NHS
South West London
Clinical Commissioning Group

Primary Care management of Overactive Bladder (OAB)

Introduction

Overactive bladder syndrome (OAB) is defined as urgency that occurs with or without urgency urinary incontinence and usually with frequency and nocturia. 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 & women, most cases have no specific cause and can have a significant impact on quality of life.

This document aims to provide advice on the management of adult men and women with OAB in primary care.

Guidance

NICE recommends that people with OAB should be initially offered conservative (non-pharmacological) treatment options prior to commencement of medication.

Conservative treatment options include:

- Lifestyle interventions
  - A trial of caffeine reduction
  - Modification of high or low fluid intake
  - Women with BMI >30 are advised to lose weight
    And
  - Bladder training for a minimum of 6 weeks

Drug treatment with antimuscarinic therapy should **only** be considered for OAB when the condition has not improved after 6 weeks of conservative management alone.

- All medicines for OAB have similar dose-related efficacy. The more expensive drugs were <u>not</u> found to confer sufficient additional benefit to justify their higher costs. More than one agent may need to be tried, due to different side effect profiles – and a trial of at least 4 weeks is suggested. (NICE CG171, 2013/ NICE NG123, 2019)

- Before commencing OAB drug treatment discuss:
  - The likelihood of success and associated common adverse effects and
  - The frequency and route of administration and
  - That some adverse effects such as dry mouth and constipation may indicate that treatment is starting to have an effect and that the patient may not see the full benefit until they have been taking the treatment for 4 weeks.
  - The long-term effects of anticholinergic medicines on cognitive function are uncertain.

- Take into consideration the 'Anticholinergic burden/load' patient may have due to other medications. This is to reduce CNS & Gastro-intestinal side effects.

- Every effort should be made to employ non-pharmacological treatment first before starting pharmacological treatments. Use antimuscarinic drugs with caution in elderly patients who are at risk of or have cognitive dysfunction.

- NICE recommends the most cost-effective agent is used. The choice of 1st, 2nd & 3rd line treatment options in this SW London OAB guidance have been chosen based upon evidence of efficacy, adverse effect profile, tolerability (including low AEC score) as well as cost effectiveness.

Developed by the SWL Urogynaecology Network Working Group & Rajiv Dhir, Lead Pharmacist - SWL CCG
Date approved: March 2021 (SWL MOG)
Review date: March 2023 or sooner if evidence/practice changes

- Do not offer oxybutynin immediate release to frail older patients who may be at higher risk of a sudden deterioration in their physical or mental health (NICE NG123; CKS LUTS in men).

- Prescribers need to review therapy four weeks after the start of each OAB drug (through a telephone review or face to face consultation). If there is no improvement, or suboptimal improvement, or intolerable adverse effects, change the dose or offer another drug of low acquisition cost as per the guidance and review again in four weeks. The international Consultation on Incontinence Questionanaire (ICIQ) is an example of an incontinence specific quality of life measure that can be used when evaluating treatment.

- If the first medicine is not effective or tolerated, offer second line medication titrating up to maximum dose after six weeks. e.g. consider trospium immediate release in elderly patients for its reduced CNS side effects or solifenacin as it is a once daily preparation to aid compliance.

- When similar dosage forms of OAB drugs are compared (Immediate Release) IR to IR; (Extended Release) ER to ER, the side effect profiles are similar. The IR formulations are generally associated with more anti-cholinergic side effects than the ER formulations which may improve compliance but are generally more expensive.

- If patient has unmanageable side-effects or there is lack of efficacy with first/ second line agents, consider mirabegron MR if there are no contraindications.

- Mirabegron (a beta-3-receptor agonist) is recommended as an option for treating the symptoms of OAB only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or who have unacceptable side effects. NICE TA290 (June 2013). MHRA, Oct 2015 issued a safety warning stating mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg, or both). Blood pressure should be measured before starting treatment and monitored regularly during treatment, especially in patients with hypertension. It should be used with caution in people with a history of QT interval prolongation or with bladder outlet obstruction.

- Currently there is very limited evidence for the use of mirabegron in combination with an antimuscarinic. More evidence would be required to assess whether combination is appropriate. However, this may be an option after specialist recommendation.

- Offer a review in primary care to people who remain on long-term drug treatment every 12 months, or every six months if they are over 75 years.

- In men with lower urinary tract symptoms (LUTS), antimuscarinic therapy is also indicated where storage symptoms persist despite use of an alpha blocker. Review at 4-6 weeks and then every 6-12 months.

- Patients not responding to medical treatment (refractory OAB) should be referred to Urology/urogynaecology department for further investigations and management.

Before starting OAB drugs

When offering anticholinergic drugs to treat OAB, take into account:

- Coexisting conditions (such as poor bladder emptying, cognitive impairment or dementia, BPH, constipation, glaucoma)
- Contraindications to antimuscarinics include myasthenia gravis, urinary retention, severe ulcerative colitis, intestinal atony and paralytic ileus
- Cautions include susceptibility to angle-closure glaucoma, hypertension, arrhythmias and cardiovascular disease.
- Anticholinergic burden- use of other existing medications affecting the total antimuscarinic load (see section on **Total anticholinergic drugs** – page 4 and https://www.medichec.com/)

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- Risk of adverse effects, including cognitive impairment

Discuss with the patient:

- The likelihood of success and associated common adverse effects (these include dry mouth, constipation, vision disorders, drowsiness, dizziness, urinary retention, palpitations, tachycardia, nausea & skin reactions) and
- The frequency and route of administration and
- That some adverse effects such as dry mouth and constipation may indicate that treatment is starting to have an effect and that they may not see the full benefits until they have been taking the treatment for 4 weeks.
- The long-term effects of anticholinergic medicines on cognitive function are uncertain.

Prescribe the **lowest** recommended dose when starting a new OAB drug to reduce the likelihood of side-effects.

Prescribing in elderly people/ people diagnosed with dementia or people with multimorbidity

Prescribe anticholinergic drugs with caution in older people or people with frailty or multimorbidity's as they are more likely to experience adverse effects such as constipation, urinary retention, dry mouth, dry eyes, sedation, confusion, delirium, photophobia and falls.
Antimuscarinic drugs may affect cognitive function (reduced cognition) in elderly people and those with dementia, hence when prescribing this group of drugs in elderly patients the following should be considered:

- In older people being treated for urinary incontinence, every effort should be made to employ non-pharmacological treatments first.
- Use antimuscarinic drugs with caution in elderly patients who are at risk of, or have, cognitive dysfunction.
- In older people who are being prescribed antimuscarinic drugs for control of urinary incontinence, consider the anticholinergic burden including other existing medications. Modifications to medications to help reduce CNS or GI adverse effects may be considered.
- Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction. Review medication to identify and minimise use of drugs that adversely affect cognitive function. Avoid prescribing anticholinergics with acetylcholinesterase inhibitors and in those patients with dementia.
- Antimuscarinics known to cross the blood-brain barrier (e.g. oxybutynin) have the potential to cause CNS related side-effects (such as confusion). The evidence reviewed by NICE was not sufficient to recommend one treatment over another. However, it was noted that oxybutynin in particular is believed to be a drug that has the potential to impact on cognition.

Total Anticholinergic load

There is increasing awareness and concern regarding the accumulation of anticholinergic 'burden' or 'load' associated with antimuscarinic agents. Combining medicines with anticholinergic activity might have cumulative harmful effects when given to a person with more than one clinical condition, especially in older people.

Anticholinergics have long been linked to impaired cognition and falls risk, but (more recently) they have also been linked to increase mortality in older patients.

Various anticholinergic burden or risk scales have been devised to aid medication reviews so that certain drugs can either be stopped, or the medication regimen altered to reduce this burden. However, there is no single standard anticholinergic burden scale to aid medication reviews, one example is the

Anticholinergic Cognitive Burden (ACB) Scale, which scores drugs with anticholinergic effects on a 4-point scale (0-3):

- 0 – no anticholinergic activity scored
- 1 – low activity score
- 2 – moderate activity
- 3 – high activity

Anticholinergic drugs have a cumulative effect on cognition. The Anticholinergic Effect on Cognition (AEC) scale has been developed by the South London and Maudsley NHS Foundation Trust. This scale aims to help clinicians, (see link/or refer to App from Medichec). The Anticholinergic Effect on cognition (AEC) Tool - https://www.medichec.com/) can be used to identify which drugs have an anticholinergic effect on cognition and defines the extent of this effect. The AEC scale takes into account the anticholinergic effect of a drug, the extent of this effect, whether it is able to penetrate the brain or not and whether there are in fact reports of cognitive impairment with the drug to support the score given.

The individual AEC Scores of drugs are recommended to be added together for each patient to calculate the total AEC score. Consider carrying out a medication review for all patients with a total AEC score of 3 or above to see whether the total score can be reduced to the minimum possible e.g. discontinuing a medicine if there is no absolute need, or where appropriate, to switch to a medicine with a lower ACB score.

Highly anticholinergic medicines include tricyclic antidepressants, urinary antispasmodics such as oxybutynin and 1st generation antihistamines such as chlorphenamine; these should be avoided if possible. There may be less awareness of those drugs with a low anticholinergic burden, such as opioids, loratadine, cetirizine, ranitidine and loperamide for example, the effects of which may be additive.

Anticholinergics are commonly associated with adverse effects if discontinued suddenly and may require slow withdrawal. Withdrawal symptoms may include anxiety, nausea, vomiting, headache and dizziness.

How to use the scale:

• Allocate a score to each of the patient's medicines using the AEC scale

• Add the scores for the patient's medicines to get a total score for that patient

• It is recommended that:
  - Any individual medicines with a score of 2 or 3, especially in older people with cognitive impairment, dementia or delirium should be reviewed.
  - Patients with a total AEC score of 3 or above should be reviewed.

• Look at ways to reduce this score (if possible) by:
  - Withdrawing a medicine for which there is no current indication/need or considering a treatment break if appropriate.
  - Swapping to another agent with a lower AEC score (being mindful of interactions, formulary choices, evidence, pharmacokinetics etc.)

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Pharmacological treatment of Overactive Bladder (OAB)

Initial assessment:

Try to identify relevant predisposing and precipitating factors and any other diagnosis. Initiate use of a bladder diary.

Conservative management:

- Lifestyle advice: modify fluid intake (1 to 1.5 litres/24 hours), lose weight if body mass index (BMI >30), reduce caffeine and alcohol intake.
- Treat chronic cough/constipation.
- Bladder training for at least SIX weeks.
- Pelvic floor muscle training for at least THREE months.

Review after 6 weeks. If suboptimal/no improvement, consider pharmacological treatment.

Before starting a medicine to treat OAB

Take account of and reduce risk of anticholinergic effects on cognition (AEC)

- See **table 1** - page 6 for AEC scores of OAB medicines taken from www.medichec.com.
- Check AEC load of other medicines that the patient is taking.
- Consider co-existing conditions (dementia, cognitive impairment, poor bladder emptying).
- Consider risk of anticholinergic effects in elderly patients who are more likely to experience constipation, urinary retention, dry mouth, blurred vision, glaucoma, sedation and falls.

Before commencement of treatment, review current medication for drugs which can contribute to development of OAB e.g. diuretics, antidepressants, calcium channel blockers, typical antispyschotics (chlorpromazine etc.), ACE inhibitors, ARBs, hydroxychloroquine, benzodiazepines.

Counsel patients (NICE NG123):

- The likelihood of the medicine being successful.
- The common adverse effects (constipation, dry mouth, blurred vision, glaucoma).
- Some adverse effects of anticholinergic medicines such as dry mouth and constipation may indicate that the medicine is starting to have an effect.
- Substantial benefits may not be seen for at least 4 weeks. Symptoms may continue to improve over time.
- Long term effects of anticholinergic medicines for OAB on cognitive function are uncertain.

1st line

Solifenacin 5 to 10 mg daily OR
Trospium Immediate Release (IR) 20 mg twice daily
Trospium has no CYP450 3A4 drug interactions unlike other OAB medicines- **see table 2**

2nd line

Consider the **other 1st line option** not tried (for most patients both drugs should be trialled before moving to a 3rd line option). If this is not appropriate, consider other OAB drugs or alternatively consider 3rd line option.

3rd line

Mirabegron MR 50 mg daily (NICE TA 290)
25 mg daily in moderate renal or hepatic impairment
Contraindicated in severe uncontrolled hypertension (systolic blood pressure (BP) ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg). Check BP before starting treatment and regularly during treatment - MHRA guidance.

REVIEW after 4 to 8 weeks' treatment.

If effective and tolerated, continue treatment.

INEFFECTIVE or NOT TOLERATED - STOP and REFER to secondary care specialist.

REVIEW at 6 MONTHS
Consider a 4-week drug holiday to see if treatment is still required.
If still required, continue treatment.
Review annually (or every 6 months for patients >75 years).

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Licensed doses of antimuscarinic drugs – table 1

Antimuscarinic adverse effects can limit treatment success. Adverse effects can be reduced by starting at a low dose and gradually increasing until a satisfactory clinical response is achieved. Preferred drug choices are highlighted in bold.

Drug	Dose (Max. dose)	28 day costs (Max. dose)	Comments	Side effects	AEC Score*
Oxybutynin IR	2.5-5mg bd (5mg qds)	£1.86 - £2.00 £4.00	Adjust according to response Do not offer to frail, elderly people or those with Parkinson's disease	The most common adverse reactions reported during clinical trials by > 5% of patients were dry mouth, constipation, diarrhoea, headache, somnolence and dizziness	**3**
Solifenacin Solifenacin liquid	5mg od (10mg od)	£2.46 £3.09 £27.62	Treat patients with severe renal impairment (creatinine clearance of ≤ 30ml/min) and moderate hepatic impairment with a **maximum daily dose of 5mg od**. The SPC for solifenacin recommends a 7-day interval between stopping solifenacin and starting another antimuscarinic. 1mg/ml oral suspension, 150ml		**1**
Trospium IR	20mg bd	£4.26	Reduce dose to **20mg od** or **20mg on alternate days** if eGFR is 10-30mL/min Not recommended in severe hepatic impairment.	May have reduced CNS adverse effects especially in elderly. Hallucination, confusion, agitation occur mostly in the elderly. No interactions via cytochrome P450 system expected	**0**
Tolterodine IR	1-2mg bd	£14.02 - £14.56	For people with impaired liver function or severe renal impairment (eGFR ≤30mL/min) or to minimise side effects prescribe **1mg bd**	Generally, better tolerated than oxybutynin and does not require dose titration	**2**
Oxybutynin MR	5mg od (usually 10mg od)	£12.85 (£25.70)	MR are significantly more expensive than IR but may aid compliance. There should be an interval of at least 7 days between any dose changes.	The most common adverse reactions reported during clinical trials by > 5% of patients were dry mouth, constipation, diarrhoea, headache, somnolence and dizziness	**3**
Tolterodine MR (preferred brand **Neditol XL**)	2mg - 4mg od 2mg-4mg	Generic - £25.78 Brand prescribing £12.89	Reduce dose to **2mg od if impaired** liver function or severely impaired renal function (GFR ≤ 30ml/min) is present	The use of MR preparation may offer a lower incidence of dry mouth and may be suitable for patients that require once daily preparations. Cost effective to prescribe by preferred brand **– Neditol XL**	**2**
Trospium MR	60mg od	£23.05	Not to be given to patients with severe hepatic impairment. Not recommended for use in renally impaired patients (10-30mL/min/1.73m²)	No interactions via cytochrome P450 system expected	**0**
Mirabegron MR	50mg od	£27.07	Avoid if eGFR<15ml/min/1.73m² Reduce to **25mg od** in moderate renal or hepatic impairment	Beta-3 agonist. Minimises anticholinergic side effects. Contraindicated in patients with severe uncontrolled hypertension (SBP≥180mmHg or DBP≥110mmHg, or both). BP should be measured before starting treatment and monitored regularly during treatment, especially in patients with hypertension (MHRA drug update).	**0**
Oxybutynin patches 3.9mg/24hr	Apply 1 patch twice weekly	£27.20	Option in patients unable to tolerate oral oxybutynin Apply to clean, dry unbroken skin on the abdomen, hip or buttock	Adverse effects associated with transdermal oxybutynin are fewer than with oral oxybutynin.	**3**

Information about medicines in this guideline should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Prices are based on the Drug Tariff (December 2020). *AEC (Anticholinergic Effect on Cognition) score, see page 4 for further information.

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Table 2: Examples of medicines metabolised via CYP450 3A4 liver enzymes which interact with some OAB medicines but can be used with Trospium.

	Solifenacin	Mirabegron	Oxybutynin	Tolterodine
Clarithromycin	Severe	Moderate	Mild	Severe
Erythromycin				Severe
Fluconazole				Severe
Itraconazole	Severe	Moderate	Mild	Severe
Ketoconazole	Severe	Moderate	Mild	Severe
Protease Inhibitors	Severe	Moderate	Mild	Severe
Voriconazole	Severe	Moderate	Mild	Severe

Additional prescribing points

• If patient has swallowing difficulty: Offer solifenacin oral suspension.

• Do not offer oxybutynin immediate release to frail older women or patients with Parkinson's disease.

References

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