAB, solifenacin should be initiated at a dose of 5 mg daily and increased to 10 mg daily. This is the dose range where most of the benefit has been achieved in trial situations,5 and solifenacin is less likely than oxybutynin to cause dry mouth.

As Mrs MH’s depression was not under control, there may be room to cautiously increase the dosage of imipramine (especially if oxybutynin is ceased), to assist in controlling depression symptoms. The dosage recommended for treatment of depression is 75–150 mg daily.19 She may benefit from having the daily dose divided and therefore it was recommended that she use 25 mg in the morning and 50 mg at night. The morning dose could be increased further to 50 mg if necessary for control of depression provided that adverse effects like dry mouth are not still apparent due to total anticholinergic load. Imipramine may also assist in controlling Mrs MH’s pain.

Outcomes

Both oxybutynin and prazosin were ceased by the doctor. Mrs MH no longer had a dry mouth and her urinary problems had a small but noticeable improvement. Mrs MH had an appointment to visit the surgeon to have the prolapse repaired.

The GP decided to monitor blood pressure for the time being and wait until other medications had stabilised to determine if introducing another antihypertensive was still required.

The GP also decided to increase Mrs MH’s imipramine dose to 50 mg twice daily and she found that her mood improved and she was now more able to cope with her pain.

She has been taking longer walks with her dog, bladder permitting. She has lost a small amount of weight and her appetite has returned to normal.

Summary

Overactive bladder affects a large proportion of the population with many not seeking help. Pharmacists are well placed to speak to patients about this and advise on treatment options available. There are many opportunities to do this, including counselling at the time of prescription collection, during a home medicine review interview, and using community pharmacy promotions to encourage potential sufferers to seek information relating to the disorder.

References

10. Wiedemann A, Schwantes PA. Antimuscarinic drugs for the treatment of overactive bladder: are they really better?
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1. Which of the following are ALL risk factors for overactive bladder syndrome?
   a) Parkinson’s disease, asthma, high caffeine intake.
   b) High alcohol intake, stroke, diarrhoea.
   c) Obesity, diabetes, oestrogen deficiency.
   d) Heart failure, younger age, constipation.

2. Which of the following is NOT a symptom of overactive bladder syndrome?
   a) Urgency.
   b) Frequency.
   c) Nocturia.
   d) Pain on micturition.

3. Which of the following is the BEST option for someone who has found behavioural strategies in the treatment of overactive bladder syndrome only of partial benefit?
   a) Wear an incontinence pad.
   b) Cease behavioural treatment and commence oxybutynin 2.5 mg three times daily.
   c) Commence oxybutynin 2.5 mg three times daily and continue with behavioural strategies.
   d) Restrict water intake.

4. Which of the following are ALL adverse effects associated with the use of the anticholinergic agents used in the treatment of overactive bladder syndrome?
   a) Dry mouth, blurred vision, fatigue.
   b) Constipation, ankle oedema, hair loss.
   c) Sweating, double vision, hyperthyroidism.
   d) Dry mouth, diarrhoea, blurred vision.

5. Solifenacin is a bladder-selective muscarinic agent and is therefore less likely than oxybutynin to cause dry mouth?
   a) True.
   b) True, only when solifenacin is taken at the 5 mg initiation dose.
   c) False.

Questions

A score of 4 out of 5 attracts 1 CPD credit.

eMMS. Prescribing Information: Digibind Monograph. St Leonards, NSW: MediMedia; 2011.
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4. Which of the following are ALL adverse effects associated with the use of the anticholinergic agents used in the treatment of overactive bladder syndrome?
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5. Solifenacin is a bladder-selective muscarinic agent and is therefore less likely than oxybutynin to cause dry mouth?
   a) True.
   b) True, only when solifenacin is taken at the 5 mg initiation dose.
   c) False.

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