Position statement: a clinical approach to the management of adult non-neurogenic overactive bladder

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Summary

Introduction: Overactive bladder (OAB) is a highly prevalent medical condition that has an adverse impact on various health-related quality-of-life domains, including a significant psychosocial and financial burden. This position statement, formulated by members of the Urological Society of Australia and New Zealand and the UroGynaecological Society of Australasia, summarises the current recommendations for clinical diagnosis and treatment strategies in patients with non-neurogenic OAB, and guides clinicians in the decision-making process for managing the condition using evidence-based medicine.

Main recommendations:

- Diagnosis and initial management should be based on thorough clinical history, examination and basic investigations to exclude underlying treatable causes such as urinary tract infection and urological malignancy.
- Initial treatment strategies for OAB involve conservative management with behavioural modification and bladder retraining.
- Second-line management involves medical therapy using anticholinergic or β3 agonist drugs provided there is adequate assessment of bladder emptying.
- If medical therapy is unsuccessful, further investigations with urodynamic studies and cystourethroscopy are recommended to guide further treatment.
- Intravesical botulinum toxin and sacral neuromodulation should be considered in medical refractory OAB.

Changes in management as result of this statement:

- OAB is a constellation of urinary symptoms and is a chronic condition with a low likelihood of cure; managing patient expectations is essential because OAB is challenging to treat.
- At present, the exact pathogenesis of OAB remains unclear and it is likely that there are multiple factors involved in this disease complex.
- Current medical treatment remains far from ideal, although minimally invasive surgery can be effective.
- Further research into the pathophysiology of this common condition will hopefully guide future developments in disease management.

Overactive bladder (OAB) is a clinical diagnosis defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of a urinary tract infection or other obvious pathology.[1,2] Although OAB is not life threatening per se, its symptoms are often bothersome and adversely affect various health-related quality-of-life domains and sexuality, with emotional impact and invariably resulting in increased health care cost.[3,4]

The proposed pathophysiology mechanisms for OAB are not completely understood. Conditions such as urinary tract infection, bladder stones or bladder tumours can cause OAB. Sometimes no identifiable cause for overactive bladder can be found; this is termed idiopathic OAB. In OAB, the detrusor can contract inappropriately, regardless of how much urine is stored in the bladder. Such detrusor overactivity can originate from dysfunctions of bladder epithelium or the detrusor muscle itself. The myogenic theory suggests that age-related changes in bladder smooth muscle often result in detrusor hyperexcitability,[5] while the neurogenic theory advocates that detrusor overactivity can occur following denervation at the spinal or cortical level, resulting in hyperactive voiding secondary to spinal micturition reflexes.[6]

It is estimated that 16% of the adult population over 40 years of age suffers from OAB,[7] with increasing prevalence with age in both men and women, and in the presence of medical comorbidities such as congestive heart failure and diabetes mellitus.[8] At present, there are no published national data on the exact prevalence of OAB in Australia. Despite the high prevalence especially among older people,[3,7] OAB is likely underdiagnosed and undertreated due to lack of awareness, embarrassment and the misconception that OAB is a natural consequence of ageing.[2,3] OAB and urinary incontinence symptom severity often progress over time. Up to 60% of men with bladder outlet obstruction have evidence of detrusor overactivity;[3,7] however, OAB can exist independently of bladder outlet obstruction in older men,[9] adding to the complexity of male lower urinary tract symptom management.

Over the past 5 years, there have been considerable advances in our understanding of OAB pathophysiology and treatment strategies using novel pharmacological agents and minimally invasive surgical interventions. This statement summarises the current key recommendations for clinical diagnosis and treatment strategies to assist clinicians in their decision making in managing non-neurogenic OAB using evidence-based medicine. We conducted a MEDLINE literature search for English language original and review articles on non-neurogenic OAB over the past 10 years. Published guidelines from international organisations[1,2,8,10-14] were also included.

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Recommendations: clinical assessment and management strategies

History

It is important to differentiate uncomplicated non-neurogenic OAB from alternative or co-existing lower urinary tract symptom diagnoses such as bladder outlet obstruction (commonly from benign prostatic enlargement), neurogenic bladder or underactive bladder (Box 1). Although urinary urgency, frequency and nocturia with or without incontinence are hallmarks of OAB,[2,11] it is important to enquire about other lower urinary tract symptoms that may be present in patients with bladder outlet obstruction or underactive bladder.[1,13] The International Consultation on Incontinence Questionnaire has been validated and used extensively, and is a useful prognostic indicator of treatment outcome.[1,2,12] At present, there is no disease-specific quality-of-life instrument for OAB patients. The rapidity of onset, duration and severity of symptoms are important, as well as assessment of the amount and type of fluid consumed during the day. Beware of medications that may contribute to lower urinary tract symptoms and acute medical conditions that precipitate or worsen urinary incontinence. In older patients, a collaborative history often needs to be taken with family members or carers. Known risk factors associated with OAB include age > 75 years, diabetes, depression and obesity.[2,3,7] Further, patients with OAB are more likely than those without OAB to have one or more comorbid conditions, including depression, sexual dysfunction and gastrointestinal disorders.[3,7]

Continence assessment includes identifying the type of incontinence (urgency, stress-related or mixed), the severity (number and size of pads used or, preferably, pad weights) and the impact on activity and/or quality of life. Red flags for specialist referral are shown in Box 2.

Physical examination

Focused abdominal and pelvic examination should be performed, and external genitalia should be examined in both sexes. In men, look for phimosis or stenosis of the meatus, and check the prostate for size, consistency and tenderness. The presence of constipation or a rectal mass should be excluded. In women, it is important to look for atrophic vaginitis, pelvic floor muscle strength, organ prolapse, and the presence of stress leakage with cough or Valsalva manoeuvre. A directed neurological examination focusing on lower limb neurological assessment (S2–4) should be performed to exclude neurological causes.

Investigations

Initial investigations to identify reversible conditions should include:

- urine microscopy and culture — to identify infection, haematuria or glycosuria;
- a bladder diary — to record times of micturition, the volumes voided, incontinence episodes, fluid intake, degree of urgency and incontinence over a 3-day period. This provides an assessment for functional bladder capacity (500–600 mL), presence of nocturnal polyuria (where nocturnal voided volume is > 33% of 24-hour volume) and difference between stress and urge incontinence;
- post-void residual urine levels — a high post-void level (> 100 mL) may suggest bladder outlet obstruction or an underactive bladder;

1 Differential diagnosis and main conditions to be excluded

- Urogenital infections: bacterial cystitis, prostatitis, urethritis
- Bladder abnormalities: bladder cancer (carcinoma in situ), bladder calculus, interstitial cystitis (bladder pain syndrome)
- Prostate or urethral abnormalities: prostate cancer, urethral calculus or stricture
- Neurological conditions: Parkinson disease, stroke, multiple sclerosis, spinal conditions
- Other: urinary retention, polyuria, psychogenic urinary frequency, constipation ◆

2 Red flags for specialist referral

- Uncertain diagnosis and inability to develop a reasonable management plan
- Lack of response to an adequate trial of conservative therapies (eg, bladder training, pelvic floor muscle therapy and drug therapy)
- Haematuria without infection; and abnormal urine cytology
- Severe (beyond the introitus) pelvic organ prolapse
- Complex medical history
- Neurological condition (eg, multiple sclerosis, spinal cord lesions, cerebrovascular disease) in which a component of neurogenic bladder is suspected
- Abnormal post-void residual urine volume ◆

- blood tests (electrolytes and creatinine, fasting glucose, and prostate-specific antigen in men) — to assess renal function, diabetes and prostate risk;
- urinary tract imaging (usually by ultrasound scan) — to ensure that there is no bladder lesion (eg, mucosal mass or bladder stone) and upper tract dilation (eg, obstructive uropathy).

In general, patients with uncomplicated OAB symptoms, a negative urine test result, a bladder diary consistent with OAB (reduced functional capacity < 250 mL) and minimal post-void residual urine can be managed without the need for specialist referral or invasive tests such as formal video urodynamic study or cystoscopy[1,12,14] (Box 2 and Box 3).

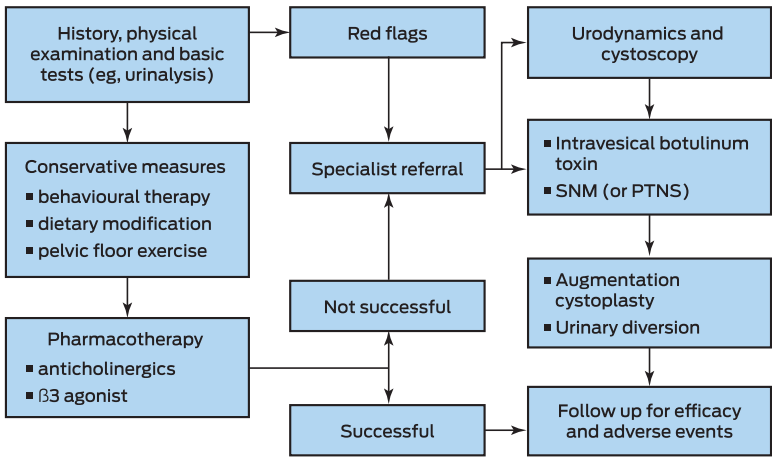
Stepwise approach to treatment options

Behavioural modification and physical therapy

The conservative approach to non-neurogenic OAB involves first-line management through weight loss with diet and exercise, behavioural modifications with removal of bladder irritants, as well as bladder retraining and pelvic floor exercises.[10,15] Caffeine-based products (eg, coffee, tea and carbonated soft drinks), alcohol, and medications (eg, diuretics) are major causes of acute incontinence. Behavioural modification with bladder retraining (eg, gradually increasing timed voiding) improves central control of bladder function by relearning the cortical inhibition of detrusor contractions. However, this type of treatment requires high levels of patient motivation and encouragement, and suffers from high relapse rates.[2]

The evidence surrounding conservative treatment is inconclusive,[16] and a 2012 Cochrane review[17] found that bladder training in isolation is no different to no bladder training. Some studies showed that a combination of bladder retraining and anticholinergic treatment may result in higher symptomatic improvement than anticholinergic drugs or bladder training alone.[17]

3 Diagnosis and treatment algorithm for non-neurogenic overactive bladder in adults



PTNS = percutaneous tibial nerve stimulation; SNM = sacral neuromodulation. ◆

various formulations available, such as immediate release, extended-release and transdermal preparations (gel or patch), and each medication has varying efficacy and differing side effect profiles.[10,11,14,17] Selection of agent is dependent on cost, efficacy, tolerability, compliance and route of administration. While the difference in efficacy of anticholinergics reached statistical significance in individual clinical trials, a recent Cochrane review[19] showed that solifenacin and fesoterodine might be preferred for superior efficacy over oxybutynin and tolterodine, but that fesoterodine and oxybutynin have a higher risk of withdrawal owing to adverse events and higher risk of dry mouth. Dry mouth, constipation, headache and blurred vision are common adverse effects reported in clinical trials.[12,18] Recent evidence from randomised trials indicated low incidence of urinary retention when anticholinergics are used in patients with established bladder outlet obstruction.[20] Low compliance to anticholinergic drugs may be due to inadequate drug efficacy, intolerable side effects, poor patient education and follow-up, unmet expectations, and cost issues.[11,14,17]

Medical therapy

Oral pharmacotherapy is the second-line treatment for non-neurogenic OAB.[12-14,17] Although multiple compounds have been investigated, the mainstays of oral pharmacotherapy are anticholinergic drugs (eg, oxybutynin, solifenacin) and β3-adrenergic receptor agonists (eg, mirabegron) (Box 4).

A recent Cochrane meta-analysis showed that anticholinergics are superior to placebo, with reductions in frequency, urgency and incontinence.[18] The mechanism of action of anticholinergic drugs is mediated through inhibition of the muscarinic receptors on the detrusor myocyte, which is responsible for bladder contraction, leading to less spontaneous detrusor activity.[18] Of the five subtypes of muscarinic receptors (M1–M5), M2 and M3 predominate in the bladder myocyte, with M3 being the most potent.[18] There are

The β3-adrenergic receptor agonist mirabegron represents a new class of drug. Mirabegron targets the β3-adrenoceptor, causing direct relaxation of the detrusor muscle, inhibition of spontaneous contractile activity in the bladder, and reduction in bladder afferent activity.[20-22] Pooled analysis of published studies showed that mirabegron 50 mg was associated with a reduction in mean micturition per 24 hours and incontinence episodes per 24 hours.[21] Mirabegron is well tolerated, with negligible dry mouth; however, there is an increase in cardiovascular events (most commonly hypertension) associated with its use.[20] It has advantages over anticholinergics in its side effect profile, with negligible effects on cognition, and is safer in patients with bladder outlet obstruction.[22]

The current oral medical therapies are relatively fast acting and most patients report clinical efficacy within 2–4 weeks. While there

4 Pharmacotherapy and surgical options in non-neurogenic overactive bladder

Therapy	Mechanism of action	Advantages	Disadvantages
Anticholinergics	Target predominantly M2 and M3 receptors, causing inhibition of bladder contraction	Oxybutynin (oral and patch) is PBS listed	Antimuscurinic side effects (dry eye, dry mouth, retention, constipation, confusion)
β3 agonists	Target β3 adrenoceptor, causing direct bladder relaxation and decreased bladder afferent activity	Can be used in combination with anticholinergics No anticholinergic side effects	Increased cardiovascular risks including hypertension and headaches
Intravesical botulinum toxin	Inhibits release of acetylcholine at neuromuscular junction	Minimally invasive (can be performed under local anaesthetic) PBS listed	Risk of elevated post-void residual urine levels requiring intermittent self-catheterisation or temporary catheterisation Lasts 6–9 months; requires repeat injections
Sacral neuromodulation	Central modulation of S3 afferent signal	Does not cause retention or need to self-catheterise Single treatment required Trial of therapy (temporary lead) Treats painful bladder, urinary retention and faecal incontinence	Requires high expertise Battery change every 5–7 years (depending on symptom control)
Surgery	Disruption of bladder contraction (or removal of bladder)	Last resort for recalcitrant overactive bladder	General anaesthesia surgical risks Irreversible Risk of metabolic disturbance, bladder rupture and malignant change

PBS = Pharmaceutical Benefits Scheme. ◆

is a lack of head-to-head comparisons of mirabegron with anticholinergic drugs, quantitative synthesis of the literature found that the effect of mirabegron did not significantly differ from that of other OAB agents,[22] other than that the tolerability profile of mirabegron offers potential to improve patient adherence to treatment. At present, Pharmaceutical Benefits Scheme funding is available for oral and topical oxybutynin formulations only. Combination therapy with solifenacin and mirabegron is well tolerated and has been found to significantly improve OAB symptoms, with no additional safety findings, compared with monotherapy or placebo.[23]

OnabotulinumtoxinA (botulinum toxin) may be considered following failure of oral medical therapy. It inhibits muscle contraction by inhibiting the release of acetylcholine at the neuromuscular junction and prevents abnormal bladder contractions. The current recommended dose in treating non-neurogenic OAB is 100 IU,[24] and cystoscopy is used to place injections throughout the bladder under local or general anaesthesia, either in the clinic or theatre setting. Urinary improvement usually occurs within 2 weeks, and clinical response (decreased incontinence episodes and urinary frequency) may be seen in 60–90% of patients.[24,25] The effect usually lasts between 6 and 12 months, and no drug tolerance problems have been reported; however, the patient will need to undergo repeat injections for life.[24,25] Adverse events include urinary tract infection, and about 5% of patients need to perform short term clean intermittent catheterisation because of elevated post-void residual urine levels.[25]

Requirements for Pharmaceutical Benefits Scheme funding are urinary incontinence due to idiopathic OAB; inadequate control by therapy involving at least two alternative anticholinergic drugs; age $\geq$ 18 years; at least 14 episodes of urinary incontinence per week; and willingness and ability to self-catheterise.[11,17,25] Contraindications to botulinum toxin use include an untreated urinary tract infection, pregnancy, breastfeeding, and neuromuscular compromise (eg, myasthenia gravis).[17,25]

Surgical treatment

Surgical options in the management of non-neurogenic OAB include minimally invasive procedures such as sacral neuromodulation and percutaneous tibial nerve stimulation. Open surgery is now rare and is only performed if all other options have failed (Box 4).

Minimally invasive procedures. Sacral neuromodulation minimises urgency and bladder contraction through central modulation of the sacral ascending afferent signals. It is a minimally invasive procedure involving percutaneous insertion of a lead into the S3 foramen, which provides electrical nerve stimulation to the bladder and perineum. There are two stages in sacral neuromodulation: stage 1 consists of a trial test with either a temporary or permanent lead, and stage 2 involves a permanent sacral neuromodulation implant. A temporary lead can be placed to provide stimulation for a short trial period (7–14 days), after which a permanent lead and generator are surgically implanted.

Compared with anticholinergics, patients reported improvement in urge incontinence with sacral neuromodulation.[11,26] Prospective studies have shown a response rate of about 85% in patients with OAB at one year, and 56% of patients with OAB with incontinence and 40% with OAB without incontinence achieved greater than 50% improvement in baseline symptoms at 5 years.[26] Further, sacral neuromodulation is effective in patients with faecal incontinence[26,27] and may be effective in patients with a hypocontractile bladder.[27] Most complications are minor, such as implant site discomfort or infection (< 10%). While advances in device technology and surgical techniques have reduced device-related complications such as lead migration (rare), patients will need to undergo revision surgery to replace the battery generator every 5 to 7 years.[26,28]

Percutaneous tibial nerve stimulation is an outpatient procedure that uses the tibial nerve for temporary neuromodulation in a similar manner to that of sacral neuromodulation. A small acupuncture needle is placed just above the medial malleolus and connected to an external pulse generator. Treatment initially involves weekly 30-minute sessions for 12 weeks followed by monthly maintenance treatments. Clinical trials comparing percutaneous tibial nerve stimulation with sham procedure showed more than 50% improvement in bladder symptoms such as urgency, voided volume and bladder capacity;[11,29] however, efficacy is often not sustained once treatment ceases.

Surgery. Surgery for non-neurogenic OAB may be undertaken when all treatments have failed. However, it is now infrequently performed since the introduction of newer medical therapies (eg, botulinum toxin) and minimally invasive surgical options (eg, sacral neuromodulation).[11,12,14] The two main surgical options are augmentation cystoplasty and urinary diversion with or without cystectomy. The choice of type of open surgery is largely dependent on the surgeon's expertise and patient preferences.

Augmentation cystoplasty involves a detubularised segment of bowel, usually ileum, to enlarge the bladder by means of a patch sutured to a bivalved bladder. This results in interrupted coordination of detrusor contraction and an increase in bladder capacity. Owing to the functional changes in the bladder and possible mucus secretion from the bowel surface, 10–75% of patients will need to perform long term self-catheterisation.[30] Long term complications such as metabolic disturbance are not uncommon and have been reported in up to 70% of patients;[30] formation of bladder stones, de novo bladder rupture and risk of squamous cell cancer are uncommon.[31] Urinary diversion uses a segment of bowel, usually distal ileum, to create a conduit, leaving the patient with a permanent stoma bag; reported complications include stoma-related issues (< 15%), ureteral stricture (rare) and metabolic disturbance (about 15% of patients will have a degree of persistent metabolic acidosis).[32]

Conclusion

OAB is a chronic medical condition with a low likelihood of cure, and managing patient expectations is essential. At present, the exact pathogenesis of OAB remains unclear and is likely to involve multiple factors. Current medical treatment remains far from ideal due to poor compliance and high discontinuation rates. Understanding the efficacy and safety profiles of various treatment options allows clinicians to make informed decisions about the most suitable treatment option for their patients. Further research into the pathophysiology of this condition will hopefully guide future developments in disease management.

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