North Central London
Joint Formulary Committee

Pharmacological management of Overactive Bladder (OAB) Syndrome in Primary Care

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Document control

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26/05/2016	0.5	Updates following May 2016 JFC meeting
03/06/2016	1.0	Published version
26/10/2016	1.1	Updated: Purpose amended to specific "pharmacological management" Drug selection principles amended to specify when solifenacin + mirabegron combination considered Summary of treatment recommendations updated

Document management

Groups / Individuals who have overseen the development of this guidance:	Pritesh Bodalia, JFC
Groups which were consulted and have given approval:	UCLH & RNOH Urology, Urogynaecology and Care of the Elderly teams
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Contents

1. Target audience

Primary care GPs and practice nurses.

2. Purpose

To provide a treatment algorithm for the pharmacological management of Overactive Bladder Syndrome in Primary Care.

The guidance is based on best available evidence, incorporating recommendations from NICE Clinical Guideline 171 (Urinary incontinence, 2013), NICE Technology Appraisal 290 (Mirabegron, 2013). The recommendations follow an independent review of the literature (level 1, grade A evidence) by the NCL JFC and consultation with key urology stakeholders.

3. General treatment principles

- When offering anti-cholinergic drugs to treat OAB consider co-existing conditions (for example, poor bladder emptying), use of existing medication affecting the total anti-cholinergic load and risk of adverse effects.
- The exclusion of other pathologies including stones, infection or malignancy (where appropriate) is important. Refer to Section 3.1 for red flag symptoms requiring referral to secondary care
- The use of bladder diaries to assess symptoms is recommended
- Before OAB drug treatment starts, discuss with patients:
  - 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 they may not see the full benefits until they have been taking the treatment for 4 weeks
  - fluid and lifestyle advice (including caffeine and fluid reduction)
- Prescribe the lowest recommended dose when starting a new OAB drug treatment
- If OAB drug treatment is effective and well-tolerated, do not change the dose or drug

3.1. Red flag symptoms requiring referral to Secondary Care

- Visible haematuria
- Recurrent or persistent UTI associated with haematuria in women aged ≥ 40 years
- Microscopic haematuria in women aged ≥ 50 years
- Suspected malignant mass arising from the urinary tract
- Abnormal DSE or PSA
- Family history of bladder cancer
- Loss of weight
- Bone pain
- Persistent bladder or urethral pain
- Clinically benign pelvic mass
- Faecal incontinence
- Suspected neurological disease
- Voiding difficulty
- Suspected or confirmed urogenital fistulae
- Previous continence / pelvic cancer surgery
- Previous pelvic radiation therapy
- Suspected or confirmed acute kidney injury

4. Drug selection principles

- Offer oxybutynin immediate-release (**not** if frail or elderly) or tolterodine immediate-release first to patients with OAB or mixed UI who have good performance status
- If oxybutynin immediate-release is not effective or well tolerated, offer tolterodine immediate-release
- **Do not** offer oxybutynin to patients with frailty (due to potential impact on cognitive function based on crossing of the blood-brain barrier); offer tolterodine immediate-release as the first-line agent or solifenacin if an anti-cholinergic is indicated
- Review treatment after 4 weeks (refer to section 5)
- If immediate release anti-cholinergic treatment(s) for OAB or mixed UI are not effective or well tolerated, offer solifenacin
- If solifenacin alone is not effective despite dose optimisation, and the patient is unsuitable for invasive procedures, consider treatment with a combination of solifenacin and mirabegron. This combination has been shown to be effective at improving mean voided volume, micturition frequency and urgency.
- Offer mirabegron, as an alternative, if anti-cholinergics are contra-indicated or clinically ineffective
- Do not use flavoxate, propantheline, trospium, fesoterodine, tolterodine MR or imipramine for the treatment of urinary incontinence (UI) or OAB
- Offer transdermal oxybutynin patches to patients unable to take oral medication
- There is no reason to expect patches or modified-release preparations of anti-cholinergic drugs to be more effective

4.1. Contraindications to antimuscarinic treatment

- Myasthenia gravis
- Significant bladder outflow obstruction
- Urinary retention
- Severe ulcerative colitis
- Toxic megacolon
- Gastrointestinal obstruction or intestinal atony

4.2. Caution with antimuscarinic treatment

Antimuscarinic treatment should be used with caution in the elderly (especially if frail), in those with autonomic neuropathy, hiatus hernia or reflux oesophagitis, and in those susceptible to angle-closure glaucoma.

Antimuscarinic treatment may worsen hyperthyroidism, coronary artery disease, congestive heart failure, hypertension, prostatic hyperplasia, arrhythmias and tachycardia.

Several commonly prescribed medications that are not within the anticholinergic class have significant anticholinergic effects, which when taken with known anticholinergic medication can increase the risk of adverse effects and have the potential to cause anticholinergic syndrome. These include:

- Antihistamines
- Tricyclic antidepressants
- Drugs for asthma and COPD
- Cold preparations
- Second generation antipsychotics (clozapine, olanzapine, quetiapine)
- Hyoscine

4.3. Antimuscarinic Syndrome

A confusional state with characteristic features related to dysfunction of the autonomic parasympathetic (cholinergic) nervous system. Symptoms classified into systemic and CNS manifestations:

- Systemic (peripheral) symptoms: blurred visions, photophobia, non-reactive mydriasis, loss of accommodation response, flushed and dry skin, dry mouth, tachycardia, hypertension and fever. Gastrointestinal and urinary motility are frequently reduced.
- CNS symptoms: delirium, agitation, disorientation and visual hallucinations. Ataxia, choreoathetosis, myoclonus and seizures may also occur without peripheral symptoms

5. Reviewing Overactive Bladder drug treatment

- Offer a face-to-face or telephone review 4 weeks after the start of each new OAB drug treatment. Ask the patient if they are satisfied with the therapy:
  - If improvement is optimal, continue treatment
  - If there is no or suboptimal improvement or intolerable adverse effects change the dose, or try an alternative OAB drug (see above), and review again 4 weeks later
  - Consider the use of objective measures such as bladder diaries, if feasible, to quantify the level of improvement
- Offer review before 4 weeks if the adverse events of OAB drug treatment are intolerable
- If second-line or third-line therapies are no more effective or tolerable than previous therapies revert to the previous and less expensive treatment and consider referral to secondary care
- Offer a further face-to-face or telephone review if a patient's condition stops responding optimally to treatment after an initial successful 4-week review
- Due to concerns around risk of cognitive impairment, falls and all-cause mortality associated with anticholinergic use, review patients who remain on long-term drug treatment annually (or every 6 months for patients over 75 years).
  - Consider a 'drug holiday' for 4 weeks, and if successful discontinue treatment. Some patients will be able to manage their symptoms without long-term pharmacological therapy and have no further problems.
  - For those patients whose symptom control decline and were better managed whilst on treatment, restart.
- STOP anti-cholinergic drugs where the following is suspected or being investigated:
  - Dementia (increased confusion, agitation)
  - Chronic glaucoma (acute exacerbation of glaucoma)
  - Chronic constipation (exacerbation of constipation)
  - Chronic prostatism (urinary retention)
- If the patient wishes to discuss the options for further management (non-therapeutic interventions and invasive therapy) refer to a specialist secondary care centre to arrange urodynamic investigation to determine whether detrusor over-activity is present and responsible for OAB symptoms
  - If detrusor over-activity is present and responsible for the OAB symptoms, refer the patient back to the centre that conducted the urodynamic investigation if the patient would like to consider invasive therapy [note: referral to another centre will likely result in repeat tests and investigations being conducted as the information can be difficult to interpret]
  - If detrusor over-activity is not present refer to secondary care for further discussion concerning future management

6. Drug summary

- If otherwise healthy: oxybutynin IR → tolterodine IR → solifenacin → mirabegron ± solifenacin
- If frail / elderly: tolterodine IR → solifenacin → mirabegron ± solifenacin
- If unable to swallow: transdermal oxybutynin
- If contra-indicated to an anti-cholinergic: mirabegron
- See Table 1 for quick reference to pharmacological therapies
- See Appendix 1 for summary flow diagram.

Table 1: OAB pharmacological therapy quick reference

Name	Initial dose	Maximum dose	Dosage adjustments*	Main side effects
Oxybutynin immediate-release	2.5mg - 5mg twice-daily or thrice-daily	5mg four-times daily	Nil	Dry mouth, constipation, blurred vision, dry eyes, cognitive impairment
Tolterodine immediate-release	2mg twice-daily	2mg twice-daily	Reduce to 1mg twice-daily if necessary to minimise side effects. Use with caution in severe renal impairment.	Dry mouth, constipation, blurred vision, dry eyes
Solifenacin	5mg once-daily	10mg once-daily	Dose should not exceed 5mg daily in severe renal impairment or moderate hepatic impairment or those on potent CYP3A4 inhibitors. Should not be used in patients with severe hepatic impairment.	Dry mouth, constipation, blurred vision, dry eyes, low rate of cognitive impairment
Mirabegron	50mg once-daily	50mg once-daily	Dose should not exceed 25mg daily in moderate renal or hepatic impairment and those on potent CYP3A4 inhibitors. Should not be used in patients with severe renal or hepatic impairment.	Tachycardia, urinary-tract infection
Oxybutynin transdermal (Kentera)	1 patch applied twice-weekly to clean, dry unbroken skin on abdomen, hip or buttock (delivers 3.9mg / 24 hours)	1 patch applied twice-weekly	Rotate application site. Use with caution in patients with renal or hepatic impairment.	Skin irritation or pruritis, low incidence of dry mouth and constipation

Appendix 1: Summary of treatment recommendations