NHS PrescQIPP

Drugs for urinary frequency, enuresis and incontinence

This bulletin focuses on drugs for urinary frequency, enuresis and incontinence. There are numerous preparations on the market that vary widely in acquisition costs. Solifenacin is the drug with highest spend in this therapeutic category. Nationally over £66 million is spent annually on solifenacin products (ePACT October - December 2013). Over £41 million is spent annually on the combined use of oxybutynin extended release ((ER) including modified release (MR) products), tolterodine ER, fesoterodine and trospium products.

QIPP projects in this area are aimed at either reviewing the continued need for antimuscarinics or switching to a less costly treatment where appropriate.

This bulletin provides the rationale for new patients (adult women and men) with overactive bladder (OAB) to be commenced on oxybutynin immediate release (IR) or tolterodine IR and for current patients to be considered for a switch to oxybutynin IR, tolterodine IR or tolterodine ER. It also reviews the place in therapy of antimuscarinics and offers guidance and support material for organisations considering reviewing antimuscarinic prescribing in OAB as a QIPP project.

This bulletin does not review the place of antimuscarinics for bladder dysfunction and urinary incontinence (UI) in children.

Support material is available on the PrescQIPP website, available at:
http://www.prescqipp.info/resources/viewcategory/224-urinary-incontinence

Recommendations

- Conservative management, with lifestyle advice and bladder training, should be the initial management option for OAB. Drug treatment should only be considered for OAB when the condition has not improved with conservative management alone.
- Women and men with stress incontinence should only be offered lifestyle advice or pelvic floor muscle training. If this fails, referral to a multidisciplinary team (MDT) for further treatment options including invasive treatment should be considered.
- Commence new patients on oxybutynin IR or tolterodine IR as first-line treatment options. Ensure that oxybutynin is not prescribed in frail elderly or neurogenic patients and that the lowest effective dose is initiated then dosage titrated upwards slowly. Take into account coexisting conditions, the use of other existing medication affecting the total anticholinergic load and the risk of adverse effects.
- It will be necessary for each CCG to gain local specialist opinion and consensus for second-line choices. Neditol XL®, a branded version of tolterodine ER, may be considered as an alternative option to tolterodine IR or oxybutynin IR if once-daily dosing is required as it has the lowest acquisition cost.

- Review all patients on oxybutynin ER, tolterodine ER, solifenacin, fesoterodine, trospium or propiverine for suitability for a switch to oxybutynin IR or tolterodine IR if these options have not previously been tried and are not contra-indicated. If a switch to IR oxybutynin or IR tolterodine is not suitable or appropriate, consider a switch to Neditol XL®, or other locally agreed second-line choice.
- Prescribers need to review therapy four weeks after the start of each OAB drug treatment (through a telephone review or face to face consultation). Ask if improvement is optimal then continue. If there is no improvement, or suboptimal improvement, or intolerable adverse effects, change the dose or offer another drug of low acquisition cost and review again in four weeks. Optimal improvement is subjective and the International Consultation on Incontinence Questionnaire (ICIQ) is one example of an incontinence specific quality of life measure used for the assessment of symptoms to evaluate therapy (Attachment 1).
- If the second drug offered fails, then referral to the MDT for other treatment options that include invasive therapy or treatment with mirabegron could be considered.
- Review patients who remain on long-term drug treatment for UI or OAB annually (or every six months if over 75 years).
- In men with lower urinary tract symptoms (LUTS), antimuscarinic therapy is also indicated for the more bothersome storage symptoms of frequency and urgency which may be the main presenting symptoms in some patients with LUTS or still a problem despite the use of alpha blockers. A review as above can be considered in male patients.

As with all switches, these should be tailored to the individual patient.

Background

Urinary incontinence (UI) is defined as '*the complaint of any involuntary urinary leakage*' and is a social or hygienic problem.[1] UI may occur as a result of a number of abnormalities of function of the lower urinary tract, or as a result of other illnesses, and these tend to cause leakage in different situations.

Overactive bladder[2] (OAB) is defined as urgency that occurs with or without urgency UI and usually with frequency (more than eight times per day) and nocturia (more than twice per night). These combinations of symptoms are suggestive of detrusor overactivity, but can be the result of other forms of urethrovesical dysfunction.

OAB affects about 12% of men and women.[3] More women than men exhibit incontinence and overall 33% have OAB with urgency incontinence (OAB wet) and 66% have OAB without urgency incontinence (OAB dry). In women, the prevalence of OAB ranges from 0.2% aged 15-64 years and 2.5% in those aged 65 years; it increases up to middle age, then plateaus or falls between 50 and 70 years. There is a steady prevalence with more advanced age.[2]

Stress incontinence is the complaint of involuntary leakage on effort or exertion or on sneezing or coughing.

Mixed UI is involuntary urine leakage associated with both urgency and exertion, effort, sneezing or coughing.

Antimuscarinic agents inhibit parasympathetic stimulation of the detrusor smooth muscles that are involved in bladder contraction through muscarinic receptors (of which the M3 subtype is predominantly involved). However, these drugs also inhibit muscarinic receptors in other parts of the body, which can lead to dose limiting adverse effects e.g. dry mouth (M1 and M3 subtype in salivary glands), constipation and blurred vision.

National guidance

The National Institute for Health and Care Excellence (NICE) clinical guidelines (CG) for UI in women[2, 4] and the management of LUTs in men[5] define the treatment pathways.

The guidelines recommend that patients with OAB are initially offered conservative treatment options:

- Lifestyle advice. A trial of caffeine reduction and modification of high or low fluid is recommended. Women with a BMI >30 are advised to lose weight.
- Bladder training for a minimum of 6 weeks.

Women with mixed UI should be offered:

- Lifestyle advice.
- Bladder training for a minimum of 6 weeks.
- Trial of supervised pelvic floor muscle training of at least three months as first-line treatment.

Women and men with stress UI should be offered:

- Lifestyle advice.
- Pelvic floor muscle training.

Drug treatment with antimuscarinic therapy should ONLY be considered for OAB (and mixed UI in women) when the condition has not improved with conservative management alone.[2]

- NICE CG 171[2] specifically recommends oxybutynin IR or tolterodine IR or once daily darifenacin (please see efficacy section below - price increase of darifenacin means it is no longer cost effective) as first-line treatment options. These allow factors such as coexisting conditions, frequency of doses and risk of adverse effects to be taken into account when choosing a drug treatment.
- If the first treatment for OAB or mixed UI is not effective or well tolerated, offer another drug with the lowest acquisition cost. Currently Neditol®XL (a branded tolterodine ER preparation) is the least costly option, although local procurement negotiations may also influence the choice of second-line agent.
- Women should be offered alternative treatments (including mirabegron[6]) through referral to MDT if they do not want to try another OAB drug. Mirabegron[6] is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects. Prescribing of mirabegron will be in line with locally agreed pathways.

Alpha blockers may be offered to men with bothersome moderate to severe LUTS. NICE[5] also recommends considering offering an antimuscarinic in addition to an alpha blocker to men who still have the bothersome storage symptoms (of frequency and urgency) after treatment with an alpha blocker.

In order to evaluate therapy, NICE recommends the use of incontinence specific, quality of life scales when therapies are being evaluated e.g. the International Consultation on Incontinence has developed a comprehensive questionnaire, the ICIQ[7] (Attachment 1).

Urinary symptoms can also arise due to neurological disease in the brain, the suprasacral spinal cord, the sacral spinal cord or the peripheral nervous system, e.g. as in dementia, Parkinson's disease, multiple sclerosis and peripheral neuropathy. NICE CG 148[8] recommends to offer antimuscarinic drugs to people with spinal cord disease (for example, spinal cord injury or multiple sclerosis) and symptoms of an overactive bladder such as increased frequency, urgency and incontinence. Recommendations are to consider antimuscarinic drug treatment in people with conditions affecting the brain (for example, cerebral palsy, head injury or stroke) and symptoms of an overactive bladder. Also when prescribing antimuscarinics, take into account that:

- Antimuscarinics known to cross the blood-brain barrier (for example, oxybutynin) have the potential to cause central nervous system-related side effects (such as confusion).

- Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections.
- Antimuscarinic treatment may precipitate or exacerbate constipation.

Efficacy

13 OAB drugs were reviewed in the NICE[2] CG: darifenacin, fesoterodine, oxybutynin IR, oxybutynin extended release ER, oxybutynin (transdermal), oxybutynin (topical gel), propiverine, propiverine ER, solifenacin, tolterodine IR, tolterodine ER, trospium and trospium ER.

NICE concluded[2,9] that there is a lack of evidence to show a difference in clinical effectiveness between OAB drugs; the relative cost effectiveness was determined mostly by the difference in cost. The guideline also states that the lack of evidence showing long term efficacy of OAB therapy should restrict the number of OAB drugs tried before seeking alternative recommended treatment. More expensive OAB drugs do not confer sufficient additional benefit to justify their higher cost. There is a lack of data about the efficacy of second-line drug treatment after the first drug has failed. Evidence also suggests high rates of discontinuation with all OAB drugs because of adverse effects and that there is a lack of data on long term efficacy.

The probability of any drug being cost effective at £20,000 per QALY was highest for oxybutynin IR and tolterodine IR. All other drugs had no more than a 5% chance of being cost effective at that threshold. This analysis also took account of the higher discontinuation rate of oxybutynin compared with other OAB drugs.

It should be noted that although darifenacin remained the most cost-effective once-daily alternative drug treatment option, since publication of the guidelines the price has increased and this is no longer the case.

Safety

Anticholinergic side effects include palpitations, memory impairment, delirium, constipation, sedation, increased number of falls (due to hypotension), dry mouth, dry lips, dry eyes and urinary retention. The elderly are more sensitive to anticholinergic side effects, and people with dementia have a high risk of adverse cognitive and psychiatric effects from these drugs. It is reported that up to 23% of patients are likely to discontinue oxybutynin tablets because of intolerable adverse effects, such as dry mouth.[10]

A Cochrane review[11] summarised that IR tolterodine caused less of a dry mouth than IR oxybutynin and also that ER preparations of oxybutynin and tolterodine may be preferred to IR oxybutynin and tolterodine as these can also cause less of a risk of dry mouth. Solifenacin might be preferred for better efficacy and less risk of dry mouth against tolterodine IR. Fesoterodine might be preferred to tolterodine ER for superior efficacy but has a higher risk of withdrawal due to adverse events and higher risk of dry mouth. However, the review also stated that there was little or no evidence available about quality of life, costs, or long-term outcomes in these studies. There were insufficient data from trials of other anticholinergic drugs to draw any conclusions.

NICE stated: *"The network analysis outputs for discontinuation rates were more conclusive. It showed that oxybutynin (IR), propiverine (IR) and fesoterodine all had clinically significantly higher discontinuation rates than other OAB drugs"*[2]

Prescribers need to take account of the following before offering drugs to treat OAB:

Woman's coexisting conditions

- For example, poor bladder emptying. Antimuscarinics are also contraindicated in myasthenia gravis, narrow-angle glaucoma or shallow anterior chamber and conditions with gastrointestinal obstruction.

- Any history of QT prolongation, risk of torsades de pointes (TdP) or risk of TdP under certain conditions such as overdose, drug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome). Drug interactions of antimuscarinics[12] include:
  - Class IA and III antiarrhythmics (e.g. amiodarone, dronedarone, quinidine)
  - Antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol)
  - Tricyclic antidepressants
  - Citalopram, escitalopram
  - Some antimicrobial agents (e.g. erythromycin, pentamidine)
  - Chloroquine
  - Antihistamines (e.g. astemizole, mizolastine)
  - Antiretrovirals (e.g. ritonavir, saquinavir, lopinavir).

Use of other existing medication affecting the total anticholinergic load

- There is increasing awareness and concern regarding the accumulation of anticholinergic "burden" (ACB) or "load" associated with antimuscarinic agents as a result of taking multiple medications, leading to increased adverse events, especially in the elderly.[13,14] Drugs with established and clinically relevant cognitive anticholinergic effects are considered to be definite anticholinergics and have an ACB score of 2 or 3[15] (see Attachment 7 data collection worksheet). Patients with an ACB score greater than 3 have a high risk of mortality. For each point increase in total ACB score, a 0.33-point decline in Mini-Mental State Examination over 2 years has been suggested.[16] Furthermore, each additional point in total ACB score has been correlated with a 26% increase in the risk of death in a recently published study.[16] NICE[2] recommends that oxybutynin should not be offered to frail elderly due to the risk of impairment of daily functioning (which is common), chronic confusion and in rare cases acute delirium. Frailty is defined as older patients with multiple co-morbidities, functional impairments such as walking or dressing difficulties, and any degree of cognitive impairment. Patients at high risk of anticholinergic load should be prescribed OAB drugs with caution and should only be prescribed these drugs after a full medication review.

Risk of adverse effects (as above)

- There is a greater chance that patients will continue treatment, tolerate mild side effects and/or accept second-line drug treatment, if they receive information about adverse effects and the time taken to see full benefits to develop. Offer patients a patient information leaflet (PIL), or direct them to NHS Choices or patient.co.uk. A summarised PIL is provided in Attachment 2.
- NICE also recommends to discuss the frequency and route of administration, that some adverse effects such as dry mouth and constipation may indicate that the treatment is starting to have an effect, and that they may not see the full benefit until they have been taking the treatment for four weeks.
- Antimuscarinics should be used with caution in patients with bladder outflow obstruction, e.g. benign prostatic hyperpasia (BPH) in men as antimuscarinic drugs may aggravate bladder outflow and cause retention. In BPH in men, it is important to address and treat the predominant symptoms, i.e. voiding or storage symptoms, according to NICE guidelines.[5]

Table 1 on the following page summarises cautions, contra-indications and drug interactions.

Table 1: Summary of cautions, contra-indications and drug interactions of oral anti-muscarinics

Drug	Recommended dosage	Renal impairment	Hepatic impairment	Interaction with potent inhibitors of cytochrome P450, e.g. ketoconazole, itraconazole, HIV protease inhibitors	ACB score[15]	Prolongation of QT interval[12]
Oxybutynin IR[17]	Elderly - 2.5mg twice daily, up to 5mg twice daily. Adults -5mg three times daily, up to four times daily.	Use with caution	Use with caution	No interaction documented	3	Not documented
Oxybutynin ER[18]	5-10mg daily (max 20mg)	Use with caution	Use with caution	Use with caution	3	Not documented
Tolterodine IR[19]	1-2 mg twice daily	1mg twice daily if eGFR <30ml/min	1mg twice daily	Not recommended	3	Yes
Tolterodine ER[20]	2-4mg daily	2mg daily if eGFR <30ml/min	2mg daily	Not recommended	3	Yes
Solifenacin[21]	5-10mg daily	5mg if eGFR <30ml/min	Moderate – use with caution –max 5mg daily	Max 5mg daily	3	Yes

Drug	Recommended dosage	Renal impairment	Hepatic impairment	Interaction with potent inhibitors of cytochrome P450, e.g. ketoconazole, itraconazole, HIV protease inhibitors	ACB score[15]	Prolongation of QT interval[12]
Fesoterodine[22]	4-8mg daily	4mg daily if eGFR <30ml/min	Moderate - 4mg daily	Max 4mg (avoid in all renal and hepatic impairment)	3	SPC[22] states to use with caution
Trospium[23]	20mg twice daily	20mg daily or every 2nd day if eGFR <30ml/min	Mild to moderate – use with caution Severe - Not recommended	No interactions reported	3	Clinical relevance of increased QT interval not established in SPC[23]
Trospium ER[24]	60mg daily	Not recommended	Mild to moderate – use with caution. Severe – do not. use	Not documented	3	Clinical relevance of increased QT interval not established in SPC[24]
Darifenacin[25]	7.5mg-15mg daily	No dosage adjustment. Use with caution	Mild - no dosage adjustment Moderate – 7.5mg max, only use if benefits outweigh risks Severe – contra-indicated	Contra-indicated	3	No
Propiverine[26]	15mg twice daily to four times daily	Severe – 30mg	Severe – no data	Pharmacokinetic interactions have not been performed	3	No

Further comments

- The SPC for solifenacin[21] recommends a 7 day interval between stopping solifenacin and starting another antimuscarinic.
- Trospium is hydrophilic and does not cross the normal blood-brain barrier in significant amounts and, therefore, has minimal central anticholinergic activity.[27]

There is a significant difference in costs between the antimuscarinic drugs. Table 2 below illustrates the cost differences.

Table 2: Antimuscarinic product and price comparison – Drug Tariff January 2014[28], MIMS January 2014[29]

Product	Cost per 28 days
Oxybutynin 2.5mg twice daily to 5mg four times daily	£1.97 - £6.34
Tolterodine 1mg -2mg twice daily	£2.94 - £3.07
Neditol® XL 2mg- 4mg daily	£11.60 - £12.89
Oxybutynin ER 5mg – 10mg daily	£12.85 - £25.70
Trospium ER 60mg daily	£23.05
Trospium 20mg twice daily	£23.93
Darifenacin 7.5mg – 15mg daily	£25.48
Tolterodine ER 4mg daily	£25.78
Fesoterodine 4mg-8mg daily	£25.78
Solifenacin 5mg-10mg daily	£25.78 - £33.52

Switching options and savings available

There are several potential switch/review options for antimuscarinic products (although clinicians may choose other options according to the clinical need of the patient). These include:

1. Discontinue therapy

Review the patient and if there is no, or suboptimal improvement, discontinue therapy. Take into account if the patient is elderly and frail, has multiple co-morbidities affecting treatment and their anticholinergic load. In care homes, evaluate if there has been a reduction in incontinence pads used or if a catheter is being used. An example of a questionnaire to assess improvement of symptoms and quality of life (QOL) is available as Attachment 1.

2. Oxybutynin ER

For patients that have not previously tried oxybutynin IR, switching all patients to oxybutynin IR at the equivalent twice daily dose **could save £16,000 per year per 100,000 patients nationally.**

Total annual savings are approximately £9 million nationally.

If once daily dosing is still needed, then switching to Neditol® XL **could save £4,500 per year per 100,000 patients nationally.**

Total annual savings are approximately £2.5 million nationally.

3. Tolterodine ER, fesoterodine, trospium, propiverine

For patients that have not previously tried tolterodine IR, switching all patients to tolterodine IR twice daily (at an equivalent dose) **could save £45,000 per year per 100,000 patients nationally.**

Total annual savings are approximately £25.3 million nationally.

If once daily dosing is still preferred, then switching to once daily Neditol® XL **could save £20,800 per year per 100,000 patients nationally.**

Total annual savings are approximately £11.8 million nationally.

NB. Propiverine was excluded from the data pack as usage was low compared to the other drugs, however it would still be appropriate to consider a switch as detailed above.

A brand (Detrusitol®) to generic (tolterodine) switch **could result in annualised savings of £470,000.**

4. Solifenacin

For patients that have not previously tried oxybutynin IR or tolterodine IR, switching all patients to oxybutynin IR twice daily or tolterodine IR **could save approximately £104,000 per year per 100,000 nationally.**

Total annual savings are approximately £58 million nationally.

If once daily dosing is preferred or a switch to oxybutynin IR or tolterodine IR is not considered appropriate, a switch to Neditol XL® **could save £60,000 per 100,000 patients nationally.**

Total annual savings are approximately £33.9 million nationally.

NB. The lowest recommended dose should be prescribed when starting a new OAB drug.

As a general guide:

- Oxybutynin ER 5mg could be switched to oxybutynin 2.5mg twice daily or Neditol XL® 2mg
- Oxybutynin ER 10mg could be switched to oxybutynin 5mg twice daily or Neditol XL® 4mg
- Tolterodine ER 2mg could be switched to tolterodine 1mg twice daily or Neditol XL® 2mg
- Tolterodine ER 4mg could be switched to tolterodine 2mg twice daily or Neditol XL® 4mg.

The savings above illustrate the maximum savings available. In reality the total amount would not be achieved and may be somewhere between the highest and lowest levels shown as different options would be suitable for different patients. The data pack shows prescribing data at CCG level and annual savings available for each CCG for the above switches.

Summary

- **There is no strong evidence to suggest that solifenacin, fesoterodine, trospium or oxybutynin ER have advantages in efficacy and tolerability over oxybutynin IR or tolterodine IR, however they are significantly more costly. Switching treatment to oxybutynin IR or tolterodine IR can lead to significant savings. If oxybutynin IR or tolterodine IR is unsuitable for the patient then switching treatment to Neditol® XL (a branded tolterodine ER) or other locally agreed second-line option will also provide savings.**
- **Patients on long term UI therapy should be reviewed regularly to assess whether there is a continued need for treatment.**

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Additional PrescQIPP resources

 Briefing

 Data pack

 Audit, patient letters, patient fact sheet, ICIS questionnaire

Available for download here:
http://www.prescqipp.info/resources/viewcategory/224-urinary-incontinence

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