UROLOGICAL SOCIETY OF AUSTRALIA AND NEW ZEALAND

UGSA

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

Authors

Vincent Tse, Clinical Associate Professor, Concord Hospital, University of Sydney, Australia
Jennifer King, Pelvic Floor Unit, Westmead Hospital, University of Sydney, Australia
Caroline Dowling, Royal Melbourne Hospital, University of Melbourne, Australia
Sharon English, Christchurch Pubic Hospital, New Zealand
Katherine Gray, Brisbane Urology Clinic, Queensland, Australia
Richard Millard, Prince of Wales Hospital, University of New South Wales, Australia
Helen O'Connell, Professor of Surgery, University of Melbourne, Australia
Samantha Pillay, Calvary Hospital, North Adelaide, Australia
Jeffrey Thavaseelan, Fiona Stanley Hospital, Perth, Australia

Corresponding Author

Dr Vincent Tse, MB MS FRACS (Urol)

Clinical Associate Professor, Department of Urology
Suite 101, Concord Hospital Medical Centre, Hospital Rd., Concord, NSW 2139, AUSTRALIA
Tel : +612 9767 8334 Fax : + 612 9767 8331 Email : vwmtse@gmail.com

Keywords

Overactive Bladder, Guideline, Incontinence, Urodynamics, Bladder

Section One – Diagnosis and Clinical Assessment

Section Two – Conservative Management

Section Three – Surgical Management

INTRODUCTION

The definition of the overactive bladder syndrome (OAB) was refined by the International Continence Society (ICS) in 2008. It is characterised by urgency, with or without urge incontinence, and is often associated with frequency and nocturia, in the absence of pathologic 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 urge incontinence component in the symptomatology, or 'OAB-wet' when there is an incontinence component. OAB can be neurogenic in origin or non-neurogenic (idiopathic), and should not be confused with incontinence. 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 incontinence (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 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 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 [5,6], European Association of Urology [7], International Consultation on Incontinence (ICI)[1], and the NICE guidelines of the United Kingdom [8].

The Panel

The guidelines committee consists of nine members (8 urologists and 1 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.

SECTION ONE

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 urgency incontinence, frequency and nocturia. Urgency with or without urgency incontinence must be present for the diagnosis of OAB [11].

A clear understanding of the lower urinary tract symptom 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, pad size, number of pads used, and number of urinary incontinence 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 overactive 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 overactive bladder. This applies to stress urinary incontinence 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.

Table 1 includes “red flag” symptoms or signs and conditions that necessitate referral to a specialist.

Table 1. Symptoms/Signs and Conditions that Require Specialist Referral

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

Obstructive sleep apnea 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 apnea be identified. Referral to sleep studies and use of continuous positive airways pressure (CPAP) 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, 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 digital rectal examination.

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 hematuria (in the absence of infection) or sterile pyuria. In the case of *recurrent* UTIs, microscopic hematuria 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 hour 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 (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 hematuria 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, hematuria, 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 hematuria. Urodynamic testing (possibly with imaging and electromyogram) is useful in those refractory to conservative medical therapy and essential in those with underlying neurological disease.

SECTION TWO

Conservative Management

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 central nervous system (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 urge urinary incontinence (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 since 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.

Urinary incontinence (UI) was improved, but not cured, by timed bladder voiding at intervals of between 2.5 and 4 hours in 2 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 incontinence [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.

Medical Therapy

Antimuscarinic Medications

oxybutynin, solifenacin, tolterodine, 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 versus 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.

In terms of 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 incontinence episodes and is associated with a lower rate of dry mouth (9.6% versus 68% for oxybutynin IR, a 9 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 (PBS) 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, incontinence 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 incontinence episodes by 50-80%, and reduction has been shown in both men and women [39]. Several studies have also demonstrated that weight loss can assist in OAB symptom improvement [22].

Care should be exercised when prescribing antimuscarinic agents in the elderly population. The NOBLE study showed that older people (>65 years) were disproportionately affected; over 30% have OAB

compared with 16.5% of the overall population [3]. Urgency and urgency incontinence in the elderly may be due to lesions in the bladder or the CNS [40]. Diagnoses such as Parkinson's disease, 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 prolapse 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 incontinence [45], and there is 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 mcg was already sufficient in some patients to reduce nocturnal frequency. A dose of 100 mcg 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 mcg) 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 incontinence episodes and micturition frequency per 24 hours 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 to 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 mg and 100 mg once daily for 12 weeks in men with lower urinary tract symptoms and bladder outlet obstruction (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 incontinence 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 years 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 over 65 years of age.

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

SECTION THREE

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 incontinence. 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 post-injection [70]. Complete continence was also more common after botulinum toxin-A than placebo (31% versus 12%). In a study run across 72 sites in the US 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 incontinence 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 incontinence 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 incontinence 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 OAB patients resulted in reductions of 29% in daily frequency, 38% in daily urgency and 59% in daily incontinence 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% to 48.1%; 2.2 to 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% versus 7% in the placebo patients [74].

The risk of elevated PVR urine volumes 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 neurogenic OAB patients 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 PBS 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

Level of Evidence: 1

Grade of Recommendation: A

Sacral neuromodulation (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 posterior 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], 5 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 2/51 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 approximately 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 proven idiopathic DO can still benefit from SNM [106].

There is 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 versus 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 period 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 is available, clinicians need to make decisions with their patients based on the relative merits and complications of each modality as it is applied to the patient's particular situation. (Expert Opinion).

Magnetic resonance imaging, 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 residual volume and those patients with bowel dysfunction may receive benefits to both their symptomatologies 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): Percutaneous Tibial Nerve Stimulation

Level of Evidence: 2

Grade of Recommendation: C

PTNS, which was developed in the 1960s in an animal model, utilises the posterior 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 minute 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 incontinence 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 versus 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]. Urge incontinence episodes also improved (3 to 0.3 per day in PTNS and 1.8 to 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 mL 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 incontinence 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 TGA 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

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 augmentation cystoplasty (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 vesicoureteric reflux) were reported in 32 SCI patients [125]. Good outcomes were also reported in the antimuscarinic-refractory multiple sclerosis patient [126].

A group from the United Kingdom 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 (DM) 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 DM 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 DM; while short term results may support DM 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 incontinence 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 : (1) in the frail elderly who is not physically fit or cognitively suitable to be managed with either pharmacological or surgical options; (2) 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: B

Several retrospective reviews concluded regular cystoscopy should be performed in patients with permanent catheters [132,133]. One group recommend cystoscopy every 12 to 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 % transitional cell carcinoma and, where the method of detection was known, 42% were found on screening cystoscopy. Interestingly, more than 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, DM, 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 screening of all patients with SCI for bladder cancer is recommended.
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).

ACKNOWLEDGEMENTS

The authors would like to thank Anne Norgrove for her assistance with editing the draft.

REFERENCES:

1. Abrams P, Andersson KE, Birder L et al. Fourth international consultation on incontinence recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn 2010; 29(1): 213-40
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001; 87(9):760-766
3. Stewart WF, Van Rooyen JB, Cundiff GW et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003; 20(6): 327-336

4. Deloitte Access Economics. The economic impact of incontinence in Australia. Continence Foundation of Australia. 2011 (Accessed online at: http://www.continence.org.au/data/files/Access_economics_report/dae_incontinence_report__19_april_2011.pdf
5. Gormley EA, Lightner DJ, Burgio KL et al. Diagnosis and treatment of overactive bladder (nonneurogenic) in adults: AUA/SUFU guideline. J Urol 2012 Dec; 188(6 Suppl): 2455-63.
6. Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (nonneurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015 Jan 23 doi: 10.1016/j.juro.2015.01.087. [Epub ahead of print]
7. Lucas MG, Bedretdinova D, Bosch JLHR et al. Guidelines on Urinary Incontinence. Update April 2014. European Association of Urology 2014. Accessed online at http://uroweb.org/wp-content/uploads/20-Urinary-Incontinence_LR.pdf
8. National Institute for Health and Care Excellence. Urinary Incontinence: the management of urinary incontinence in women. Clinical guideline 171. Issued September 2013. Last modified January 2015. Available at: www.nice.org.uk/guidance/cg171
9. Oxford Centre for Evidence-Based Medicine (OCEBM). Levels of evidence. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
10. Nambiar A, Lucas M. Chapter 4: Guidelines for the diagnosis and treatment of overactive bladder (OAB) and neurogenic detrusor overactivity (NDO). Neurourol Urodyn. 2014 Jul 2;33 Suppl 3:S21–5.
11. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61(1):3749.
12. Jura YH, Townsend MK, Curhan GC, Resnick NM, Grodstein F. Caffeine intake, and the risk of stress, urgency and mixed urinary incontinence. J Urol. 2011 May; 185(5): 1775–80.
13. Maserejian NN, Wager CG, Giovannucci EL, Curto TM, McVary KT, McKinlay JB. Intake of caffeinated, carbonated, or citrus beverage types and development of lower urinary tract symptoms in men and women. Am J Epidemiol. 2013 Jun 6; 177(12): 1399–410.
14. Minassian VA, Sun H, Yan XS, Clarke DN, Stewart WF. The interaction of stress and urgency urinary incontinence and its effect on quality of life. Int Urogynecol J. 2015 Feb; 26(2): 269–76.
15. Chung DE, Sandhu JS. Overactive bladder and outlet obstruction in men. Curr Urol Rep. 2011 Feb 2; 12(1): 77–85
16. Danforth TL, Ginsberg DA. Neurogenic lower urinary tract dysfunction: how, when, and with which patients do we use urodynamics? Urol Clin North Am. 2014 Aug 5; 41(3): 445–52, ix.
17. Hoshiyama F, Hirayama A, Tanaka M et al. The impact of obstructive sleep apnea syndrome on nocturnal urine production in older men with nocturia. Urology. 2014 Oct 3; 84(4): 892–6.
18. Sexton CC, Coyne KS, Thompson C, Bavendam T, Chen CI, Markland A. Prevalence and effect on health-related quality of life of overactive bladder in older americans: results from the epidemiology of lower urinary tract symptoms study. J Am Geriatr Soc. 2011 Aug 1; 59(8): 1465–70.
19. Bryant CM, Dowell CJ, Fairbrother G. Caffeine reduction education to improve urinary symptoms. Br J Nurs 2002 Apr 25-May 8; 11(8): 560-5
20. Tomlinson BU, Dougherty MC, Pendergast JF, Boyington AR, Coffman MA, Pickens SM. Dietary caffeine, fluid intake and urinary incontinence in older rural women. Int Urogynecol J Pelvic Floor Dysfunct 1999; 10(1): 2-8.
21. Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake? BJU Intl 2008; 102(1): 62-6

22. Subak LL, Wing R, West DS et al. Weight loss to treat urinary incontinence in overweight and obese women. NEJM 2009; 360(5): 481-490
23. Fantl JA, Wyman JF, McClish DK et al. Efficacy of bladder training in older women with urinary incontinence. JAMA 1991 Feb 6; 265(5): 609-13.
24. Jarvis GJ, Millar DR. Controlled trial of bladder drill for detrusor instability. Br Med J 1980 Nov 15; 281(6251): 1322-3.
25. Colombo M, Zanetta G, Scalambrino S, Milani R. Oxybutynin and bladder training in the management of female urinary urge incontinence: a randomized study. Int Urogynecol J 1995; 6(2): 63-7.
26. Burgio KL, Goode PS, Richter HE, Markland AD, Johnson TM 2nd, Redden DT. Combined behavioral and individualized drug therapy versus individualized drug therapy alone for urge urinary incontinence in women. J Urol 2010 Aug; 184(2): 598-603.
27. Fitzgerald MP, Lemack G, Wheeler T, Litman HJ; Urinary Incontinence Treatment Network. Nocturia, nocturnal incontinence prevalence, and response to anticholinergic and behavioral therapy. Int Urogynecol J Pelvic Floor Dysfunct 2008 Nov; 19(11): 1545-50.
28. Goode PS, Burgio KL, Locher JJ et al. Effect of behavioral training with or without pelvic floor electrical stimulation on stress incontinence in women: a randomized controlled trial. JAMA 2003 Jul 16; 290(3): 345-52.
29. Mattiasson A, Masala A, Morton R, Bolodeoku J; SOLAR Study Group. Efficacy of simplified bladder training in patients with overactive bladder receiving a solifenacin flexible-dose regimen: results from a randomized study. BJU Int 2010; 105(8): 1126-35
30. Sherburn M, Bird M, Carey M, Bo K, Galea MP. Incontinence improves in older women after intensive pelvic floor muscle training: an assessor-blinded randomized controlled trial. Neurourol Urodyn 2011; 30(3): 317-24
31. Alhasso AA, McKinlay J, Patrick K, Stewart L. Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Cochrane Database Syst Rev 2006, Issue 4. Art. No.: CD003193.
32. Chapple CR, Khullar V, Gabriel Z, Dooley JA. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. Eur Urol 2005 Jul; 48(1): 5-26.
33. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008; 54(3): 543-62.
34. McDonagh MS, Selover D, Santa J, Thakurta S. Drug class review: agents for overactive bladder. Final report. Update 4. Portland, Oregon: Oregon Health & Science University, March 2009.
35. Shamliyan TA, Kane RL, Wyman J, Wilt TJ. Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. Ann Intern Med 2008 Mar 18; 148(6):459-73.
36. Novara G. Galfano A, Secco S et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol 2008 Oct; 54(4): 740-63.
37. Matthiasson A, Blaakaer J, Hoye K, Wein AJ; Tolterodeine Scandinavian Study Group. Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. BJUI 2003; 91(1): 54-60
38. Burgio KL, Kraus SR, Menefee S et al. Behavioural therapy to enable women with urge incontinence to discontinue drug treatment. Ann Intern Med 2008; 149(3): 161-9
39. Kaya S, Akbayrak T, Baksac S. Comparison of different treatment protocols in the treatment of idiopathic detrusor overactivity : a randomized controlled trial. Clin Rehabil 2011; 25(4): 327-38
40. Tadic SD, Griffiths D, Murrin A, Schaefer W, Aizenstein HJ, Resnick NM. Brain activity during bladder filling is related to white matter structural changes in older women with urinary incontinence. Neuroimage 2010; 51(4): 1294-1302

41. Wagg A, Wyndaele JJ, Sieber P. Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. Am J Geriatr Pharmacother 2006; Mar; 4(1): 14-24
42. Chapple C, Du Beau C, Ebinger U, Rekeda L, Viegas A. Darifenacin treatment of patients > 65 years with overactive bladder: results of a randomized, controlled, 12 week trial. Curr Med Res Opin 2007; 23(10): 2347-58.
43. Menchen LC, Smith AL. Overactive bladder prevalence after surgery for pelvic organ prolapse. Current Bladder Dysfunction Reports 2012; 7(1): 19-26
44. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogen therapy for urinary incontinence in post- menopausal women. Cochrane Database Syst Rev. 2012a, Issue 10. Art. No.: CD001405
45. Robinson D, Cardozo L, Akeson M, Hvistendahl G, Riis A, Norgaard JP. Antidiuresis: a new concept in managing female daytime urinary incontinence. BJU Int. 2004 May; 93(7): 996-1000.
46. Lose G, Mattiasson A, Walter S et al. Clinical experiences with desmopressin for long-term treatment of nocturia. J Urol 2004; 172(3): 1021-5
47. van Kerrebroek P, Rezapour M, Cortesse A, Thuroff J, Riis A, Norgaard JP. Desmopressin in the treatment of nocturia: a double-blind, placebo controlled study. Eur Urol 2007; 52: 221-229
48. Weiss J, Zinner N, Klein B, Norgaard JP. Desmopressin orally disintegrating tablet effectively reduces nocturia: results of a randomized, double-blind, placebo-controlled trial. Neurourol Urodyn 2012; 31: 441-447
49. Sand PK, Dmochowski RR, Reddy J, van der Meulen EA. Efficacy and safety of low dose desmopressin orally disintegrating tablet in women with nocturia: results of a multicentre, randomized, double-blind, placebo-controlled, parallel group study. J Urol Sep 2013; 190(3): 958-64
50. Zong H, Yang C, Peng X, Zhang Y. Efficacy and safety of desmopressin for treatment of nocturia: a systematic review and meta-analysis of double-blinded trials. Int Urol Nephrol 2012 Apr; 44(2): 377-384
51. Ebell MH, Radke T, Gardner J. A systematic review of the efficacy and safety of desmopressin for nocturia in adults. J Urol 2014 Sep; 192(3): 829-35
52. Hashim H, Malmberg L, Graugaard-Jensen C, Abrams P. Desmopressin, as a “designer-drug,” in the treatment of overactive bladder syndrome. Neurourol Urodyn. 2009; 28(1): 40-6
53. Betmiga. TGA-approved Product Information. Astellas Pharma Australia Pty Ltd. Date of most recent amendment: 6 January 2015
54. Khullar V, Amarenco G, Angulo JC et al. Efficacy and tolerability of mirabegron, a beta3-adrenoceptor agonist, in patients with overactive bladder: Results from a randomised European-Australian phase 3 trial. Eur Urol 2013a Feb; 63(2): 283-95.
55. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013a Apr; 189(4): 1388-95.
56. Herschorn S, Barkin J, Castro-Diaz D et al. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β-adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology. 2013 Aug; 82(2): 313-20.
57. Nitti VW, Khullar V, van Kerrebroeck P et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. Int J Clin Pract. 2013b Jul; 67(7): 619-32.
58. Chapple CR, Kaplan SA, Mitcheson D et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta3-adrenoceptor agonist, in overactive bladder. Eur Urol 2013a Feb: 63(2): 296-305
59. Malik M, van Gelderen EM, Lee JH et al. Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study. Clin Pharmacol Ther. 2012 Dec; 92(6): 696-706.

60. Martin N, Lewis RA, Vogel R, Sheth N, Sargent B, Swearingen D. Randomised, double-blind, placebo-controlled study to assess the ocular safety of mirabegron in normotensive IOP research subjects. Eur Urol 2012; Suppl 11(2): e686 (Abstr)
61. Sacco E, Bientinesi R. Mirabegron : A review of recent data and its prospects in the management of overactive bladder. Ther Adv Urol 2012; 4(6) : 315-324
62. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and Safety of the beta3-Adrenoceptor Agonist Mirabegron in Males with Lower Urinary Tract Symptoms and Bladder Outlet Obstruction. J Urol 2013c Oct; 190(4): 1320-7.
63. Khullar V, Cambronero J, Angulo J et al. Efficacy of mirabegron in patients with and without prior antimuscarinic therapy for overactive bladder: a post hoc analysis of a randomized European- Australian Phase 3 trial. BMC Urol 2013b Sep 18; 13: 45.
64. Wagg A, Cardozo L, Nitti VW et al. The efficacy and tolerability of the beta-3 adrenoreceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients. Age Ageing 2014; 43(5): 666-75
65. Sahai A, Khan SK, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomised, double-blind, placebo controlled trial. J Urol 2007; 177: 2231-2236
66. Flynn M, Amundsen C, Perevich MA, Liu F, Webster GD. Outcome of a randomised, double-blind, placebo controlled trial of botulinum toxin-A for refractory overactive bladder. J Urol 2009; 181: 2608-2615.
67. Dmochowski R, Chapple C, Nitti V et al. Efficacy and safety of onabotulinum toxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomised, dose ranging trial. J Urol 2010; 184: 2416-2422
68. Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinum toxinA in a randomised, placebo controlled, dose-finding study in idiopathic overactive bladder. Neurourol Urodynam 2011; 30: 556-562
69. Denys P, Le Normand L, Ghout I et al. Efficacy and safety of low doses of onabotulinum toxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double -blind, randomised, placebo controlled dose-ranging study. Eur Urol 2012; 61: 520-529
70. Tincello D, Kenyon S, Abrams K et al. Botulinum toxin A versus placebo for refractory detrusor overactivity in women: a randomised blinded placebo controlled trial of 240 women (the RELAX study). Eur Urol 2012; 62: 507-514
71. Nitti V, Dmochowski R, Herschorn S et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomised, placebo controlled trial. J Urol 2013d;189:2186-2193
72. Chapple C, Sievert K-D, MacDiarmid S et al. OnabotulinumtoxinA 100U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo controlled trial. Eur Urol 2013b; 64: 249-256
73. Cui Y, Wang L, Liu L et al. Botulinum toxin-A injections for idiopathic overactive bladder; a systematic review and meta-analysis. Urol Int 2013; 91(4): 429-38
74. Mangera A, Apostolidis A, Andersson KE et al. An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. Eur Urol 2014; 65(5): 981-990
75. Bauer R, Gratze C, Roosen A et al. Patient reported side-effects of intradetrusor botulinum toxin A for idiopathic overactive bladder syndrome. Urol Int 2011; 86(1): 68-72

76. Kessler T, Khan S, Panicker J, Roosen A, Elneil S, Fowler CJ. Clean intermittent self-catheterisation after botulinum neurotoxin type A injections: short-term effect on quality of life. Obstet Gynecol 2009; 113(5): 1046-51
77. Karsenty G, Baverstock R, Carlson K et al. Technical aspects of botulinum toxin type A injection in the bladder to treat urinary incontinence; reviewing the procedure. Int J Clin Pract 2014; 68(6): 731-742
78. Manecksha RP, Cullen IM, Ahmad S et al. Prospective randomised controlled trial comparing trigone-sparing versus trigone-including intra-detrusor injection of abobotulinum toxinA for refractory idiopathic detrusor overactivity. Eur Urol 2012; 61(5): 928-935
79. Krhut J, Samal V, Nemec D, Zvara P. Intradetrusor versus sub-urothelial onabotulinum toxin A for neurogenic detrusor overactivity: a pilot study. Spinal Cord 2012; 50(12): 904-907
80. Alloussi SH, Lang C, Eichel R et al. Videourodynamic changes of botulinum toxin A in patients with neurogenic bladder dysfunction and idiopathic detrusor overactivity refractory to drug treatment. World J Urol 2012; 30(3): 367-373
81. Kuo HC. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to anti-muscarinics. Neurourol Urodynam 2011; 30(7): 1242-1248
82. Schmidt RA, Senn E, Tanagho EA. Functional evaluation of sacral nerve root integrity. Report of a technique. Urology 1990; 35: 388-392
83. Siegel S, Noblett K, Mangel J et al. Results of a prospective, randomized, multicentre study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn. 2015; 34(3): 224-30
84. Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. J Urol 2006; 175 (3 Pt 1): 835–841.
85. Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. Cochrane Database Syst Rev 2009; Issue 2. Art. No.: CD004202.
86. Siddiqui NY, Wu JM, Amundsen CL. Efficacy and adverse events of sacral nerve stimulation for overactive bladder: a systematic review. Neurourol Urodyn 2010; (29 Suppl 1): S18–S23.
87. Weil EH, Ruiz-Cerda JL, Eerdmans PH, Janknegt RA. Sacral root neuromodulation in the treatment of refractory urinary urge incontinence: a prospective randomized clinical trial. Eur Urol 2000; 37(2):161–171.
88. Schmidt RA, Jonas U, Oleson KA et al. Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group. J Urol 1999; 162(2): 352–357.
89. Everaert K, Kerckhaert W, Caluwaerts H et al. A prospective randomized trial comparing the 1-stage with the 2-stage implantation of a pulse generator in patients with pelvic floor dysfunction selected for sacral nerve stimulation. Eur Urol 2004; 45(5): 649–654.
90. Hassouna MM, Siegel SW, Nyeholt AA et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. J Urol 2000; 163(6): 1849–1854.
91. Spinelli M, Bertapelle P, Cappellano F et al. Chronic sacral neuromodulation in patients with lower urinary tract symptoms: results from a national register. J Urol 2001; 166(2): 541–545.
92. Kessler TM, Buchser E, Meyer S et al. Sacral neuromodulation for refractory lower urinary tract dysfunction: results of a nationwide registry in Switzerland. Eur Urol 2007; 51(5): 1357–1363.
93. Aboseif S, Tamaddon K, Chalfin S, Freedman S, Kaptein J. Sacral neuromodulation as an effective treatment for refractory pelvic floor dysfunction. Urology 2002; 60(1): 52–56.
94. Siegel SW, Catanzaro F, Dijkema HE et al. Long-term results of a multicentre study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. Urology 2000; 56 (6 Suppl 1): 87–91.

95. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol 2007; 178(5): 2029–2034.
96. Janknegt RA, Hassouna MM, Siegel SW et al. Long-term effectiveness of sacral nerve stimulation for refractory urge incontinence. Eur Urol 2001; 39(1): 101–106.
97. Sutherland SE, Lavers A, Carlson A, Holtz C, Kesha J, Siegel SW. Sacral nerve stimulation for voiding dysfunction: one institution's 11-year experience. Neurourol Urodyn 2007; 26(1): 19–28
98. Amundsen CL, Romero AA, Jamison MG, Webster GD. Sacral neuromodulation for intractable urge incontinence: are there factors associated with cure? Urology 2005; 66(4): 746–750.
99. Daniels DH, Powell CR, Braasch MR, Kreder KJ. Sacral neuromodulation in diabetic patients: success and complications in the treatment of voiding dysfunction. Neurourol Urodyn 2010; 29(4): 578–581.
100. Marcelissen TA, Leong RK, de Bie RA, van Kerrebroeck PE, de Wachter SG. Long-term results of sacral neuromodulation with the tined lead procedure. J Urol 2010; 184(5): 1997– 2000.
101. Groenendijk PM, Lycklama á Nyeholt AA, Heesakkers JP et al. Urodynamic evaluation of sacral neuromodulation for urge urinary incontinence. BJU Int 2008; 101(3): 325–329.
102. Cappellano F, Bertapelle P, Spinelli M et al. Quality of life assessment in patients who undergo sacral neuromodulation implantation for urge incontinence: An additional tool for evaluating outcome. J Urol 2001; 166(6): 2277–2280.
103. Rashid TG, Ockrim JL. Male incontinence: onabotulinum toxin A and sacral nerve stimulation. Curr Opin Urol 2013; 23(6): 545-51
104. Peeters K, Sahai A, De Ridder D, Van Der Aa F. Long-term follow-up of sacral neuromodulation for lower urinary tract dysfunction. BJU Int. 2014 May; 113(5): 789-94
105. Al-Zahrani AA, Elzayat EA, Gajewski JB. Long term outcome and surgical interventions after sacral neuromodulation implant for lower urinary tract symptoms: 14 year experience at 1 centre. J Urol 2011; 185(3): 981-6
106. South MMT, Romero AA, Jamison MG, Webster GD, Amundsen CL. Detrusor overactivity does not predict outcome of SNM test stimulation In Urogynaecol J Pelvic Floor Dysf 2007; 18(12): 1395-8
107. Marcelissen TA, Leong RK, Nieman FH, de Bie RA, van Kerrebroeck PE, de Wachter SG. The effect of pulse rate changes on the clinical outcome of sacral neuromodulation J Urol 2011; 185(5): 1781-5
108. Leong RK, Marcelisson TA, Nieman FH, de Bie RA, van Kerrebroeck PE, de Wachter SG. Satisfaction and patient experience with sacral neuromodulation: results of a single center sample survey. J Urol 2011; 185(2): 588-92
109. Parnell BA, Howard JF Jr, Geller EJ. The effect of sacral neuromodulation on pudendal nerve function and female sexual function. Neurourol Urodyn. 2014 Feb 24. doi: 10.1002/nau.22579. [Epub ahead of print]
110. Amundsen CL, Richter HE, Menefee S et al. The Refractory Overactive Bladder: Sacral NEuromodulation vs. BoTulinum Toxin Assessment: ROSETTA trial. Contemp Clin Trials. 2014 Mar; 37(2): 272-83
111. Shepherd JP, Lowder JL, Leng WW, Smith KJ. InterStim Sacral Neuromodulation and Botox Botulinum-A Toxin Intradetrusor Injections for Refractory Urge Urinary Incontinence: A Decision Analysis Comparing Outcomes Including Efficacy and Complications. Female Pelvic Med Reconstr Surg. 2011 Jul; 17(4): 199-203
112. Smits MA, Oerlemans D, Marcelissen TA, van Kerrebroeck PE, de Wachter SG. Sacral neuromodulation in patients with idiopathic overactive bladder after initial botulinum toxin therapy. J Urol. 2013 Dec; 190(6): 2148-52
113. Roth TM. Sacral neuromodulation and cardiac pacemakers. Int Urogynecol J. 2010 Aug;21(8):1035-7

114. Finazzi-Agro F, Petta F, Sciobica F, Pasqualetti P, Musco S, Bove P. Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: a randomized, double-blind, placebo-controlled trial. J Urol 2010; 184(5): 2001-6
115. Peters KM, Carrico DJ, Perez-Marrero RA et al. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. J Urol 2010; 183(4): 1438-43
116. Peters KM, MacDiarmid SA, Wooldridge LS et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy OrBIT) trial. J Urol 2009; 182(3): 1055-61
117. Peters KM, Carrico DJ, Wooldridge LS, Miller CJ, MacDiarmid SA. Percutaneous tibial nerve stimulation for the long-term treatment of overactive bladder: 3-year results of the STEP study. J Urol. 2013 Jun; 189(6): 2194-201
118. MacDiarmid SA, Peters KM, Shobeiri SA et al. Long term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. J Urol 2010; 183(1): 234-40
119. Klingler HC, Pycha A, Schmidbauer J, Marberger M. Use of peripheral neuromodulation of the S3 region for treatment of detrusor overactivity: A urodynamic-based study. Urology. 2000 Nov 1; 56(5): 766-71.
120. Burton C, Sajia A, Latthe PM. Effectiveness of posterior tibial nerve stimulation for overactive bladder: a systemic review and meta-analysis. Neurourol Urodyn. 2012; 31(8): 1206-16
121. Cody JD, Nabi G, Dublin N et al. Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy. Cochrane Database System Rev. 2012b, Issue 2. Art. No.: CD003306
122. Awad SA, al-Zahrani HM, Gajewski JB, Bourque-Kehoe AA. Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. Br J Urol 1998 Apr; 81(4): 569-73
123. Bramble FJ. The treatment of adult enuresis and urge incontinence by enterocystoplasty. Br J Urol 1982 Dec; 54(6): 693-6
124. Edlund C, Peeker R, Fall M. Clam ileocystoplasty: Successful treatment of severe bladder overactivity. Scand J Urol Nephrol 2001 Jun; 35(3): 190-5
125. Khastgir J, Hamid R, Arya M, Shah N, Shah PJ. Surgical and patient reported outcomes of 'clam' augmentation ileocystoplasty in spinal cord injured patients. Eur Urol. 2003;43(3):263–9
126. Zachoval R, Pitha J, Medova E et al. Augmentation cystoplasty in patients with multiple sclerosis. Urol Int. 2003; 70(1): 21–6.
127. Johnson EU, Singh G. Long-term outcomes of urinary tract reconstruction in patients with neurogenic urinary tract dysfunction. Indian J Urol. 2013 Oct; 29(4): 328-37
128. Gilbert SM, Hensle TW. Metabolic consequences and long-term complications of enterocystoplasty in children. J Urol 2005; 192: 1935
129. Cartwright PC, Snow BW. Bladder autoaugmentation: partial detrusor excision to augment the bladder without use of bowel. J Urol 1989 Oct; 142(4) : 1050-3
130. Leng WW, Blalock HJ, Fredriksson WH, English SF, McGuire EJ. Enterocystoplasty or detrusor myomectomy? Comparison of indications and outcomes for bladder augmentation. J Urol 1999 Mar; 161(3): 758-63
131. Karsenty G, Vidal F, Ruffion A, Chartier-Kastler E. Treatment of neurogenic detrusor hyperactivity: detrusor myomectomy. Prog Urol. 2007 May; 17(3): 580-3
132. El Masri WS, Fellows G. Bladder cancer after spinal cord injury. Paraplegia 1981; 19: 265–270
133. Stonehill WH, Dmochowski RR, Patterson AL, Cox CE. Risk factors for bladder tumors in spinal cord injury patients. J Urol 1996; 155(4): 1248–1250

134. El Masri WS, Patil S, Prasanna KV, Chowdhury JR. To cystoscope or not to cystoscope patients with traumatic spinal cord injuries managed with indwelling urethral or suprapubic catheters? That is the question! Spinal Cord (2014); 52(1)**:** 49–53
135. Yang CC, Clowers DE. Screening cystoscopy in chronically catheterized spinal cord injury patients. Spinal Cord. 1999 Mar; 37(3): 204-7
136. Kalisvaart JF, Katsumi HK, Ronningen LD, Hovey RM. Bladder cancer in spinal cord injury patients. Spinal Cord 2010; 48(3): 257–261