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# Guidelines

## Conjoint Urological Society of Australia and New Zealand (USANZ) and Urogynaecological Society of Australasia (UGSA) Guidelines on the management of adult non-neurogenic overactive bladder

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Due to the myriad of treatment options available and the potential increase in the number of patients afflicted with overactive bladder (OAB) who will require treatment, the Female Urology Special Advisory Group (FUSAG) of the Urological Society of Australia and New Zealand (USANZ), in conjunction with the Urogynaecological Society of Australasia (UGSA), see the need to move forward and set up management guidelines for physicians who may encounter or have a special interest in the treatment of this condition. These guidelines, by utilising and recommending evidence-based data, will hopefully assist in the diagnosis, clinical assessment, and optimisation of treatment efficacy. They are

divided into three sections: Diagnosis and Clinical Assessment, Conservative Management, and Surgical Management. These guidelines will also bring Australia and New Zealand in line with other regions of the world where guidelines have been established, such as the American Urological Association, European Association of Urology, International Consultation on Incontinence, and the National Institute for Health and Care Excellence guidelines of the UK.

### Keywords

overactive bladder, guideline, urinary incontinence, urodynamics, bladder

### Introduction

The definition of the overactive bladder syndrome (OAB) was refined by the ICS in 2008. It is characterised by urgency, with or without urgency urinary incontinence (UUI) and is often associated with frequency and nocturia, in the absence of pathological or metabolic factors that would explain these symptoms [1]. OAB presence suggests underlying detrusor overactivity (DO) but may be caused by other voiding or lower urinary tract dysfunction [1]. OAB can be classified as 'OAB-dry' when there is no UUI component in the symptomatology, or 'OAB-wet' when there is an UI component. OAB can be neurogenic in origin or non-neurogenic (idiopathic), and should not be confused with UI. Although OAB can occur at any age, these guidelines will focus on the adult population and mainly on non-neurogenic

OAB but, where relevant, will also include recommendations for its neurogenic counterpart.

### Epidemiology

OAB can affect people of all ages. Neurogenic OAB tends to be associated with suprasacral and suprapontine pathology; the more common of these include suprasacral spinal cord injury (SCI), multiple sclerosis and spina bifida disease. In the non-neurogenic group, several authors reported its prevalence as being approximately 16% in some European and American cohorts [2,3]. OAB is recognised as a common disorder affecting quality of life (QOL) worldwide. There is also a significant economic cost involved. In 2010 in Australia, the total financial cost of UI (excluding burden of disease) was estimated to be nearly \$43 billion [4].

## Clinical Relevance

Due to the potential increase in the number of patients afflicted with OAB who will require treatment, the Functional and Female Urology Special Advisory Group (FUSAG) of the USANZ, in conjunction with the Urogynaecological Society of Australasia (UGSA), see the need to move forward and establish management guidelines for physicians who may encounter or have a special interest in the treatment of this condition. These guidelines, by utilising and recommending evidence-based data, will hopefully assist in the diagnosis, clinical assessment, and optimisation of treatment efficacy. They will also bring Australia and New Zealand in line with other regions of the world where guidelines have been established, such as the AUA [5,6], European Association of Urology [7], International Consultation on Incontinence (ICI) [1], and the NICE guidelines of the UK [8].

## The Panel

The guidelines committee consists of nine members (eight urologists and one urogynaecologist), all of whom have a specialist interest in OAB management. The committee is divided into three subcommittees each specialising in a particular area: Clinical Assessment and Diagnosis, Conservative Management, and Surgical Management. A thorough literature review of the last 10 years, up to the end of 2014, was undertaken by each subcommittee to formulate a series of management recommendations, based on the Oxford Level of Evidence scale (OCEBM) [9]. Recommendations for clinical areas which do not have a sufficient evidence base may be formed by expert opinion from a consensus of the committee members. The drafting of the guidelines is supported by the executive board of both USANZ and UGSA, with no industry involvement, and with the final draft presented to, and endorsed by, the board of directors of both societies prior to submission for publication. These guidelines are a direct result of *ex gratis* time and effort put in by individual committee members.

## 1. Diagnosis and Clinical Assessment

Although there is no formal evidence, it is well accepted that history and examination is a fundamental initial step in the evaluation of a patient with OAB [10].

### 1a: History

**Level of Evidence: 4**

**Grade of Recommendation: C**

OAB symptoms that may be elicited on history include the triad of urinary urgency with or without UUI, frequency and

nocturia. Urgency with or without UUI must be present for the diagnosis of OAB [11] (Table 1).

A clear understanding of the LUTS must be established, including the rapidity of onset, duration and, in particular, the severity of the symptoms. This can be assessed by pad usage including pad weight, size, and number used, and number of UI episodes per day. A bladder diary is essential to further clarify this and is discussed in more detail later.

It is important while taking the history to include assessment of the fluid intake including the amount and type of fluids. Caffeine, present in coffee, tea, green tea and caffeinated soda can influence and exacerbate urinary urgency and frequency by various mechanisms including a direct effect within receptors of the bladder wall [12]. Artificial sweeteners present in diet drinks may influence OAB symptoms although this association is not conclusive [13]. Alcohol also plays a well-recognised role in exacerbation of symptoms.

Other urological problems may need management preceding, or concurrently, with management of the OAB. This applies to stress UI and outflow obstruction, both of which may present with mixed symptoms [14,15]. In this situation a referral to a specialist is suggested.

Neurogenic OAB can occur not only in common neurological diseases such as multiple sclerosis, Parkinson's disease, post cerebrovascular accident and spinal cord pathology but also in systemic conditions such as diabetes. It should be managed by a specialist due to the potential complexity of the condition and possible need for advanced testing such as video urodynamics [16]. OAB symptoms may be the first presentation in some neurological conditions and therefore an important component of a thorough history is evaluating for presence, or absence, of non-urological symptoms that may be neurological in origin.

Obstructive sleep apnoea is a common cause of nocturia through the effect of increased brain natriuretic peptide [17]. In this case the patient's presenting symptom may be nocturia and only by directed questioning, examination, and review of a bladder diary will the possibility of sleep apnoea be identified.

**Table 1** Symptoms/signs and conditions that require specialist referral

Symptoms	Haematuria Recurrent UTI Sterile pyuria Nocturnal Incontinence Life-long incontinence Significant obstructive symptoms Associated bowel symptoms/constipation
Signs	Neurological symptoms Over-distended bladder Neurological deficits
Surgical history	Evidence of pelvic or prostatic malignancy Past urological surgery
Medical history	Past incontinence surgery Pelvic radiation/pelvic malignancy Neurological disease

Referral to sleep studies and use of continuous positive airways pressure may be useful in reducing the symptoms.

A thorough medical history is important both for establishing other causes for the OAB symptoms, and to ensure there is no contraindication or the potential for complications with the introduction of treatment for OAB. Conditions to consider include cardiac history, in particular a prolonged QT interval, uncontrolled hypertension, narrow angle glaucoma, functional gastrointestinal pathology, myasthenia gravis, and renal and liver impairment.

It is vitally important to pay special attention to the elderly afflicted with OAB. OAB is more common with ageing [18], and this population generally has a lower physiological reserve to deal with adverse effects of treatment, as well as the clinical investigations preceding it. Elderly individuals who are at higher risk, such as those with cognitive dysfunction, weakness, reduced mobility, constipation, and glaucoma, and patients on polypharmacy, especially anticoagulants and drugs with anticholinergic effects, should be identified during the clinical assessment phase.

It is important to review the medication list of all patients. Some medications, such as diuretics, may cause increased urinary frequency, and there is a growing number of medications that have additive anticholinergic effects or interact with OAB drugs, particularly the  $\beta_3$  agonists.

### 1b: Examination

#### Level of Evidence: 4

#### Grade of Recommendation: C

General examination of the patient is important for alerting the physician to other possible mechanisms contributing to the voiding symptoms and the potential for complications related to treatment. These include obesity, cognitive state, hand coordination, and gait disturbance. A focused abdominal and pelvic examination is essential; particularly look for an over-distended bladder, pelvic mass or pelvic tenderness.

In the male, examination of the external genitalia may assist in excluding obstructive pathology. Pay particular attention to the urethral meatus, which may be stenosed, and the prostate, which should be assessed by DRE.

In the female, a vaginal examination should be performed, with particular attention to the presence of atrophic vaginitis, assessment of pelvic floor muscle strength using the Oxford grading, the presence of stress leakage with cough and valsalva, and the presence of pelvic organ prolapse (POP). Ideally, the latter two should be carried out in the upright position.

A neurological examination should be included if there is suspicion of an undiagnosed underlying neurological disorder.

A focused S2–S4 examination including sensation, anal tone and bulbocavernosus reflex may be useful.

### 1c: Investigations

#### Level of Evidence: 4

#### Grade of Recommendation: C

Initial investigations recommended include urine microscopy and culture to exclude infection, microscopic haematuria (in the absence of infection) or sterile pyuria. In the case of recurrent UTIs, microscopic haematuria or persistent sterile pyuria, consider referral to a specialist.

A bladder diary is useful in supporting the diagnosis of OAB, as well as for excluding polydipsia, nocturnal polyuria where nocturnal volume voided is >20–33% of 24 h volume, and compromised functional capacity with voids <250 mL. This should document the time, type and volume of fluid taken, urine volume voided, and leakage episodes.

Finally, a post-void residual urine volume (PVR) is important to exclude obstruction and incomplete emptying.

Three essential elements are necessary before the management pathway for OAB is followed: a negative urine test, a bladder diary consistent for OAB, and minimal PVR, in the patient with uncomplicated OAB symptoms, as elicited on history and examination.

Complicated cases, such as patients with neurological disease, presence of microscopic haematuria or who have failed conservative treatment options, may require specific tests which are generally performed at specialist level. These include renal ultrasound to check for upper tract damage, caused by the high pressures generated from the bladder, frequently seen in neurogenic overactivity. Cystoscopy is required when there is recurrent UTI, haematuria, or persistent pyuria, and for assessment of possible obstructive pathology. Cystoscopy should also be considered in the patient who is refractory to medical therapy, as patients with bladder tumours may present with urinary frequency even in the absence of microscopic haematuria. Urodynamic testing (possibly with imaging and electromyogram) is useful in those refractory to conservative medical therapy and essential in those with underlying neurological disease.

## 2. Conservative Management

### 2a. Lifestyle modifications and behavioural therapies

#### Level of Evidence: 1b – 2

#### Grade of Recommendation: B

Conservative management of OAB includes lifestyle modifications involving diet, fluid intake, and weight loss, and

behavioural and physical therapies such as bladder training (BT) and pelvic floor muscle training (PFMT).

### Lifestyle modifications

Patients should be encouraged to make lifestyle modifications.

*Reduce caffeine intake* Caffeine effects include CNS stimulation and smooth muscle relaxation. Some studies have shown that reduction in caffeine intake resulted in improvement in OAB symptoms. One randomised controlled trial (RCT) found that caffeine reduction together with BT resulted in greater reductions in urgency and frequency compared to BT alone [19]. In another study, the relationship between a decrease in the amount of dietary caffeine consumed and fewer daytime episodes of involuntary urine loss approached significance [20].

*Modify high fluid intake* A higher fluid intake may result in increased urinary frequency, worsening OAB symptoms. One study showed a 25% reduction in fluid intake reduced frequency and urgency [21]. The baseline intake of fluids must be taken into account before deciding to modify intake. There was no evidence to suggest increasing fluid intake improves urinary symptoms.

*Lose weight* One well performed study showed that a weight loss of 8% over 6 months reduced UUI episodes by 42% compared to 26% in controls [22].

### Behavioural and physical therapies

Behavioural therapies include BT and scheduled voiding, where carers initiate the decision to void. Different strategies may be used, as no single regimen has yet been proven ideal. As well as following a voiding pattern, the patient should be instructed on bladder function and fluid intake, including caffeine restriction, and bowel habits. Patients may be asked to void according to a fixed voiding schedule. Alternatively, patients may be encouraged to defer voiding until the urgency sensation settles. 'Timed voiding' is voiding initiated by the patient, while 'prompted voiding' is voiding initiated by the caregiver.

UI was improved, but not cured, by timed bladder voiding at intervals of between 2.5 and 4 h in two key RCTs, which compared BT with no intervention [23,24]. BT has been compared with other treatments for UI in a number of other RCTs. BT alone is as effective as oxybutynin, tolterodine and solifenacin in controlling UUI and nocturnal UI [25–29].

PFMT is usually used in conjunction with urge suppression techniques [23,24,30].

**Recommendations Behavioural interventions are effective for improvement of UI in women.**

**The effectiveness of BT diminishes after the treatment has ceased.**

### 2b. Medical therapy

*Antimuscarinic Medications: Oxybutynin, Tolterodine, Solifenacin, Darifenacin*

**Level of Evidence: 1a**

**Grade of Recommendation: A**

Antimuscarinic agents have been shown to work synergistically with behavioural therapy and BT [31]. There are many well-conducted RCTs looking at individual antimuscarinics as well as four systematic reviews [32–35], with the latter showing rates for improvement or cure of UUI based on short-term treatment of up to 3 months. There was no significant difference in efficacy across these agents, even when looking at immediate release (IR) formulation vs extended release (ER), which indicates that ER and IR formulations of antimuscarinics can offer similar clinical efficacy in short-term cure and improvement rates. It was also clear in these studies that patients who have more bothersome symptoms are more likely to experience symptom improvement.

For adverse effects of antimuscarinics, dry mouth is the most prevalent. It is more common with oxybutynin IR than tolterodine IR, but less than for darifenacin, 15 mg daily [34,36]. Oxybutynin ER has higher rates of dry mouth than tolterodine ER. Transdermal (TD) oxybutynin is effective in reducing UI episodes and is associated with a lower rate of dry mouth (9.6% vs 68% for oxybutynin IR, a nine times difference). The TD formulation had an overall higher rate of withdrawal due to allergic skin reaction [34]. M3-selective blockers are generally associated with fewer antimuscarinic side-effects than their non-selective counterparts; solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER [34]. In general, discontinuation rates were similar for each treatment arm in comparative RCTs, irrespective of differences in the occurrence of dry mouth.

More than half of patients will discontinue antimuscarinic agents within the first 3 months because of failure in efficacy, bothersome side-effects, and the financial burden. Many of the currently available M3-antagonists are not listed on the Pharmaceutical Benefits Scheme in Australia and patients are not subsidised. If the antimuscarinics are effective but causing significant side-effects, the clinician should try to maintain the drug therapy while offering conservative and supportive treatment. This can include oral moisturisers for dry mouth, and laxatives, a diet adequate in fibre and regular physical activity for constipation.

Concomitant behavioural modification (BT, PFMT, electrical stimulation) and antimuscarinic therapy have been shown to improve outcome parameters such as frequency, voided volume, UI and symptom inconvenience [37,38]. Behavioural treatments have also been shown to be equally efficacious as antimuscarinics in reduction of OAB symptoms. Behavioural therapies may improve UI episodes by 50–80%, and reduction has been shown in both men and women [39]. Several studies have also shown that weight loss can assist in OAB symptom improvement [22].

Care should be exercised when prescribing antimuscarinic agents in the elderly population. The National Overactive Bladder Evaluation (NOBLE) study showed that older people (aged >65 years) were disproportionately affected; >30% have OAB compared with 16.5% of the overall population [3]. Urgency and UUI in the elderly may be due to lesions in the bladder or the CNS [40]. Diagnoses such as Parkinson's disease, myasthenia gravis, dementia and Alzheimer's disease are of particular importance in the elderly as medications used to control these conditions may potentiate or reduce the effects of anticholinergics. It is important to consult the patient's treating neurologist if planning to use an antimuscarinic agent for OAB in this group. Oxybutynin IR may worsen cognitive function, with the ER formulation safer as it does not cause delirium in the short term. Solifenacin, tolterodine and darifenacin have not been demonstrated to impair cognitive function in the healthy elderly [41,42].

As the population ages, there will also be an increase in the proportion of women developing POP. Some patients with POP present with OAB symptoms, but there is poor correlation between the two. There is some data to show that repair of POP may improve OAB symptoms in up to 80% of patients, but there is also the risk that a small but significant percentage of patients (<20%) develop *de novo* OAB [43].

**Recommendations Offer behavioural treatment as well as antimuscarinic drugs for adults with UUI.**

**Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinics for UUI (<30 days).**

**The combination of BT with antimuscarinic drugs may result in greater improvement of UI.**

**Exercise caution when prescribing antimuscarinics in the elderly, especially those with a background of dementia, Alzheimer's disease, and other neurological conditions.**

*Tricyclic Antidepressants: Imipramine, Amitriptyline, Nortriptyline*

**Level of Evidence: 4**

**Grade of Recommendation: C**

There are no recent studies on the use of tricyclic antidepressants for OAB. Generally their use is reserved for patients who cannot tolerate antimuscarinic medication or in whom these medications are contraindicated. The recent availability of a  $\beta_3$  agonist, mirabegron, may see their use decrease further.

*Topical Oestrogens*

**Level of Evidence: 1b**

**Grade of Recommendation: A**

Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women. Besides improving vaginal atrophy, vaginal oestrogen therapy reduces UI and frequency and urgency in OAB [44].

**Recommendation Vaginal oestrogen therapy should be offered to postmenopausal women with UI, and vaginal atrophy.**

*Desmopressin*

**Level of Evidence: 1b**

**Grade of Recommendation: B**

An RCT found that nasal desmopressin was an effective and safe treatment in women with daytime UI [45], and there are data to support use of desmopressin to reduce nocturia in both men and women [46–49]. However, there is no published evidence reporting desmopressin cure rates for UI and no evidence comparing it with other non-drug treatments for UI [7].

Two recent systematic reviews showed that desmopressin may significantly decrease nocturnal frequency, and increased time to first void during sleep, resulting in an extended duration of the first sleep period and improved sleep quality. Dosage with 25  $\mu\text{g}$  was already sufficient in some patients to reduce nocturnal frequency. A dose of 100  $\mu\text{g}$  provided just more than an hour of additional sleep before the first void compared with placebo. Higher doses provided no significant increase in benefit [50,51].

The use of desmopressin carries a risk of developing hypertension and hyponatraemia (12%). Elderly patients started on this drug should have their blood pressure and serum sodium checked regularly, beginning in the first few days after starting treatment [52].

**Recommendation Desmopressin should be reserved for bothersome nocturnal frequency or proven nocturnal**

**polyuria on bladder diary, after other causes are excluded, in conjunction with appropriate monitoring of serum sodium and blood pressure. Lower dosages (<100 µg) are recommended on initiating the drug.**

### Mirabegron

**Level of Evidence: 1b**

**Grade of Recommendation: A**

Mirabegron is a novel  $\beta_3$  agonist which produces relaxation of the bladder smooth muscle. Animal and *in vitro* data indicate that mirabegron enhances the urine storage function by stimulating  $\beta_3$  adrenoceptors in the bladder [53].

Efficacy of mirabegron was evaluated in three 12-week RCTs and one pooled analysis [54–57]. Mirabegron at doses of 25, 50 and 100 mg resulted in significantly greater reduction in UI episodes and micturition frequency per 24 h than placebo, with no difference in the rate of adverse events. The dry rates on treatment averaged between 45 and 50% with placebo achieving rates of 35–40%. However, like antimuscarinic medications, the statistically significant difference is consistent only for improvement of UI, and not cure. A 100 mg dose has not been shown to confer additional benefit compared to 50 mg [54]. At doses of 50 and 100 mg, rates of dry mouth were lower compared to tolterodine 4 mg [58], and no different than placebo [54].

The comparative risk of QTc prolongation and raised intraocular pressure have been specifically addressed in RCTs [59,60], which showed no difference from placebo for doses up to 100 mg. In a randomised phase 3 trial, mirabegron was associated with an average rise in pulse rate of 2 beats per minute and 4% of participants withdrew due to adrenergic side-effects [61].

Mirabegron at doses of 50 and 100 mg once daily for 12 weeks in men with LUTS and BOO did not adversely affect voiding urodynamic parameters (maximum flow rate and detrusor pressure at maximum flow) compared to placebo [62]. A sub-group analysis of one of the pivotal phase 3 trials assessed the efficacy of mirabegron in treatment naïve patients and those who had received prior antimuscarinic therapy for OAB [63]. Similar improvements in frequency of daily UI episodes and micturitions were seen in all groups.

Mirabegron has also been studied in the elderly in a prospective sub-analysis of individual and pooled efficacy and tolerability data from three randomised, phase 3 trials, and of tolerability data from a 1-year safety trial. Age groups targeted were >65 and >75 years. The drug was well-tolerated in both age groups: hypertension and urinary infection were

among the most common adverse effects over 12 weeks and 1 year [64].

**Recommendations Mirabegron is effective for the improvement of UUI.**

**The  $\beta$ -mediated cardiovascular side-effects appear to be clinically insignificant.**

**Mirabegron is effective and well-tolerated in the elderly aged >65 years.**

**Offer mirabegron to people with UUI, but warn patients receiving mirabegron that the possible long-term side-effects remain uncertain.**

## 3. Surgical management

Patients who are refractory to behavioural and medical therapy, and desire additional therapy, should be evaluated by an appropriate specialist with an interest in the management of UI. Third-line treatment should be considered in the event of failure of, or intolerance to, two or more pharmacological therapies.

In refractory cases the following treatments may be offered: intradetrusor botulinum toxin-A, sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS). In the event one or more of these fail, the remaining options include augmentation cystoplasty, urinary diversion or permanent catheterisation. Indwelling catheters (transurethral or suprapubic) are not recommended as a management strategy for OAB, except as a last resort in selected patients, because of the adverse risk/benefit balance.

All patients who require complex treatment for their condition require ongoing follow-up in a specialist environment.

### 3a: Botulinum Toxin-A (Onabotulinumtoxin-A)

**Level of Evidence: 1**

**Grade of Recommendation: A**

The use of botulinum toxin-A as third-line treatment for DO and OAB symptoms has become clinically widespread. There is now substantial, high quality, clinical data to support its use with over 1900 participants in randomised, double-blind, placebo-controlled trials [65–72].

Several of these were dose-ranging studies [66–69]; however, the three most recent trials used a uniform dose. In a UK multicentre trial involving 227 women, a 200 IU dose of botulinum toxin-A produced a significant reduction in urinary frequency, urgency and leakage episodes in the treatment group compared to placebo at 6 months after

injection [70]. Complete continence was also more common after botulinum toxin-A than placebo (31% vs 12%). In a study run across 72 sites in the USA and Canada, 492 patients were randomised to receive either 100 IU botulinum toxin-A or placebo [71]. At week 12, the treatment group showed a significantly greater reduction from baseline in UI episodes, frequency and nocturia. There were also large, clinically significant, improvements in QOL domains in the botulinum toxin-A group, and voided volumes increased significantly. Complete continence occurred in 22.9% of treated patients compared with 6.5% of the placebo group.

Another phase 3 multicentre trial using 100 IU dose in 489 patients reported similar results [72]. At week 12, significant sustained reductions in daily UI episodes, frequency, urgency and nocturia were seen in botulinum toxin-A group over placebo. This was associated with significantly greater improvement in QOL scores. A recent meta-analysis [73] determined that, compared with placebo, botulinum toxin-A significantly decreased the mean number of daily UI episodes and daytime frequency while maximum cystometric capacity (MCC) and mean voided volume significantly increased. A systematic review and statistical comparison of standardised mean outcomes [74] reported that botulinum toxin-A injections in patients with OAB resulted in reductions of 29% in daily frequency, 38% in daily urgency and 59% in daily UI episodes (MCC improved by 58% and maximum detrusor pressure reduced by 29%).

Systemic adverse events are generally infrequent, mild and self-limiting [75], with the most common being uncomplicated UTI and urinary retention. In all but one smaller randomised trial [66], rates of UTI were significantly higher in the botulinum toxin-A treated group than in the placebo group (range 15.5–48.1%; 2.2–3.9 times higher). Infection risk may be dose related; one study reported UTI in 48.1% of patients receiving 200 IU compared with 36.4% of the 100 IU group [67]. A systematic review calculated the risk of UTI at 21% vs 7% in the placebo patients [74].

The risk of elevated PVRs and the need for clean intermittent self-catheterisation (CISC) is dose dependent but also varies with the criteria used to define urinary retention. Some earlier studies used a residual of 100 mL as an indication for CISC, and rates as high as 43% were reported. Recent studies have used more liberal and clinically sensible definitions, requiring patients to commence CISC with residuals >350 mL or >200 mL if symptomatic [71,72]. They reported 6.9% and 6.1% of patients, respectively, were required to perform CISC. Another study, using 200 IU, reported 16% of botulinum toxin-A treated patients commenced CISC compared with 4% of the placebo group [70]. In a statistical comparison of high level studies, the overall risk of CISC was calculated to be

12% [74]; however, QOL outcomes do not appear to be adversely affected by the need to perform CISC [76].

There is no universal agreement on injection technique, and sites used include sub-urothelial or intra-detrusor, trigone-including and trigone-sparing [77]. The few studies to date have not shown significant differences in outcome with varied injection depth [78,79] and there appears to be no increased risk of ureteric reflux with trigonal injections [78,80,81].

There is also no reported uniformity on optimal dosage, especially for patients with neurogenic OAB where doses up to 400 IU have been used. For idiopathic OAB there is more consensus and a dose of 100 IU is generally considered to provide a good compromise between efficacy and the risk of urinary retention. However, the UK NICE guidelines suggest an initial dose of 200 IU for refractory OAB symptoms unless there is particular concern over voiding dysfunction [8]. In Australia, bladder wall injections of botulinum toxin-A are approved under the Pharmaceutical Benefits Scheme in dosages of 200 IU for neurogenic DO (spina bifida, multiple sclerosis and SCI only), and 100 IU for idiopathic OAB symptoms.

**Recommendation** Patients with OAB symptoms who have failed to respond to supervised bladder retraining with lifestyle modification and who are refractory to, or intolerant of, two or more pharmacological therapies, may be offered bladder wall injections of botulinum toxin-A. Patients must be thoroughly counselled plus be willing and able to perform CISC if necessary.

### 3b (i): Sacral Neuromodulation (SNM)

**Level of Evidence: 1**

**Grade of Recommendation: A**

SNM is the most widely clinically applied, and has the most long-term safety and efficacy data, of three neuromodulation techniques. Neuromodulation works to address an imbalance of facilitatory and excitatory control systems by direct or indirect action on afferent nerves, predominantly the third sacral nerve (SNM) but in some cases the pudendal or tibial nerve. This electrical stimulation inhibits bladder activity by stimulating large diameter somatic afferent fibres, which in turn evoke a central inhibition of the micturition reflex in the spinal cord or brain.

Since the first report [82], over 100 000 implants have been placed worldwide. The technique has evolved over time, with a tined lead approach replacing the older style peripheral nerve evaluation-implant. The newer technique shows better efficacy [83] and this should be recognised when analysing available studies.



There are three systematic reviews [84–86], five RCTs [83,87–90] and 12 uncontrolled studies [91–102].

Therapeutic success is defined as a >50% improvement in symptoms such as leakage episodes or frequency episodes [103]. A recent study comparing SNM and standard medical therapy (SMT) demonstrated that SNM (70 subjects, 51 implanted) was superior to SMT (77 subjects) at 6 months with a therapeutic success rate of 61% in the SNM group and 42% in the SMT group [83]. Rates of adverse events were comparable in the groups (SNM 30.5% and SMT 27.3%) and notably the 6 month post-implant surgical intervention rate was low at two of 51 subjects with a full system implant (3.9%).

A large retrospective study with a mean follow-up of 46.88 months showed similar results [104], with about 70% of both the wet, and dry with urgency/frequency, OAB groups achieving therapeutic success, and 20% and 33%, respectively, achieving cure. Complication rates show device-related re-intervention of 41%, although this was reduced to 15% in those with the newer tined lead. Most re-interventions occurred within 2 years of implantation [104]. When studied prospectively, with a 5 year follow up, 56% of patients with OAB-wet and 40% who were dry achieved therapeutic success [95]. A 14-year experience from a single centre showed even higher success rates (84.8%) for OAB-wet [105]. One study showed that patients with OAB-wet and no urodynamically confirmed idiopathic DO can still benefit from SNM [106].

There are emerging data on the programming techniques used, such as changing the pulse rate [107].

Patient satisfaction has been studied in both short- and long-term studies. In the SNM vs SMT RCT, greater improvement in baseline OAB QOL at 6 months was found in the SNM group [83], and 90% of 207 patients with a mean follow-up of 77 months reporting being satisfied with the treatment [108]. Additionally, benefits on female sexual function scores have also been noted [109].

The ROSETTA trial [110] is an open-label RCT comparing botulinum toxin-A 200 IU and SNM for management of refractory UUI. Enrolment commenced in early 2012 and the primary outcome, effectiveness of treatment 6 months after starting therapy, will be analysed in 2015. Using a decision analysis, one group [111] concluded both techniques were reasonable strategies. In a small case series, patients who had previous botulinum toxin-A treatment for their OAB and then received SNM had good results, even with discontinuation of the botulinum toxin-A due to dissatisfaction with the therapy [112].

The choice to undertake SNM for refractory OAB needs to be carefully discussed with the patient. Willingness to modify the programming, ongoing cognitive capability to do so and the possibility of undertaking repeat procedures in up to 30% of

cases needs to be balanced against the potential symptomatic improvements in the refractory OAB group. Until more data are available, clinicians need to make decisions with their patients based on the relative merits and complications of each method as it is applied to the patient's particular situation (Expert Opinion).

MRI, except of the brain, is contraindicated after implantation and, in the event of pregnancy, it is recommended to turn off the program. SNM appears to be safe in the presence of a cardiac pacemaker [113]. SNM implantation requires more technical training than the use of botulinum toxin-A by doctors. However, SNM is a fully reversible treatment, it does not result in an elevated PVR and those patients with bowel dysfunction may receive benefits to both their symptomatology from the single treatment modality. The ICI now gives SNM for patients with faecal incontinence a grade B or C recommendation depending on the presence and magnitude of the sphincter defect [1].

The Medtronic InterStim Therapy (Medtronic, MN, USA), was approved by the TGA in 2006, and the smaller InterStim II was approved in 2007, for detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome.

**Recommendation** SNM should be considered for those patients with refractory OAB who are willing to undertake a minimally invasive surgical procedure and are motivated to work with programming techniques. It may have particular application in those patients who are unable to self-catheterise or in whom there is co-existing faecal incontinence.

3b (ii): PTNS

**Level of Evidence: 2**

**Grade of Recommendation: C**

PTNS, which was developed in the 1960s in an animal model, utilises the tibial nerve, a mixed sensory and motor nerve, for neuromodulation. As described in the previous section, this stimulation evokes a central inhibition of the micturition pathway in the spinal cord or brain. Stimulation is delivered in an outpatient setting, usually with a protocol of weekly 30 min visits for 12 weeks followed by a monthly visit for 12 months.

Three RCTs compared PTNS to sham procedure [114,115 (SUMiT)] and tolterodine [116 (OrBIT)]. Long-term follow-up studies of responders were performed for the SUMiT [117] and OrBIT trials [118]. Most patients studied had moderate to severe symptoms with baseline UI ranging from 2.2 to 9.8 episodes per day. In the SUMiT trial, moderate to marked improvement in bladder symptoms was reported in 54.5% of the PTNS group vs 20.9% of the sham group after

12 weeks of therapy. There was an improvement in the number of voids per day from 12.3 to 9.8 at 13 weeks in the PTNS group but only a reduction in 1.4 voids in the sham group [115]. UUI episodes also improved (3–0.3 per day in PTNS and 1.8–1 per day in the sham group) [115].

The other sham-controlled study [114] reported similar results when bladder volume was studied. A urodynamic study in 15 patients supports these findings, with bladder capacity increased from 197 to 252 mL after 12 weeks of PTNS therapy [119].

When compared to tolterodine in the OrBIT study [116], PTNS shows comparable results on assessment of bladder diary and UI episodes but, on subjective assessment, patients expressed a clear preference for PTNS. A meta-analysis confirmed this [120], and demonstrated a superior side-effect profile for PTNS.

There are minimal risks associated with PTNS. In SUMiT [115] and OrBIT [116], 12% of patients in the PTNS group reported bruising and bleeding at the needle site, and tingling and mild pain. Patients in the longer term follow-up of OrBIT report durability of results as long as the treatment is continued, with the mean time between treatments of 21 days [118].

PTNS is labour intensive for both physician and patient, and the results do not continue once the treatment is ceased. In Australia, a commercially available device with disposable needles has Therapeutic Goods Administration approval but is not reimbursed. A course of treatment would cost approximately \$800.

**Recommendation** PTNS may be useful in a moderately severe baseline group who are unsuitable for botulinum toxin-A or SNM for medical reasons or due to concerns about the side-effect profile of these treatments.

### 3c: SALVAGE OPTIONS

#### Augmentation Cystoplasty (AC)

**Level of evidence: 3 – Retrospective comparative studies only**

**Grade of recommendation: C**

Since the advent of botulinum toxin-A and neuromodulation, the indication to perform an AC to manage DO is much more limited. In this operation, a detubularised bowel segment, most commonly ileum, is grafted into the bivalved bladder wall. AC aims to improve functional bladder capacity, disrupt involuntary detrusor contraction and increase bladder compliance. There is no difference between bivalving the bladder sagittally and coronally [121].

Most of the literature on the use of AC is in neurogenic bladder dysfunction rather than non-neurogenic, especially in the management of the drug-refractory suprasacral neurological lesion which classically causes DO, reduced bladder compliance and detrusor-sphincter dyssynergia. Although there are no RCT data comparing AC with other treatment modalities for patients with OAB-wet, there are case series and retrospective comparative studies with varying duration of follow-up to 2003, but nothing since [122–124]. High satisfaction rates and improvement in urodynamic parameters (functional capacity, storage pressures and VUR) were reported in 32 patients with SCI [125]. Good outcomes were also reported in the antimuscarinic-refractory multiple sclerosis patient [126].

A group from the UK commented that although the last 10 years has witnessed a reduction in the total number of bladder reconstructive procedures in their country, these are essentially safe and effective, with long-term clinical and functional follow-up being mandatory [127]. For the non-neurogenic OAB cases, the causes could be idiopathic, or secondary to previous partial cystectomy, ageing, and pelvic irradiation. There are no studies comparing success rates between neurogenic and non-neurogenic patients in AC, but generally speaking results for the latter seem to be poorer (58% improved) than the former (90% improved) [7]. There is a small risk of malignancy associated with AC [128]. At the present time, due to the wider availability and high efficacy of pharmacological treatment as well as the advent of botulinum toxin-A and possibly neuromodulation, with or without CISC, AC is rarely indicated.

#### Detrusor Myomectomy

**Level of evidence: 3 Retrospective comparative studies only**

**Grade of recommendation: C**

Detrusor myomectomy is a rarely performed operation whereby the part of the detrusor musculature is separated and removed from the underlying mucosa. This is most commonly performed on the bladder dome due to ease of access. A 'pseudodiverticulum' is then developed in the hope of increasing bladder functional capacity, reducing storage pressures and improving urodynamic parameters and overall QOL. It was initially described in children [129].

A non-randomised study comparing AC to detrusor myomectomy initially showed lower short-time complication rates [130] but further follow-up revealed significant fibrosis of the pseudodiverticulum, which later led to the demise of this technique. Complications may include spontaneous bladder rupture and sepsis. There is a paucity of data regarding detrusor myomectomy; while short-term results may support detrusor myomectomy over enterocystoplasty

[130], studies with longer follow-up (about 6 years) reported poor urodynamic and clinical outcomes. Some authors suggest that this technique be discouraged in favour of enterocystoplasty [131].

## Urinary Diversion

**Level of evidence: 5 (Expert opinion)**

**Grade of recommendation: C**

Permanent ileal or colonic urinary conduits are very rarely indicated for refractory OAB symptoms. This indication is not to be confused with that of a devastated outlet with very poor urethral or rhabdosphincter function, such as the patient with severe post-prostatectomy UI after salvage radiotherapy with recurrent bladder neck stenosis. There is currently no evidence on the use of urinary diversion in this refractory OAB population, especially in non-neurogenic patients [121].

## Permanent Catheterisation and Need for Cystoscopic Surveillance

### Permanent Catheterisation

**Level of evidence: 5 (Expert opinion)**

**Grade of recommendation: C**

The use of a permanent catheter, either urethral or suprapubic, in the definitive management of OAB is not recommended. There are however specific patient populations whereby this option may be considered appropriate. The two more common situations would be: (i) in the frail elderly who is not physically fit or cognitively suitable to be managed with either pharmacological or surgical options; (ii) in neurologically impaired patients who are not able to tolerate medications or surgical options to maximise storage, and unable to self-catheterise or undergo urinary diversion to maximise drainage. Provided the upper urinary tract is protected, management with pads, collecting devices, or absorptive undergarments should be tried before insertion of permanent indwelling catheters due to the risk of catheter-associated infections, blockages, urethral erosion, stone formation, and dysplastic and neoplastic changes to the urothelium [5]. Suprapubic catheters are easier to manage than urethral catheters, which may also lead to urethral erosion.

### Need for Cystoscopic Surveillance

**Level of evidence: 3 (Systematic review of level 3 studies)**

**Grade of recommendation: C**

Several retrospective reviews concluded regular cystoscopy should be performed in patients with permanent catheters [132,133]. One group recommend cystoscopy every 12–24 months to exclude squamous dysplasia and malignant change, starting 2 years after catheter placement [134],

although others have proposed starting at 10 years [135]. In a study of bladder malignancies in the SCI population, 32 patients were identified with bladder cancer out of 1319 patients seen between 1983 and 2007 [136]. Of these, 47% were squamous cell cancer and 31% TCC and, where the method of detection was known, 42% were found on screening cystoscopy. Interestingly, >50% of the patients did not have an indwelling catheter, suggesting that the neurogenic bladder, and not the indwelling catheter, may be the risk factor for bladder cancer. Urologists should be vigilant in the long-term screening of all patients with SCI for bladder cancer and not just those with indwelling catheters.

**Recommendation AC, detrusor myomectomy, urinary diversion and permanent catheterisation are not recommended as a management strategy for OAB, except as a last resort in selected patients, because of the adverse risk/benefit balance.**

**Long-term cystoscopic surveillance for bladder cancer in neurogenic bladder patients with permanent catheterisation may be of benefit.**

**All patients who require complex treatment for their condition require ongoing follow-up in a specialist environment.**

## Conclusion

These guidelines were formulated to assist in the diagnosis, clinical assessment, and optimisation of treatment efficacy in patients with OAB. They should not be taken as absolutes, but rather as strategies for best practice as undertaken in Australia. Physicians should always consider individual patients' specific needs when considering treatment options.

The guidelines are a living document. It is recognised that research is ongoing in this area and, as medical knowledge expands and technology advances, treatment recommendations may change. It is envisaged that these guidelines will be reviewed and updated, where necessary, at regular intervals (currently proposed at 2–3 years).

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## Conflicts of Interest

Associate Professor Tse reports personal fees from American Medical Systems, personal fees from Allergan, personal fees from Astellas, outside the submitted work.

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Abbreviations: BT, bladder training; CISC, clean intermittent self-catheterisation; DO, detrusor overactivity; ER, extended release; FUSAG, Female Urology Special Advisory Group; IR, immediate release; MCC, maximum cystometric capacity; OAB, overactive bladder; PFMT, pelvic floor muscle training; POP, pelvic organ prolapse; PVR, post-void residual urine volume; QOL, quality of life; RCT, randomised controlled trial; SCI, spinal cord injury; SMT, standard medical therapy; TD, transdermal; UGSA, Urogynaecological Society of Australasia; (U)UI, (urge) urinary incontinence.