Overactive Bladder Syndrome (OAB): Guidelines for Prescribing
NGH-MMC-CLIN30

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Algorithm for Medical Treatment of OAB
(For further details please see NICE Guidelines (Oct 06) Management of Urinary Incontinence in Women)

**Patient History**
- Physical Examination
- Investigations
- Rule out urinary tract infection

**Diagnosis of OAB**

**Referral to Secondary Care if:**
- Haematuria (including microscopic or dipstick)
- Voiding difficulty/chronic urinary retention
- Reduced fixed voided volumes
- Bladder pain
- Recurrent urinary infections
- Significant Vaginal Prolapse
- Smoker >40yrs (urine cytology)

**Primary Care**

**Secondary Care**

**Primary Care**

**Secondary Care**

**Oxybutinin MR (5-10 mg OD)**

**If patient has experienced symptoms long term prior to first appointment consider starting medical therapy with behavioural treatment**

**Review after 6 weeks, if no improvement, add in medical therapy**

**If there is no improvement in symptoms after trying 2-3 antimuscarinics over a period of at least 8 weeks the patient should be referred to the urogynae specialist.**

*Services available at Urogynae at Northampton General Hospital.*

**Consider Transdermal Oxybutinin.**

**Consider other antimuscarinics from the following:**
- Fesoterodine MR (Use 4mg od to avoid excessive side-effects)
- Tolterodine MR,
- Solifenacin,
- Darifenacin

See guidelines for more details
1. Summary

These guidelines have been produced in response to a request from the Urogynae Centre at Northampton General Hospital and the Northamptonshire Prescribing Advisory Group (NPAG).

There are a number of antimuscarinics available for the treatment of Overactive Bladder syndrome (OAB) that possesses broadly similar efficacy profiles (Tooz-Hobson). An evidence based algorithm has been produced taking into account the tolerability profiles and costs of these agents to aid prescribing at the Urology Centre and in Primary Care.

2. Introduction

Overactive Bladder syndrome (OAB) is defined by the International Continence Society as ‘urgency, with or without urge incontinence (UI), usually with frequency and nocturia’. It is associated with high economic and social costs. Epidemiological surveys estimate that OAB affects approximately 50 million adults in Europe and the United States and prevalence increases with age. It is associated with increased risk of injury in a fall, with urge incontinence and nocturia considered as independent risk factors for falls and bone fractures, particularly in the elderly.

Non-surgical treatment is the main stay of therapy for OAB and the available options include bladder training (first line), lifestyle intervention, biofeedback medication and a combination of these options.

Until relatively recently the muscarinic (cholinergic) receptor antagonists, tolterodine and oxybutynin were the mainstay of drug treatment for OAB. These drugs block acetylcholine release from the parasympathetic nerves in the bladder thereby preventing contracting and voiding. They also exert a direct spasmolytic effect on the detrusor muscle of the bladder, increasing capacity and reducing the frequency of contractions (Booth and Pascoe). Unfortunately, the use of these antimuscarinic drugs has been limited by sub optimal efficacy or side effects due to generalised cholinergic receptor blockade. The most troubling side effects are dry mouth, blurred vision, and constipation, which often lead to discontinuation of the treatment.

Despite the proven efficacy of antimuscarinics, patient compliance with treatment is relatively low. A European survey (Milsom) found that of those seeking help from their physician; only 27% were receiving medication at the time of the survey. Patients often take less than the optimal dosages to avoid the side effects or stop taking the medication altogether and more than 70% of patients do not continue therapy beyond nine months. (Persistency data)

Establishing effective treatment for these patients is an important challenge as the symptoms of OAB have a significant impact on quality of life (Milsom). So it is important that prescribed treatment gives a good balance between efficacy and tolerability, to ensure the patients continuation with treatment.
3. Target group(s) or disease process(es)

These guidelines apply to adult female inpatients and outpatients presenting with Overactive Bladder Syndrome (OAB) in primary and secondary care.

4. Professional Group(s)

The guidelines have been produced to support prescribing by all prescribers in Primary and Secondary Care in Northamptonshire.

The guidelines have been agreed by Northamptonshire Prescribing Advisory Group (NPAG)

5. Clinical Guidelines

**Treatment of OAB**

5.1 Conservative Management

Non-pharmacological intervention is the foundation of treatment for overactive bladder. Pelvic floor muscle training and bladder training have been proven to be effective strategies and in motivated patients can be more effective than medication. Traditional non-pharmacological tools and lifestyle modification should be provided consistently as part of a balanced program for improving target symptom control. (Epstein)

NICE guidance state that lifestyle and physical therapies should be considered first line for the treatment of OAB as they do not carry the unwanted side-effects associated with drug therapy. (NICE 2006)

**Lifestyle interventions**

- A trial of caffeine reduction is recommended for the treatment of women with OAB
- Consider advising modification of high or low fluid intake in women with UI or OAB
- Women with UI or OAB and a body mass index greater than 30 should be advised to lose weight.

**Physical therapies**

- Bladder training lasting for a minimum of six weeks should be offered as first line treatment with urge or mixed UI.
- A trial of supervised Pelvic Floor Muscle training of at least 3 months duration should be offered as first line treatment to women with stress or mixed UI.

If, after a period of 3 months of these first line treatments, symptoms have failed to resolve then drug therapy may be initiated.
5.2 Drug Therapy

First line:  
Please note that it has been agreed with NHS Northamptonshire that patients in primary care can be initiated on the immediate release Oxybutynin first line as long as the patient is reviewed by the GP for side-effects within two weeks. If the patient suffers side-effects which will be intolerable long term then the patient should be switched to oxybutynin MR and the pathway followed.

Oxybutynin Modified Release 5-10mg od  
The patient should be reviewed after 4 weeks, following any changes in drug therapy, so that the symptoms of OAB and the patient’s tolerance to therapy can be reassessed.

If the antimuscarinic side effects such as dry mouth, constipation or burred vision have proved intolerable or the patient anticipates that they will prove intolerable long term then the patient can switch to the next drug in the algorithm. Alternatively the GP may refer the patient to the Urology or Urogynae Centre at Northampton General Hospital.

Second line:  
Transdermal Oxybutynin: Apply one patch twice weekly  
If the patient has symptom relief from Oxybutynin but continues to experience intolerable adverse effects then Oxybutynin patches should be considered. There is strong evidence that transdermal Oxybutynin causes less antimuscarinic side effects. However transdermal oxybutynin is associated with an increase in skin irritation at the patch site. If there is a significant reaction then change to one of the following antimuscarinics:

Tolterodine MR, Darifenacin, Solifenacin and Fesoterodine  
If Oxybutynin has not alleviated symptoms of OAB or side effects are intolerable then consider the following antimuscarinics:

At the lower dose Darifenacin is associated with less antimuscarinic side effects than extended release oxybutynin and tolterodine preparations. Modified release formulations of oxybutynin and tolterodine are better tolerated than immediate release versions. Fesoterodine should only be used at a dose of 4mg once a day as higher doses will increase the likelihood of intolerable side effects. Solifenacin can also be used as an alternative at this stage in the algorithm.

Four to six weeks after a change of drug therapy the patient should be reassessed.

If this algorithm has been followed but the patient’s symptoms of OAB are not resolved then the patient can be referred to the specialist urology or Urogynae centre at Northampton General Hospital.
5.3 Evidence for the Algorithm

The NICE (Oct 2006) guidelines for urinary incontinence in women states that:

“Treatment with darifenacin, oxybutynin, solifenacin, tolterodine and trospium in women with OAB is associated with improvements in frequency, leakage episodes and quality of life. (Propiverine reduces frequency of urination). There is no evidence of a clinically important difference in efficacy between antimuscarinic drugs. Based on the cost minimisation analysis undertaken by NICE non-proprietary immediate release (IR) oxybutynin is the most cost-effective antimuscarinic drug”. The guidelines then go on to suggest that IR oxybutynin should be offered to women as the first line treatment for OA. However IR Oxybutynin has a very poor side effect profile when compared to the extended release (ER) antimuscarinics (Chapple).

The Continence Foundation (Oct 2006) claims that more than 80% of people given non-proprietary ‘immediate release’ oxybutynin are unable to tolerate its side effects (Kelleher et al 1998) and many give up treatment altogether and remain incontinent.

Incontinence has a wider social cost, as it is often a contributory factor to loss of independence, physical deterioration and psychological problems. Known consequences of OAB are falls in the elderly leading to transfer to a care home, inability to work and relationship breakdowns. (Continence Foundation).

However, NICE concede that the cost minimisation approach does not sufficiently take into account the differences between drugs and formulations in terms of their adverse effects and tolerability profiles.

With this in mind, a review was conducted to study the tolerability and adverse effect profiles of Tolterodine MR (modified release), Transdermal Oxybutynin, Propiverine, Darifenacin, Solifenacin and Trospium. This was used to determine an algorithm for treatment of patients at the Urology centre and to aid prescribing in the primary care setting.

Oxybutynin MR and Tolterodine MR

Modified Release formulations of oxybutynin and tolterodine are better tolerated than immediate release versions according to a meta-analysis of key clinical trials of newer antimuscarinic agents for treatment of OAB (Epstein). A study (OPERA) comparing the efficacy and safety of oxybutynin MR and that of tolerodine MR reported improved efficacy of oxybutynin MR without compromising tolerability (Appell). Taking into account the cost comparison between these modified release products, Oxybutynin MR was considered the first agent of choice. Tolterodine MR was placed at the end of algorithm as this fulfils the consideration that there can be variation between patients’ responses to different antimuscarinics.
Fesoterodine M/R

Fesoterodine is a non-selective oral antimuscarinic agent. It is rapidly converted by ubiquitous esterases to its active metabolite 5-hydroxymethyl tolterodine (5HMT). Tolterodine is also converted to 5-HMT, although this occurs to a lesser extent.

When comparing the Fesoterodine MR 8mg dose against the tolterodine 4mg MR there was a much higher incident of dry mouth (28%) and constipation (5%) compared with 16% and 4% for the tolterodine group. These side-effects were also quite high when compared against the other third line antimuscarinics. Therefore it has been agreed that for greater tolerability Fesoterodine MR 4mg od dosage should be used.

When using Fesoterodine versus placebo the incidence for dry mouth was 23% and constipation 4.8% whereas previous studies indicated Tolterodine MR 4mg caused dry mouth 12.9% and constipation 3.3% respectively. Although it is appropriate to add Fesoterodine to the list of antimuscarinics available to increase patient choice it should only be used at Fesoterodine 4mg once daily dose to avoid excessive side effects, when compared to the other antimuscarinics.

Trospium

Unlike other antimuscarinics Trospium is water-soluble and crosses the blood – brain barrier poorly. Although it has been suggested that this might minimize centrally mediated events such as drowsiness, nervousness, dizziness and cognitive impairment, the limited clinical trial data do not support this (Epstein). Trials were conducted using some poorly designed studies and comparing with oxybutynin (IR). Trials comparing trospium chloride with oxybutynin MR and tolterodine MR have not been reported. (Appell). Taking all of this evidence into account I did not recommend the addition of Trospium to the algorithm overactive bladder. However it can be used for treating increased urinary frequency.

Oxybutynin transdermal (TDS)

Oxybutynin is subject to extensive hepatic and gastrointestinal presystemic metabolism. By delivering the drug transdermally, the bioavailability is increased. So a lower dose of oxybutynin is required leading to lower dose-dependent side effects. As a result the transdermal oxybutynin patch is associated with lower rates of antimuscarinic adverse effects compared to oral antimuscarinics. However some patients (up to 17%) may experience application site reactions including erythema and pruritis. (Dmochowski). Oxybutynin TDS appears to have overcome the dry mouth problem associated with oxybutynin but at the expense of application site reaction and an increase in withdrawals due to adverse events. (Chapple).
Darifenacin and Solifenacin

Darifenacin and Solifenacin are M₃ selective antimuscarinic agents and it has been suggested that these agents cause fewer cardiac and CNS related adverse events than oxybutynin or tolterodine. Trials comparing Darifenacin with active controls such as oxybutynin and tolterodine have not been reported. However in trials of Darifenacin the frequency cardiac and CNS effects is similar to that of placebo and Solifenacin appears to lengthen the corrected QT interval in a dose-dependent manner (Appell).
At the moment there is insufficient evidence to suggest an increased risk of CNS or cardiac events with less selective antimuscarinic agents (oxybutynin and tolterodine) when compared to the more selective agents, darifenacin and Solifenacin (Appell).

Darifenacin

There was no published data comparing Darifenacin and Oxybutynin ER however a meta-analysis compared it with tolterodine MR and showed that Darifenacin at a dose of 7.5mg/day had a reduced number of total withdrawals due to adverse effects. Higher doses of 15mg were not as tolerable as Tolterodine MR. It was decided to include Darifenacin in the algorithm, as the evidence from the studies was quite strong. It is also important in OAB to allow selection of an appropriate agent based on individual factors such as cost and tolerability. After discussion with the specialists it was agreed to include Darifenacin at the higher dose as the patient will already have tried Oxybutynin MR.

Solifenacin

Solifenacin was placed at the end of the algorithm after Tolterodine MR, as the evidence supporting its place in therapy was more difficult to interpret. The trials studied appeared to be subsets and extension studies of one another, so that statistical interpretation of results is more difficult to assess in a meaningful manner. (Cardozo 2004, Chapple 2004b, Chapple 2006, Chapple 2005b, Haab 2005, Kelleher 2005, Wagg 2006).

Propiverine

Three studies were reviewed (Abrams 2006, Juneman 2005 and Madersbacher 1999) they were of poor design, lacking clinical or statistical significance. The meta-analysis showed that it performed much worse than tolterodine MR with regard to patient withdrawals from therapy. There is no evidence to support the addition of propiverine to the algorithm

The results of an extensive review have been used as supporting evidence for the algorithm.

Beyond the algorithm it is widely recognised that OAB has many factors and commonly used antimuscarinics have different tolerability and safety profiles but broadly similar efficacy profiles consequently, therapy should be tailored to individual patient needs (Toozs-Hobson).
For those patients who are not satisfactorily treated using the algorithm, consultants at the Urology/Urogynae Centre may prescribe alternative antimuscarinic therapy.

6. Roles and Responsibilities

The Primary Care prescriber should refer the patient to the specialist urogynaecology team in Secondary Care if there is no improvement in OAB symptoms experienced by the patient after two or three antimuscarinics have been tried over a period of at least 8 weeks.

7. Related Trust and/or National Guidance


8. Guidance Development

This guidance was first produced in October 2008 and has been reviewed in December 2010 at the request of Northampton General Hospital Urogynae Specialist and Urologist. The guidelines have subsequently been agreed by Kettering General Hospital and approved for use in Primary and Secondary Care by Northamptonshire Prescribing Advisory Group (NPAG) in April 2011.

9. Audit

No audit planned

10. Implementation and Training

The guidelines will be available on the NGH intranet and the Northamptonshire PCT Pathway site for GPS.
11. References/Bibliography


Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein A J. How widespread are the symptoms of an overactive bladder and how are they managed? A population based prevalence study BJU Int 2001; 87(9): 760-6


Sender Hershorn, Steren Swift et al Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo controlled trial (BJU International) 2009;105,58-66


Appendix 1

Cost comparison of the different products available for the treatment of OAB

Analysis performed using MIMS Jan 2011

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Cost/Month (inc VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin MR <em>(Emselex)</em></td>
<td>7.5mg od</td>
<td>£25.08 (28 days)</td>
</tr>
<tr>
<td>Darifenacin MR <em>(Emselex)</em></td>
<td>15mg od</td>
<td>£25.08 (28)</td>
</tr>
<tr>
<td>Fesoterodine MR</td>
<td>4mg od</td>
<td>£30.93 (28)</td>
</tr>
<tr>
<td>Oxybutynin (Generic)</td>
<td>5mg tds</td>
<td>£14.26 (28)</td>
</tr>
<tr>
<td>Oxybutynin (Ditropan)</td>
<td>5mg tds</td>
<td>£15.38 (28)</td>
</tr>
<tr>
<td>Oxybutynin MR <em>(Lyrinel XL)</em></td>
<td>5mg od</td>
<td>£12.97 (30)</td>
</tr>
<tr>
<td>Oxybutynin MR <em>(Lyrinel XL)</em></td>
<td>10mg od</td>
<td>£25.94 (30)</td>
</tr>
<tr>
<td>Oxybutynin MR <em>(Lyrinel XL)</em></td>
<td>20mg od</td>
<td>£51.88 (30)</td>
</tr>
<tr>
<td>Oxybutynin transdermal <em>(Kentera)</em></td>
<td>1 patch twice weekly</td>
<td>£32.64 (28)</td>
</tr>
<tr>
<td>Solifenacin <em>(Vesicare)</em></td>
<td>5mg od</td>
<td>£33.14 (30)</td>
</tr>
<tr>
<td>Solifenacin <em>(Vesicare)</em></td>
<td>10mg od</td>
<td>£43.09 (30)</td>
</tr>
<tr>
<td>Tolterodine <em>(Detrusitol)</em></td>
<td>2mg bd</td>
<td>£36.67 (28)</td>
</tr>
<tr>
<td>Tolterodine MR <em>(Detrusitol XL)</em></td>
<td>4mg od</td>
<td>£30.93 (28)</td>
</tr>
<tr>
<td>Trospium <em>(Regurin)</em> (Only use for urinary frequency)*</td>
<td>20mg bd</td>
<td>£31.20 (30)</td>
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MR- Modified Release
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<th><strong>Title:</strong></th>
<th>Guidelines for the Selection of an Antimuscarinic in the Treatment of Overactive Bladder Syndrome (OAB)</th>
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