MedicinesUpdateExtra

NHS Greater Glasgow and Clyde

MANAGEMENT OF URINARY INCONTINENCE AND OVERACTIVE BLADDER

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- Lifestyle interventions and non-pharmacological strategies should be tried as first-line treatment.
- If pharmacological therapy is indicated, antimuscarinics should be tried first line.
- Immediate release (IR) oxybutynin, IR and modified release (MR) tolterodine and solifenacin are on the Preferred List of the Formulary.
- IR oxybutynin and IR tolterodine are significantly less expensive than other preparations on the Formulary, however, they may have less tolerability.
- MR tolterodine has similar efficacy and tolerability to solifenacin but is significantly less expensive, therefore, consider prescribing MR tolterodine prior to solifenacin.
- Patients should be reviewed 4 weeks after starting each new therapy and after a dose change.
- Patients on long term therapy should be reviewed annually or every 6 months if over 75 years.

Introduction

Urinary incontinence (UI) is defined as involuntary leakage of urine.

- **Stress UI** is involuntary urine leakage on effort or exertion or on sneezing or coughing.
- **Urgency UI** is involuntary urine leakage accompanied or immediately preceded by urgency (a sudden compelling desire to urinate that is difficult to delay).
- **Mixed UI** is involuntary urine leakage associated with both urgency and exertion, effort, sneezing or coughing.

Overactive bladder (OAB) is defined as urgency that occurs with or without UI and usually with frequency and nocturia. OAB that occurs with incontinence is known as 'OAB wet'. OAB that occurs without incontinence is known as 'OAB dry'.

Urinary incontinence is a common symptom that can affect people of all ages, with a wide range of severity and nature. While rarely life-threatening, incontinence may seriously influence the physical, psychological and social wellbeing of affected individuals.[1]

It's not clear exactly how many people are affected, but it's estimated that between 3 and 6 million people in the UK may have some degree of urinary incontinence. Urinary incontinence affects both men and women, but it tends to be more common in women.[2]

Evidence

How is urinary incontinence or OAB managed?

Lifestyle interventions and non-pharmacological strategies should be tried as first-line treatment and continued alongside drug therapy. Patients should be referred to continence services where appropriate.

Lifestyle interventions include reducing caffeine intake, modifying fluid intake and encouraging weight loss if BMI > 30.[1] Medication review is also recommended to determine if the patient is on any medicines that may contribute to UI e.g diuretics.

Non-pharmacological strategies include supervised pelvic floor muscle (PFM) training of at least 3 months duration for stress or mixed UI. Bladder training should be offered for a minimum of 6 weeks for urgency or mixed UI.[1]

The mainstay of pharmacological therapy is controlling detrusor muscle over-activity by inhibiting muscarinic receptors on the bladder.[3] If pharmacological treatment is indicated, antimuscarinics should be tried first-line. Before prescribing antimuscarinic therapy, the risk of adverse effects and the patient's other co-morbidities and existing medication should be taken into consideration.

What are the common adverse effects of antimuscarinics?

Antimuscarinics are linked to impaired cognition and falls risk, and more recently have also been linked to increased morbidity and mortality. Antimuscarinics may also be a cause of constipation and urinary retention and adverse effects are dose dependent. In addition to antimuscarinic therapy, a wide range of commonly used medicines have antimuscarinic properties and their effects may accumulate. An

anticholinergic risk scale tool can guide clinical decision-making to limit antimuscarinic load. Refer to Scottish Government Polypharmacy Guidance for further information.[4]

Patients should be made aware of the likelihood of success of treatment and the common adverse effects associated with treatment. The lowest recommended dose should be prescribed first and patients should be aware that full benefit may not be apparent until treatment has been taken for four weeks.[1] If the first treatment for OAB or mixed UI is not effective (after appropriate titration) or is not well-tolerated, another drug from the Preferred List of the Formulary should be tried. Refer to *Place in Therapy* section for further information.[1]

Is there a difference in efficacy or tolerability between antimuscarinics available on the GGC Formulary?

A Cochrane review on the treatment of OAB symptoms reported similar efficacy with immediate release (IR) tolterodine and oxybutynin, however, tolterodine was associated with less withdrawals due to adverse events (RR 0.52; 95%CI 0.4-0.66) and less risk of dry mouth (RR 0.65; 95%CI 0.6-0.71). Modified release (MR) preparations of tolterodine and oxybutynin had similar efficacy, however, there was less risk of dry mouth with MR tolterodine than MR oxybutynin (RR 0.75; 95%CI 0.59-0.95). There was no difference in risk of dry mouth between transdermal oxybutynin and MR tolterodine.[5]

Compared to IR tolterodine, solifenacin significantly improved quality of life, patient reported cure or improvement (RR 1.25; 95%CI 1.13-1.39), leakage episodes and urgency episodes. There was no difference in withdrawals due to adverse events, however, solifenacin was associated with less dry mouth (RR 0.69; 95%CI 0.51-0.94).[5]

In the Cochrane review there were insufficient data from trials of other antimuscarinics to draw any conclusions.[5]

What is the evidence for solifenacin versus MR tolterodine?

MR tolterodine and solifenacin appear to have similar efficacy. The double blind STAR trial compared solifenacin 5 mg or 10 mg daily with MR tolterodine 4 mg daily. Solifenacin was shown to be non-inferior for the primary efficacy outcome of the change in baseline of the mean number of micturitions in 24 hours. Solifenacin treatment resulted in a mean baseline to endpoint reduction of 2.45 micturitions per 24 hours compared with a reduction of 2.24 episodes for tolterodine treatment (p=0.004 for non-inferiority). Adverse events were reported to be similar in both treatment groups.[6]

A subanalysis of the STAR trial looked at the comparison of solifenacin 5 mg daily and tolterodine MR 4 mg daily. At 4 weeks the results showed no significant difference in the primary variable of OAB symptoms including urgency and frequency with solifenacin.[7]

When should patients be reviewed?

Efficacy is generally modest in terms of clinical outcomes, therefore, patients should be reviewed regularly to determine continued benefit.[3]

Patients should be reviewed 4 weeks after the start of each new drug and after a dose change. If there is no or sub-optimal improvement or intolerable adverse effects, change the dose, or try an alternative drug from the Formulary and review again 4 weeks later.[1] Patients should be reviewed before 4 weeks if adverse effects are intolerable. Patients on long-term therapy should be reviewed annually (or every 6 months if over 75 years).[1]

What about mirabegron, what is the evidence for this and when can it be prescribed?

Mirabegron is the first in a new class of drug. It is a beta-3-adrenoceptor agonist and therefore has a different mode of action to the antimuscarinics. It works by increasing mean voided volume per micturition and decreasing the frequency of non-voiding contractions.[3]

The evidence to support the efficacy of mirabegron comes from the results of three, randomised, double-blind, placebo-controlled, phase III studies.[8] The three studies compared mirabegron at a range of doses with placebo. In the first study, patients were also randomised to receive tolterodine MR 4 mg daily as an active control, though the study was not powered to detect a difference between tolterodine and mirabegron. These 3 studies showed that mirabegron significantly reduced the number of micturition and incontinence episodes compared to placebo, however, the clinical benefit was deemed to be modest as it translates to one fewer incontinence episode and one fewer micturition every 2 days.[3]

The proportions of patients discontinuing study medication because of adverse events were similar across study groups.[8] The incidence of dry mouth was similar in patients treated with mirabegron and placebo but was higher in the tolterodine treated patients. This is considered a troublesome antimuscarinic adverse effect. However, it is unclear if this lower incidence in the mirabegron group would translate into fewer discontinuations or treatment switches in clinical practice.

The Summary of Product Characteristics (SPC) for mirabegron has recently been updated to reflect new contraindications in patients with hypertension

following an EU wide review.[9] Cases of severe hypertension have been reported, which include hypertensive crisis associated with reports of cerebrovascular and cardiac events (mainly transient ischaemia attack or stroke)—some with a clear temporal relation to mirabegron use.[10] Blood pressure should be measured before treatment is started and periodically during treatment especially in hypertensive patients. Mirabegron is now contraindicated in patients with severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg.[9,10] Report suspected adverse reactions via a Yellow Card.

Mirabegron is on the Total Formulary, therefore, Preferred List alternatives should be tried first.[11]

Can mirabegron be prescribed in combination with an antimuscarinic?

There is very limited evidence for the use of mirabegron in combination with an antimuscarinic. More evidence would be required to assess whether combination therapy is appropriate prior to prescribing.

At present, the limited published evidence includes a phase II randomised controlled trial (RCT) of 12 week duration which assessed mirabegron in combination with solifenacin compared to solifenacin alone. The authors concluded that combination therapy significantly improved mean volume voided per micturition compared with solifenacin 5 mg daily. The combination was reported to be well tolerated with no important additional safety findings.[12]

A number of phase III studies assessing the combination of mirabegron and solifenacin are ongoing.[13] Preliminary results, not yet published in full, of one Phase III RCT, the BESIDE trial, have been reported. The reported results show that there was a statistically significant decrease in the mean number of daily incontinence episodes with the combination of solifenacin 5mg and mirabegron 50mg daily (increased from mirabegron 25mg after 4 weeks) in comparison to solifenacin 5mg daily.[14]

Full details of this study and the results of the other phase III studies are awaited.

Are there any pharmacological treatments available for stress UI?

Duloxetine (Yentreve®) is a serotonin and noradrenaline reuptake inhibitor and is the only pharmacotherapy licensed for stress UI.[15]

As mentioned previously, PFM exercises are first line treatment for stress UI. Duloxetine should only be prescribed as a second-line treatment for stress UI in women who prefer pharmacological to surgical treatment or are not suitable for surgery. If duloxetine is prescribed, women should be informed about its adverse effects. Early side effects such as nausea are transient and are unlikely to worsen or persist.[1]

After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy.[16]

What is the evidence for duloxetine?

A systematic review of duloxetine in stress UI analysed 10 randomised controlled clinical trials (RCTs) in 5738 women with stress UI who were randomised to take duloxetine or placebo. Duloxetine was associated with a significant reduction in the main outcome of incontinence episode frequency (IEF) (52.5% vs 33.7%; RR = 1.56; 95%CI 1.46-1.66, p < 0.00001). Adverse events were more frequent in the duloxetine treated patients (62.7% vs 45.3%; RR = 1.37; 95%CI 2.83-6.18, p< 0.00001). The most common side effect was nausea and other side effects include constipation, dry mouth, fatigue, dizziness and insomnia. Across nine trials more patients withdrew from the duloxetine treatment group (17.3% vs 3%; RR = 5.75; 95%CI 4.58-7.21, p < 0.00001). Most of the trials were of short duration up to 12 weeks and therefore more data is required to determine the long-term efficacy and safety of duloxetine.[16]

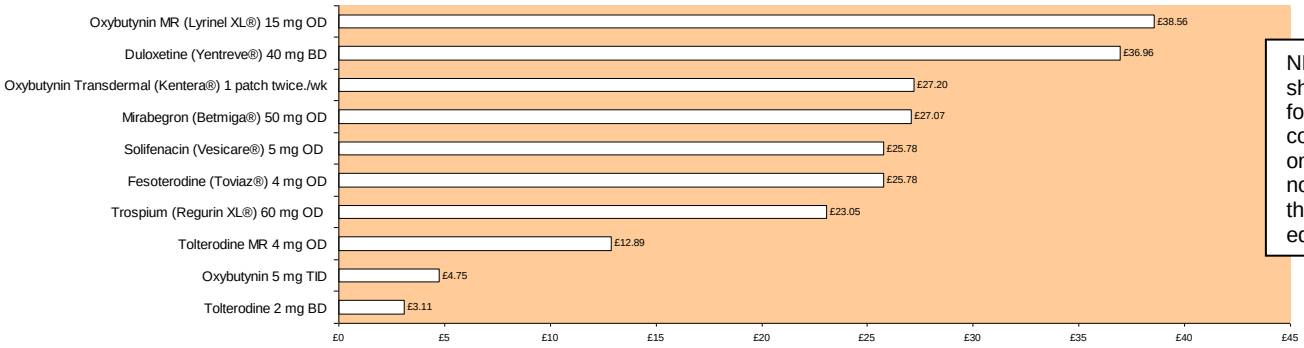
Place in Therapy

IR oxybutynin, solifenacin and tolterodine are all on the Preferred List of the Formulary. Total Formulary choices include oxybutynin MR and transdermal preparations, fesoterodine, trospium MR, mirabegron and duloxetine for stress UI. Botulinum toxin A is also on the Total Formulary restricted to specialist use for adults who have failed appropriate oral treatment options.[11] The use of botulinum is out with the scope of this bulletin.

If pharmacological therapy is indicated, how should I choose between the different treatments for OAB and urinary incontinence?

Preferred List choices should be tried first. IR oxybutynin and IR tolterodine are significantly less expensive than other preparations on the Formulary (see cost chart below), however, it is recognised that they may be less well tolerated. MR tolterodine has similar efficacy and tolerability to solifenacin but is significantly less expensive. Therefore, MR tolterodine should be considered before prescribing solifenacin.

Cost for 28 days treatment (Scottish Drug Tariff/eMIMS Oct 2015)



NB: Doses shown are for general comparison only and do not imply therapeutic equivalence.

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