**Anticholinergics and cognitive impairment in the treatment of overactive bladder**

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**Patient presents with symptoms suggestive of overactive bladder (OAB)**

General history and examination, including:
- body mass index (BMI)
- constipation
- urine dipstick
- excessive fluid intake
- alcohol use
- family history of dementia
- medical comorbidities, such as cardiovascular disease
- polypharmacy (especially anticholinergic burden and cytochrome P450-mediated drug–drug interactions).

Consider if diabetic or has UTI

Initiate bladder diary\(^1\)

Recommend lifestyle modifications with bladder re-training (for 6 weeks), behavioural therapy, and pelvic floor muscle training, if necessary; ask patient to return if no improvement\(^1\)

**Improvement?**

- Yes
- No

- Continue
- Discuss pharmacotherapy
  - Consider:
    - comorbidities
    - cognition risk factors

- risk-benefit analysis of symptoms vs risk
- anticholinergic effect on cognition

**Concerns about cognition?**\(^2\)**(A)**

- Yes
- No

- Once daily treatment preferred?
  - Yes
  - Trospium chloride 60 mg once daily
  - Darifenacin hydrobromide 7.5 mg/15 mg once daily
  - Fesoterodine fumarate 4 mg/8 mg once daily

  - No
  - Trospium chloride 20 mg twice daily

**Prescribe treatment with lowest acquisition cost**\(^1\)

**Improvement after 4 weeks?**

- Yes
- No

- Continue\(^3\)
- Therapeutic failure
  - Side-effects
  - Lack of response

  Change to another anticholinergic or therapeutic class (e.g. mirabegron\(^3\)), and/or switch to a transdermal oxybutynin patch if no concerns about cognition
  - Increase dose (in the absence of side-effects), if chosen treatment allows

**Improvement after 4 weeks?**

- Yes
- No

- Continue\(^3\)
- Refer to secondary care for refractory OAB\(^1\)

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\(^1\) The following are of particular concern for cognitive deterioration:
- physiological age
- family history of dementia
- medical comorbidities, such as cardiovascular disease
- polypharmacy (especially anticholinergic burden and cytochrome P450-mediated drug–drug interactions).

If the patient is already taking an anticholinergic with a high risk score (e.g. 2 or 3 on the AEC scale, see Table 2) and cognitive deterioration is of concern, they can be switched to a lower-scoring anticholinergic treatment or a change to a beta-3 agonist can be considered.

\(^2\) Refer to Table 3 for available preparations, prices, and notes of these once-daily antimuscarinic preparations.

\(^3\) After initial 4-week review, review at 12 months if <65 years and at 6 months if ≥65 years.
Introduction

- Overactive bladder (OAB) is a common symptom complex affecting both men and women
  - a large population-based survey in five countries reported prevalence of 11.8%\(^4\)
  - prevalence increases with age,\(^4\)
  - and a more recent study found that bothersome OAB affected almost half (46%) of women in the oldest age group (55–64 years)\(^5\)

- OAB is defined as: “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology”\(^6\)

- OAB can be treated with anticholinergics,\(^1\) which block the effect of acetylcholine at muscarinic receptors in bladder smooth muscle
  - after lifestyle changes, antimuscarinics are the most common and currently the most widely used treatment for OAB\(^7,8\)

- Recently updated guidelines highlight the impact that anticholinergic therapy for OAB may have on cognitive function\(^1,9\)

- Conflicting data are present in the literature and it is not clear whether this is a simple association due to the anticholinergics being used in adults with undiagnosed cognitive impairment or prodromal dementia, or if the cognitive impairment or dementia results from the use of these products\(^10–16\)

- Some adults will have a high anticholinergic burden due to polypharmacy and may, therefore, experience unintentional anticholinergic adverse effects\(^10,11,14\)
  - there are many chronic conditions that are often treated with products that have anticholinergic effects, such as psychiatric disorders, depression, insomnia, asthma, and pain\(^10,11\)
  - over-the-counter preparations may also contribute to the anticholinergic burden\(^17\)

- There are also differences in theoretical cognitive risk between the various products with anticholinergic actions available\(^13\)
  - tools are available to help prescribers understand the differences in putative risk profile for products commonly used for OAB and how to quantify the risk\(^18–20\)

- This algorithm aims to complement NICE Guideline 123 (NG123)\(^1\) by providing practical guidance on anticholinergics in OAB, particularly if there are concerns about cognitive function.

Anticholinergics and cognitive impairment

- Products with anticholinergic effects are mainly antimuscarinics that exert their therapeutic effect by binding to the M2 and M3 muscarinic receptors on cells in the bladder to reduce intravesical pressure, increase compliance, raise volume threshold for micturition, and reduce uninhibited contractions\(^8,21\)

- Muscarinic receptors are also present on other tissues in the body and this can result in unwanted anticholinergic effects\(^22,23\)

- The binding of antimuscarinics to the M1–M5 receptors in the brain can potentially affect cognition

- To have a detrimental effect on cognition, they must first cross the blood–brain barrier (BBB) and enter the brain by passive diffusion or facilitated transport\(^23\)

- The ease and speed of this diffusion may be affected by the characteristics of the antimuscarinic molecule:\(^22\)
  - molecular size
  - lipophilicity
Patient factors are also important in determining the permeability of the BBB:
- age, stress, and trauma are likely to increase permeability\(^2\)
- permeability may also be affected by the presence of some comorbidities (for example, Alzheimer’s-type dementia, diabetes, and multiple sclerosis)\(^2\)

Cognitive effects are likely to be reduced if the antimuscarinics can be cleared from the brain quickly:
- some can only leave the brain by passive diffusion, while others are removed via an active transport mechanism facilitated by permeability-glycoprotein (P-gp), which is present in the cell membrane\(^2,23\)

Antimuscarinics with the following characteristics (see Table 1) are likely to have a reduced effect on cognition:\(^2,23\)
- large molecular size
- hydrophilic
- can be actively transported across the cell membrane

Data on brain to plasma ratios for various antimuscarinics support this assumption, as these are highest for oxybutynin, intermediate for tolterodine and solifenacin, and lowest for darifenacin, fesoterodine, and trospium.\(^2\)

Categorising anticholinergic effect on cognition

Prior to prescribing antimuscarinics, the anticholinergic burden for the patient should be considered\(^1\)

There are many different tools available to assess this burden, including the anticholinergic cognitive burden scale, anticholinergic risk scale, anticholinergic drug scale, and anticholinergic burden classification\(^18–20\)

### Table 1: Properties of antimuscarinics that affect ability to cross the blood–brain barrier\(^22–25\)

<table>
<thead>
<tr>
<th>Antimuscarinic</th>
<th>Molecular size/chemical structure (type of amine)</th>
<th>Lipophilicity</th>
<th>P-gp substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 hydroxymethyl tolterodine (5-HMT; prodrug for tolterodine)</td>
<td>Tertiary (passive diffusion across the blood–brain barrier)</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>Tertiary</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Tertiary</td>
<td>Low–moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Tertiary</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Tertiary</td>
<td>Low–moderate</td>
<td>No</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Tertiary</td>
<td>Low–moderate</td>
<td>No</td>
</tr>
<tr>
<td>Trospium</td>
<td>Quarternary</td>
<td>Very low/hydrophilic</td>
<td>Yes</td>
</tr>
</tbody>
</table>
There is considerable variation among these tools\textsuperscript{18,19,26}:
- there are differences in the scales used, the tool's development, and the methods used in evaluating anticholinergic potency
- factors such as the selectivity of products to specific muscarinic receptor subtypes and the ability of a product to enter the brain have not always been considered
- many scales are founded on subjective ratings of anticholinergic activity based on the clinical experience and observed cognitive impairment
- some products are omitted from the tools; it is unclear if this is due to a lack of anticholinergic activity, or if they were not assessed

The anticholinergic effect on cognition (AEC) scale, developed by Bishara et al., includes nearly 300 products and is based on robust scientific methodology\textsuperscript{26,27}:
- for each product, a score is provided that considers:
  - the muscarinic binding affinity
  - whether it is selective for the target tissue
  - the extent to which it penetrates the BBB
  - reported cognitive adverse effects

This AEC scale can be used in patients presenting with OAB to help quantify the anticholinergic burden and, therefore, cognitive risk\textsuperscript{26,27}:
- the AEC scale is available as a regularly updated web-based app at: www.medichec.com\textsuperscript{27}

In older people presenting with symptoms of cognitive impairment, dementia, or delirium, all individual products with an AEC score of 2 or 3 should either be stopped, or the patient switched to an alternative product with a lower AEC score (preferably 0)\textsuperscript{26}

If a patient has a total AEC score of 3 or above, a medication review should be performed to see if it is possible to reduce the patient’s anticholinergic burden\textsuperscript{26}

Table 2 shows the AEC score\textsuperscript{27} for the seven antimuscarinic agents reviewed in Evidence Review C of the NICE guideline\textsuperscript{1}

<table>
<thead>
<tr>
<th>Antimuscarinic</th>
<th>AEC score\textsuperscript{27}</th>
<th>Recommendation\textsuperscript{27}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>0</td>
<td>“Safe to use”</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>0</td>
<td>“Safe to use”</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>0</td>
<td>“Safe to use”</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>0</td>
<td>“Safe to use”</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>“Caution required”</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>2</td>
<td>“Review and withdraw or switch”</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>3</td>
<td>“Review and withdraw or switch”</td>
</tr>
<tr>
<td>Propiverine</td>
<td>“Limited data – unable to scope”</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Anticholinergic effect on cognition (AEC) scores\textsuperscript{27} for the seven antimuscarinic agents for the treatment of OAB considered in Evidence Review C of NICE Guideline 123\textsuperscript{1} and mirabegron
Management algorithm

- The algorithm on page 1 summarises the treatment pathway for patients who present with OAB where concerns exist over the risk of cognitive impairment.

- Primary treatment of OAB, especially in the elderly, should follow a non-surgical approach and incorporate non-pharmaceutical measures.

- If anticholinergics are needed, a review of the patient’s medication is warranted prior to prescribing treatment.
  - the review should consider the patient’s comorbidities, the potential effect on cognition, anticholinergic load, and the level of polypharmacy.

- If there are no cognitive concerns, treatment can be prescribed according to cost and patient need.
  - treatment choice (including product formulation and whether topical application is needed) should be individualised according to each patient’s needs.

- Where a cognitive concern exists, anticholinergics of choice are likely to be darifenacin, fesoterodine, or trosiprim (Table 3), due to their lower risk of an effect on cognition.

- Solifenacin can be used where cognitive impairment is not a significant concern or where one of the other anticholinergics has not been effective, but an anticholinergic is not contraindicated; the patient should be monitored closely for any change in cognitive function.
  - while it is somewhat selective, it can readily penetrate the BBB and, as it is not a substrate for P-gp, it is not cleared rapidly from the brain.

- If treatment failure is seen, an alternative anticholinergic, a different drug class (for example, mirabegron), or a transdermal patch should be trialled.
  - NICE recommends mirabegron as an option only for people in whom antimuscarinics are contraindicated or clinically ineffective, or have unacceptable side-effects.

- In cases of refractory OAB, a referral to secondary care should be made.

### Table 3: Once-daily antimuscarinic preparations with AEC score of zero

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Available preparations</th>
<th>Cost per 30 days</th>
<th>Undesirable effects: very common (≥1/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropism chloride 60 mg OD</td>
<td>Regurin XL</td>
<td>£23.05</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Darifenacin hydrobromide 7.5 mg/15 mg OD</td>
<td>Emselex</td>
<td>£25.48</td>
<td>Constipation, dry mouth</td>
</tr>
<tr>
<td>Fesoterodine fumarate 4 mg/8 mg OD</td>
<td>Toviaz</td>
<td>£25.78</td>
<td>Dry mouth</td>
</tr>
</tbody>
</table>

Refer to the summary of product characteristics for the full list of undesirable effects, indications, precautions for use, drug interactions, etc.
References

1. NICE. Urinary incontinence and pelvic organ prolapse in women: management. NICE Guideline 123. NICE, 2019 (last updated June 2019). Available at: www.nice.org.uk/ng123


3. NICE. Mirabegron for treating symptoms of overactive bladder. Technology appraisal guidance 290. NICE, 2013. Available at: www.nice.org.uk/ta290


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Regurin XL 60mg Prescribing information

Read the SPC before prescribing. Prolonged release capsules, hard, containing 60 mg of trospium chloride.

**Indication:** Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder.

**Dosage and administration:** One capsule once daily (equivalent to 60 mg of trospium chloride per day). Regurin XL 60 mg should be taken with water on an empty stomach one hour before a meal.

**Contra-indications:** Trospium chloride is contraindicated in patients with urinary retention, severe gastro-intestinal conditions (including toxic megacolon), myasthenia gravis, narrow-angle glaucoma, and tachyarrhythmia. Trospium chloride is also contraindicated in patients who have demonstrated hypersensitivity to the active substance or to any of the excipients. Precautions: Trospium chloride should be used with caution by patients with obstructive conditions of the gastrointestinal tract such as pyloric stenosis, with obstruction of the urinary flow with the risk of formation of urinary retention, with autonomic neuropathy, with hiatus hernia associated with reflux oesophagitis and in whom fast heart rates are undesirable e.g. those with hyperthyroidism, coronary artery disease and congestive heart failure. Regurin XL 60 mg should not be given to patients with severe hepatic impairment and caution should be exercised in patients with mild to moderate liver impairment. Regurin XL 60 mg is not recommended for renally impaired patients. Before commencing therapy organic causes of urinary frequency, urgency, and urge incontinence, such as heart disease, renal disease, polydipsia, or infections, or tumours of urinary organs should be excluded.

**Interactions:** Potentiation of the effect of medicinal products with anticholinergic action (such as amantadine, tricyclic antidepressants), enhancement of the tachycardic action of β-sympathomimetics; decrease in efficacy of pro-kinetic agents (e.g. metoclopramide).

**Pregnancy and lactation:** Clinical data on exposure during pregnancy or lactation are not available for Regurin XL 60 mg. Caution should be exercised when prescribing to pregnant or breastfeeding women.

**Side-effects:** Dry mouth is very common (>10%). Common (<10%) Dry eye, dyspepsia, constipation, constipation aggravated, abdominal pain, abdominal distension, nausea and nasal dryness; uncommon (<1%) flatulence; rare (<0.1%) tachycardia, vision disturbance, asthenia, micturition disorders, urinary retention and rash. For other very rare side effects, please see the Regurin XL SPC.

**Presentations and basic NHS prices:** Regurin XL packs contain 28 prolonged release capsules. Each capsule contains 60mg of trospium chloride. £23.05. MA Number: PL 46302/0194

**Legal category:** POM

**Marketing Authorisation Holder:** Mylan Products Ltd., Station Close, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.

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**Adverse events:** Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Contura Ltd. (Telephone 01707 853 000).