

# Managing overactive bladder in primary care

DUDLEY ROBINSON, MOHAMMED BELAL, PARASKEVE GRANITSIOTIS, RIZWAN HAMID, PHILIP TOOZS-HOBSON AND ARUN SAHAI

As the understanding of the mechanisms that underlie the overactive bladder have increased, so its diagnosis and management have become more complex. This article, based on a consensus group meeting, provides guidance on the current management of overactive bladder in primary care.

Overactive bladder (OAB) is the term used to describe the symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.<sup>1</sup>

## HOW COMMON IS OAB?

Epidemiological studies from North America have reported a prevalence of OAB in women of 16.9%, increasing with age to 30.9% in those over the age of 65 years.<sup>2</sup> Further data from Europe have shown the overall prevalence in men and women over the age of 40 years to be 16.6%.<sup>3</sup> Frequency was the most commonly reported symptom (85%), while 54% complained of urgency and 36% of urgency incontinence. The European Prospective Investigation into Cancer and Nutrition (EPIC) study, a cross-sectional telephone survey conducted in Canada and four European countries including the UK, utilised the International Continence Society terminology (more specific for the current OAB definition) and found the prevalence of OAB to be 12.8% in women and 10.8% in men.

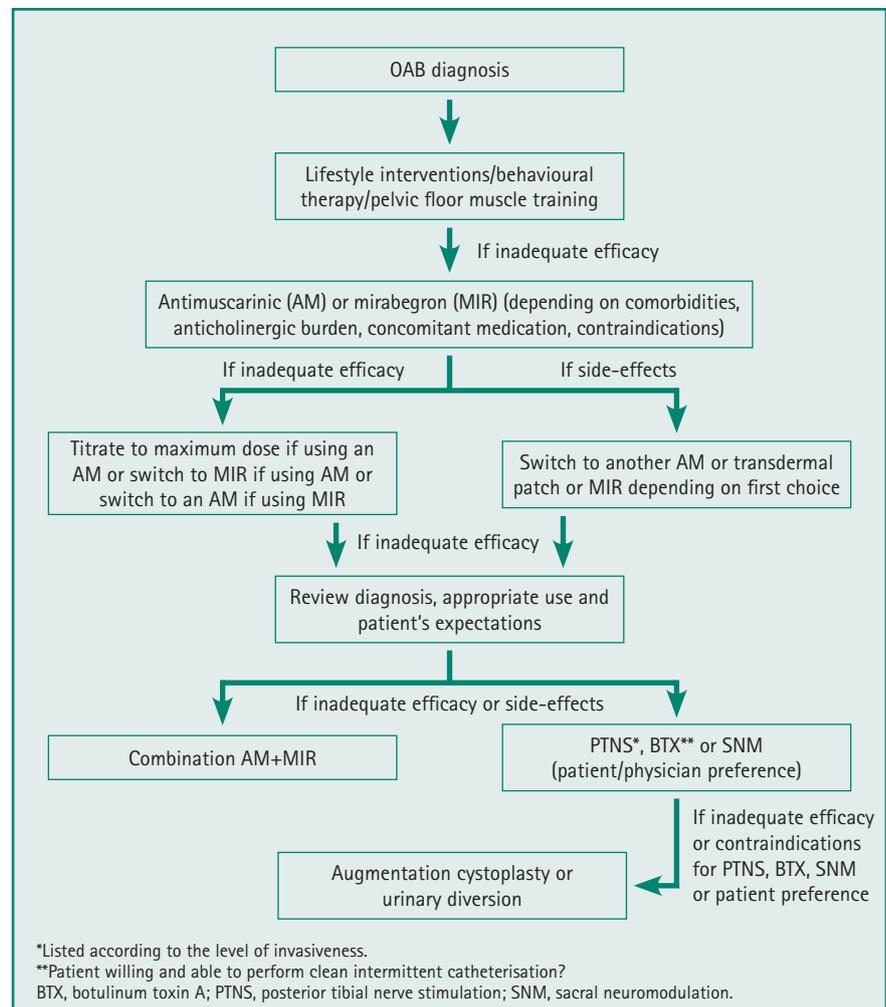


Figure 1. A management algorithm for OAB suggested by the authors

Dudley Robinson, Consultant Urogynaecologist, King's College Hospital, London; Mohammed Belal, Consultant Urological Surgeon, University Hospitals Birmingham; Paraskeve Granitsiotis, Consultant Urological Surgeon, Western General Hospital, Edinburgh; Rizwan Hamid, Consultant Urological Surgeon, University College London Hospitals and London Spinal Injuries Unit, Stanmore; Philip Toozs-Hobson, Consultant Urogynaecologist and Honorary Reader, University of Birmingham Women's and Children's NHS Foundation Trust; Arun Sahai, Consultant Urologist and Honorary Senior Lecturer, Guy's Hospital, London

**HOW DO OAB PATIENTS PRESENT IN PRIMARY CARE?**

OAB usually presents with a multiplicity of symptoms. Urinary urgency is the hallmark symptom of OAB, and patients will often complain of increased daytime frequency and nocturia with or without urgency incontinence. However, women commonly have stress incontinence (mixed incontinence) or nocturnal enuresis and coital incontinence, in addition to OAB. Men may present with a mixture of storage and voiding lower urinary tract symptoms, especially in those with benign prostatic hyperplasia (BPH).

There are no specific clinical signs in women with OAB, but it is important to look for vulval excoriation, urogenital atrophy, post-void residual urine and demonstrable stress incontinence. In men, a digital rectal examination may be important depending on the age of the patient.

In both sexes, it is important to exclude pathology that may mimic OAB, such as urinary tract infection (UTI) and bladder cancer (see red flag section, below), and urogenital prolapse or a pelvic mass in women. Furthermore, OAB may be a secondary effect, for example, of bladder outflow obstruction in males related to BPH.

**WHAT INVESTIGATIONS SHOULD BE PERFORMED?**

Although OAB is a symptomatic diagnosis, all patients require a basic assessment in order to confirm the diagnosis, as well as excluding any other underlying cause for lower urinary tract dysfunction. This should include a urine dipstick/midstream urine for culture and sensitivity (screening for UTI and haematuria) and an assessment of a post-void residual urine.

In addition, a frequency/volume chart is useful to evaluate fluid intake and voiding patterns. As well as the number of voids and incontinence episodes, the mean volume voided over a 24-hour period can be calculated, as well as the diurnal and

nocturnal volumes. Analysis of voiding diaries helps to make a diagnosis of OAB, in addition to being useful in monitoring treatment.

**INITIAL PRIMARY CARE MANAGEMENT**

All patients with OAB benefit from advice regarding simple lifestyle measures that can help alleviate symptoms. Many patients drink too much and should be told to reduce their fluid intake to between 1 and 1.5 litres per day, avoiding tea, coffee and alcohol.

Lifestyle interventions may also be combined with behavioural therapy. Bladder retraining has been shown to be effective, and both NICE and the International Consultation on Incontinence (ICI) recommend that bladder retraining should be considered as first-line treatment in all women with OAB.<sup>4,5</sup>

**WHAT ABOUT DRUG THERAPY IN OAB?**

While a conservative approach is justified initially, drug therapy remains integral in the management of patients with OAB. A number of different antimuscarinic agents are available, all of which have level 1 evidence and a grade A recommendation (Box 1).<sup>6</sup>

**WHAT ARE THE CHALLENGES IN CURRENT OAB MANAGEMENT?**

Persistence with medication remains a problem across many different chronic disease states. Evidence suggests that adherence with antimuscarinic therapy tends to be lower than in other chronic health conditions, such as osteoporosis, hypertension and diabetes.<sup>7</sup>

Historically, adherence with immediate-release preparations has been reported to be low, with only 18% of patients continuing therapy at six months.<sup>8</sup> This has not substantially improved, despite the introduction of long-acting slow-release preparations and more efficacious bladder-selective drugs. A recent retrospective analysis of antimuscarinic prescribing in the UK has shown persistence rates at 12 months to range from 14% to 35%, with little difference noted between the different medications.<sup>9</sup>

**Box 1. Antimuscarinic drugs recommended for the management of OAB**

- Darifenacin
- Fesoterodine
- Oxybutynin
- Propiverine
- Solifenacin
- Tolterodine
- Trospium

**WHY DO PATIENTS STOP DRUG THERAPY?**

The reasons why adherence and persistence with OAB therapy remain poor are often due to lack of efficacy or because of the troublesome side-effects associated with antimuscarinic drugs, such as dry mouth, constipation, blurred vision and somnolence.<sup>10</sup>

**WHAT HAPPENS TO PATIENTS WHO DISCONTINUE THERAPY?**

A recent study of 103 250 patients in North America has shown that only 5.8% continue with first-line therapy and 51.3% discontinue treatment.<sup>11</sup> A further 34.6% tend to stop and later reinstate treatment, while 5.8% switch to a second-line drug. Of those who switch therapy, 81% have been shown to discontinue a second-line drug. This concept has been described as antimuscarinic cycling, and the evidence would suggest that persistence rates with medication decrease with second- and third-line therapies, and that switching medication does not improve patient symptoms.<sup>12</sup> Consequently, it is important to try and tailor drug therapy to the individual, as the first and second opportunities with medication are the most likely to succeed.

**HOW MANY ANTIMUSCARINIC DRUGS SHOULD BE TRIED?**

The evidence suggests that patients are less likely to persist with medication after failure of first- or second-line drug therapy. Therefore, in keeping with the NICE guidelines, it would seem sensible to switch to an alternative treatment strategy following failure with two antimuscarinic agents.<sup>4</sup>

For those patients with intolerable side-effects or a contraindication to antimuscarinic therapy, mirabegron (Betmiga), a beta-3 agonist, may be a suitable alternative.<sup>13,14</sup> Conversely, for those patients with inadequate efficacy, combination therapy with an antimuscarinic and mirabegron may offer greater efficacy.<sup>15</sup> Offering an alternative medication earlier in the treatment pathway may improve persistence and adherence with medication, as well as improving patient satisfaction and cost-effectiveness.

### WHO SHOULD BE REFERRED TO SECONDARY CARE?

Patients who complain of refractory OAB symptoms or deteriorating symptoms should be referred to secondary care to consider more invasive second-line therapy. Those patients who are unable to tolerate oral therapy may also benefit from an alternative approach. Urodynamic investigations remain integral in the investigation of patients with refractory lower urinary tract symptoms, and their care should be reviewed in a local multidisciplinary meeting.<sup>4</sup>

### SHOULD SOME PATIENTS BE REFERRED DIRECTLY TO SECONDARY CARE?

The majority of women presenting with OAB will have a number of lower urinary tract symptoms, although in those women who present with complex or unusual symptoms, immediate referral to secondary care should be considered. Patients who present with 'red flag' symptoms, such as recurrent lower UTI, bladder pain or haematuria, should be referred immediately for further investigation (Box 2). In addition, patients who complain of recurrent urinary symptoms following previous investigation and management may also benefit from prompt referral.

### WHAT TREATMENT OPTIONS ARE AVAILABLE FOR REFRACTORY OAB?

Patients with refractory symptoms may benefit from more invasive therapies such as intravesical botulinum toxin A (Botox – BTX), neuromodulation, posterior tibial nerve stimulation (PTNS) or, in a small number of patients, reconstructive surgery.

#### Botulinum toxin

If the patient is willing and able to self-catheterise, NICE recommends intravesical BTX as first-line therapy for refractory symptoms.<sup>4</sup> The efficacy and safety of BTX 100u has been reported in a large, multicentre, phase 3 study of 557 OAB patients.<sup>16</sup> Overall, there was a significantly greater reduction in daily incontinence episodes with BTX compared to placebo, 22.9% of patients achieved complete continence, and there was a corresponding significant improvement in health-related quality of life. The most commonly reported adverse effect was UTI; self-catheterisation rates were 5.4%.

#### Sacral neuromodulation

In patients unable to self-catheterise, the recommended second-line therapy is sacral neuromodulation (SNM). SNM incorporates temporary test stimulation, either by percutaneous nerve evaluation (PNE) in an outpatient setting or implantation of a tined lead in theatre, which allows patients and physicians to assess efficacy over a trial period.<sup>17</sup> If this is effective, as ascertained by the treating physician in conjunction with the patient, a second procedure is undertaken where implantation of a tined lead, typically into the S3 foramen, is then connected to a pulsed generator.

SNM has been shown to be an effective treatment for OAB in more than 40 studies. While the reported success rates for subjects who received the implantation varied between 60% and 100%, an intention-to-treat (ITT) analysis in a recent systematic review revealed success rates between 21% and 48% for one-stage implantation with PNE and 75% to 80% for two-stage implantation.<sup>18</sup> A recent prospective multicentre trial reported 36-month data using the two-stage technique.<sup>19</sup> Of 340 patients who received stimulation, 272 had the permanent implant. Therapeutic success was seen in 76% at 36 months; complete continence was achieved in 43%. The most frequent adverse events reported were undesirable change in stimulation (18%),

#### Box 2: Red flag symptoms/history in OAB requiring referral

- Bladder/pelvic pain
- Haematuria
- Recurrent lower urinary tract infection
- Recurrent incontinence
- Significant voiding symptoms
- Pelvic irradiation
- Radical pelvic surgery
- Failed continence surgery
- Suspected urinary tract fistula

implant site pain (13%), lack of efficacy (6%), lead migrations (4%) and implant site infections (4%). Surgical reintervention was required in 32%.

#### Posterior tibial nerve stimulation

If neither BTX nor SNM are appropriate, then posterior tibial nerve stimulation (PTNS) may be considered as a third-line option. The mechanism of action for PTNS is through stimulation of the S3 sacral nerve plexus, using a retrograde pathway through direct stimulation of the posterior tibial nerve, accessed just above the ankle. PTNS has been shown to be a safe and effective treatment option, with objective outcome comparable to that of pharmacotherapy.<sup>20</sup> A recent systematic review and meta-analysis reported a pooled subjective success rate of 61.4% and an objective success rate of 60.6%.<sup>21</sup>

#### RECONSTRUCTIVE SURGERY

Only after considering all other conservative therapies should reconstructive surgery be discussed. This may involve an augmentation cystoplasty or urinary diversion.

#### CONCLUSIONS

OAB is a common and distressing condition that is known to have a significant effect on a patient's quality of life. The clinical diagnosis of OAB is often one of exclusion, although urodynamic investigations are helpful in those patients with refractory or unusual symptoms. The majority of patients will benefit from conservative measures in the first instance, although many will

eventually require drug therapy (see Figure 1). While antimuscarinic drugs are currently integral to the medical management of OAB, their usage is often associated with poor adherence and persistence, which may result in the cycling of medications. The evidence would suggest that this is not effective in treating patient symptoms and therefore, after the failure of two antimuscarinic drugs, an alternative approach should be adopted. For patients with intolerable adverse effects, mirabegron may offer an alternative mode of treatment, while for those patients complaining of lack of efficacy, combination therapy may be useful. In patients with OAB symptoms refractory to medical therapy, BTX offers a safe and minimally invasive technique in secondary care before considering SNM or PTNS.

### Acknowledgements

The content of this manuscript is based on a meeting of the authors hosted by Allergan Ltd. Jango Communications kindly provided editorial support.

### Declaration of interests

Dudley Robinson has worked for Astellas Pharma, Pfizer, Allergan, Ferring Pharmaceuticals and Ixaltis. Mohammed Belal has worked for Allergan and Speciality European Pharma, and has received a travel grant from Astellas Pharma. Paraskeve Granitsiotis has worked for or received travel grants from Astellas Pharma, Allergan, Pfizer, Medtronic and Speciality European Pharma. Rizwan Hamid has worked for or received grants from Allergan, Astellas Pharma, Laborie, Pfizer, Medtronic, Laborie and Wellspect Healthcare. Philip Toozs-Hobson has worked for or received grants from Astellas Pharma, Pierre Fabre Laboratories, Speciality European Pharma, Allergan and Boston Scientific. Arun Sahai has worked for or received grants from Allergan Ltd, Astellas Pharma and Pfizer.

### REFERENCES

- Haylen BT, de Ridder D, Freeman RM, *et al.* An International Urogynaecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J* 2010;21:5–26.
- Stewart WF, Corey R, Herzog AR, *et al.* Prevalence of overactive bladder in women: results from the NOBLE program. *Int Urogynaecol J* 2001;12:S66.
- Milsom I, Abrams P, Cardozo L, *et al.* How widespread are the symptoms of overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760–6.
- NICE. Urinary incontinence in women: management. Clinical guideline CG171. September 2013, updated November 2015 (<https://www.nice.org.uk/guidance/cg171>; accessed 19 June 2017).
- Moore K, Dumoulin C, Bradley C, *et al.* Adult conservative management. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence*, 5th edition. Paris: Health Publication Ltd, 2013;1101–28.
- Andersson KE, Chapple CR, Cardozo L, *et al.* Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence*, 5th edition. Paris: Health Publication Ltd, 2013;631–700.
- Yeaw J, Benner JS, Walt JG, *et al.* Comparing adherence and persistence across six chronic medication classes. *J Manag Care Pharm* 2009;15:728–40.
- Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. *Br J Obstet Gynaecol* 1997;104:988–93.
- Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int* 2012;110:1767–74.
- Benner JS, Nichol MB, Rovner ES, *et al.* Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int* 2010;105:1276–82.
- Chancellor MB, Migliaccio-Walle K, Bramley TJ, *et al.* Long term patterns of use and treatment failure with anticholinergic agents for overactive bladder. *Clin Ther* 2013;35:1744–51.
- Chancellor MB, Yehoshua A, Waweru C, *et al.* Limitations of anticholinergic cycling in patients with overactive bladder (OAB) with urinary incontinence (UI): results from the CONsequences of Treatment Refractory Overactive bladder (CONTROL) study. *Int Urol Nephrol* 2016;48:1029–36.
- Khullar V, Amarenco G, Angulo JC, *et al.* Efficacy and tolerability of mirabegron, a beta-3 adrenoceptor agonist, in patients with overactive bladder: results from a randomised European–Australian phase 3 trial. *Eur Urol* 2013;63:283–95.
- NICE. Mirabegron for treating symptoms of overactive bladder. Technology appraisal guidance TA 290. June 2013 (<https://www.nice.org.uk/guidance/ta290>; accessed 19 June 2017).
- MacDiarmid S, Al-Shukri S, Barkin J, *et al.* Mirabegron as add-on treatment to solifenacin in patients with incontinent overactive bladder and an inadequate treatment response to solifenacin monotherapy. *J Urol* 2016;196:809–18.
- Nitti V, Dmochowski R, Herschorn S, *et al.* Onabotulinumtoxin A for the treatment of patients with overactive bladder and urinary incontinence: results of a phase III randomised placebo controlled trial. *J Urol* 2013;189:2186–93.
- Schmidt RA, Senn E, Tanagho EA. Functional evaluation of sacral nerve root integrity. Report of a technique. *Urology* 1990;35:388–92.
- Monga AK, Tracey MR, Subbaroyan A. A systematic review of clinical studies of electrical stimulation for treatment of lower urinary tract dysfunction. *Int Urogynecol J* 2012;23:993–1005.
- Siegel S, Noblett K, Mangel J, *et al.* Three-year follow-up results of a prospective, multicenter study in overactive bladder subjects treated with sacral neuromodulation. *Urology* 2016;94:57–63.
- Peters KM, Macdiarmid SA, Wooldridge LS, *et al.* Randomised trial of percutaneous tibial nerve stimulation versus extended release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol* 2009;182:1055–61.
- Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. *Neurourol Urodyn* 2012;31:1206–16.