Review

New developments in the diagnosis and management of overactive bladder

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Practice Points

- Thorough history and a careful examination alone are often sufficient to diagnose overactive bladder syndrome.
- Treatment can be commenced without urodynamic confirmation of detrusor overactivity.
- First-line management strategies should include fluid advice, bladder training and pelvic floor exercises.
- Anticholinergic medication should be started in those who fail to respond to conservative management.
- Further investigation should be considered in those with refractory overactive bladder or where there is doubt regarding the diagnosis.
- At present, urodynamic investigation is the most widely available and reliable way of diagnosing detrusor overactivity, which is present in most patients with overactive bladder.
- Those with overactive bladder who are refractory to medical treatment, should be considered for intravesical botox, neuromodulation or surgical intervention.

SUMMARY Overactive bladder syndrome is a common, debilitating condition that significantly affects quality of life. Urodynamic investigation is expensive, invasive and associated with a risk of urinary tract infection. A number of alternative diagnostic tools have been proposed, which may play an important role in the diagnosis overactive bladder in the future. Promising new treatments in those who do not respond to lifestyle modification or anticholinergic therapy include β-adrenergic agonists and transdermal neuromodulation.

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Definitions

The International Continence Society defines overactive bladder (OAB) syndrome as urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, in the absence of a urinary tract infection or other obvious pathology [1]. OAB is a symptomatic diagnosis but is assumed to be caused by detrusor overactivity (DO), which is diagnosed by invasive urodynamic investigations.

The key symptom of OAB is urgency, which is the complaint of a sudden compelling desire to pass urine that is difficult to defer [2].

Epidemiology & prevalence

OAB is a common problem and has a significant impact on quality of life [3]. One population-based study suggested that patients with OAB have worse quality of life scores than those with hypertension, depression, asthma and diabetes [4].

The EPIC study, a multinational population-based survey, suggested that the prevalence in adults was approximately 12% and that this increases with age [4]. The EpiLUTS study, a cross-sectional survey conducted across the USA, UK and Sweden, suggested a slightly lower prevalence of 4.4–9.3% in women and 4.1–10.8% in men [5]; again, prevalence increased with age.

The NOBLE study suggests approximately 16% of adults aged 18 years and over in North America suffer from OAB [6]. Prevalence is similar in men and women and increases with age in both sexes [7].

The economic costs of managing OAB are significant. In 2009, disease-specific total expenditure for this syndrome exceeded US$24.9 billion (GB£15.6 billion) in the USA [8].

Etiology

The mechanisms that underlie OAB and DO are not completely understood. The pathogenesis of OAB is multifactorial, differing between individuals and altering over time in any one person [9]. Several theories have been proposed.

The neurogenic hypothesis of DO deals with the changes in CNS pathways, leading to imbalances that tend to increase bladder excitation, reduce inhibition and increase afferent input [10]. Damage to central inhibitory pathways or sensitization of peripheral afferent terminals in the bladder can unmask primitive voiding reflexes that trigger bladder overactivity.

The myogenic hypothesis suggests that partial denervation of the detrusor causes an alteration of the properties of the smooth muscle ('denervation supersensitivity'), leading to increased spontaneous excitability [11]. In addition, propagation of excitation over abnormal large distances allows spread of spontaneous excitation to affect a greater proportion of the bladder. Alterations in the functional properties of detrusor myocytes is seen in DO [12].

The peripheral autonomic (integrative) hypothesis suggests that spontaneous localized contractions (micromotions) are a normal physiological mechanism for reporting the state of bladder filling, determined by interactions of the various functional cell types in the bladder wall (e.g., interstitial cells) [13]. Alterations in the properties or interactions of any of these cells will lead to exaggerated micromotions, hence OAB, and/or excessive propagation and hence DO.

The afferent nerve hypothesis suggests that spontaneous bladder contractions during bladder filling may play a role in DO and OAB [14]. These smooth muscle contractions may generate afferent nerve activity contributing to DO and OAB syndrome.

Transmitters released from the urothelium may affect detrusor muscle contractility by altering the excitability of afferent nerves [15]. Absence of the urothelial layer can lead to an increase in the spontaneous activity of the detrusor [16], and chronic injury to the urothelium has been shown to cause a decrease in voided volumes and an increase in urinary frequency [17]. Hence, the urothelium may play an important role in the pathophysiology of OAB.

Although, by definition, urinary infection must be absent in order to diagnose OAB, it has been suggested that low-count bacteriuria may play a role in the pathogenesis of OAB [18].

Symptoms

Urgency with at least one other symptom is essential for the diagnosis of OAB [19]. The most commonly seen symptoms accompanying urgency include increased daytime frequency and nocturia. Nocturia is the complaint that the individual has to wake up at night one or more times to void [20]. OAB symptoms have been shown in numerous studies to have a significant negative impact on the health-related quality of life, emotional well-being and work productivity of affected individuals [21]. Patients have the

social inconvenience of urgency and increased visits to the bathroom. They may also have to limit their fluid intake and wear protective pads if there is associated urgency incontinence. Patients with OAB are more isolated, more likely to be depressed and have a lack of adequate sleep [22]. Elderly patients with OAB are more likely to be affected by falls and associated fractures [23].

OAB is sometimes categorized into OAB wet (where urgency incontinence is present) and OAB dry (where there is no incontinence).

Diagnosis

History

A thorough history and examination is vital in diagnosing OAB. The history should include duration, severity and frequency of symptoms. Incontinence and pad use should be established. In females, obstetric and gynecological history is important, as well as a history of any previous prostate surgery in males.

A frequency/volume chart or voiding diary is an important tool in diagnosing OAB and is a way of objectively evaluating lower urinary tract symptoms [24]. This should include urine output volumes in addition to timing of voids. Bladder diaries may include information on bladder sensation, fluid intake, pad usage and incontinence episodes. Studies have shown that the bladder diary should be filled in for at least 3 or 4 days to get an accurate record of the patients voiding habits [25].

There are a number of validated questionnaires, including the International Consultation on Incontinence Questionnaire, to measure OAB symptoms and to help assess their severity and effect on quality of life [26].

Examination

It is important to exclude endocrine or neurological causes and pelvic malignancy. An abdominal and pelvic examination should be carried out to rule out any abdominal or pelvic masses in female patients and to evaluate prostatic enlargement or malignancy in male patients. Vaginal examination should aim to identify pelvic organ prolapse, atrophy or stress incontinence. Neurological examination should also be performed.

Investigations

A urine dipstick test should be performed in order to rule out infection and look for blood or glucose, which may represent other underlying pathologies. Initial investigations should also include simple bedside tests such as height, weight and blood pressure measurements.

Flow studies

Uroflowmetry should be performed in both men and women to screen for voiding dysfunction and exclude significant residuals of urine.

Pressure/flow cystometry

OAB is a clinical diagnosis and urodynamics should only be performed when conservative and medical measures to manage OAB have failed.

Conversely, cystometry is essential for a diagnosis of DO, which is a urodynamic observation [2]. DO is characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. DO is thought to be the underlying cause for the symptom of urgency that drives the other symptoms of OAB.

A retrospective study in 2006 found 64% of patients with OAB symptoms have DO on urodynamic investigations; 30% of those with DO on urodynamics did not complain of OAB symptoms [27].

Alternatives to urodynamic studies

Urodynamic investigation is an expensive, invasive test, which can be uncomfortable and is associated with a 1.8–6.0% risk of urinary tract infection [28]. There are a number of alternative diagnostic tools that have been proposed.

Bladder wall thickness

Ultrasound measurement of bladder wall thickness has been proposed as a diagnostic tool for DO. There have been some studies that suggest a significant increase in bladder wall thickness between normal subjects and females with non-neurogenic DO [29]. Some centers measure bladder wall thickness via transvaginal ultrasound in women with urinary symptoms and have produced results with good reproducibility [30]. In men, an increase in bladder wall thickness may relate to bladder outlet obstruction rather than OAB [31]. Currently, there is no standardized noninvasive method of measuring bladder wall thickness and, at present, it is unlikely to be a reliable and reproducible diagnostic test for OAB.

Near-infrared spectrometry

Doppler ultrasound studies have revealed significant variations in blood flow of the bladder

during the voiding cycle [32]. Near-infrared spectromety (NIRS) is a noninvasive method for detecting hemodynamic changes during bladder filling and voiding. Near-infrared light penetrates the skin and underlying tissues and is absorbed by naturally occurring chromophores such as oxyhemoglobin and deoxyhemoglobin. This enables the detection of oxygen-dependant changes in biological tissue by the measurement of the relevant chromophores in relation to baseline [33]. A recent prospective cohort study showed NIRS as a promising future diagnostic tool for DO with high reproducibility and specificity [30]. A larger, prospective pilot study suggested that NIRS was an unreliable method for detecting DO in women with OAB symptoms [34], however, the study did suggest that due to acceptable sensitivity (80.6%), NIRS may be of use as a screening test. Further large-scale studies are required.

MRI

Mapping cerebral blood flow via functional MRI has shown some promise as a noninvasive tool for diagnosing OAB. Differences have been seen in subjects with OAB and healthy controls [35]. Due to high costs and limited availability, it is unlikely that functional MRI will become an important diagnostic tool for OAB in the near future.

■ Biomarkers

Nerve growth factor

Nerve growth factor (NGF) is produced by the urothelium, smooth muscle and mast cells [36]. NGF is believed to be involved in the physiology of the lower urinary tract and the pathophysiology of DO of the urinary bladder where it is synthesised by PKC- and PKA-dependent intracellular pathways [37]. Chronic administration of NGF into the spinal cord or bladder of rats has been shown to induce bladder hyperactivity [38]. In humans, levels of NGF in bladder tissue have been demonstrated to increase in patients with bladder outlet obstruction [39], and in those with both idiopathic [40] and neurogenic DO [41]. Measuring tissue NGF requires invasive bladder biopsy. Urinary NGF levels have also been shown to increase in those with OAB [42] in addition to a number of other urinary conditions including interstitial cystitis and painful bladder syndrome [43]. Owing to its limited specificity for DO, urinary NGF may be a more useful tool in monitoring response to treatment rather than in diagnosing DO.

Prostaglandins

Prostaglandins are regulators of lower urinary tract function with a role in both the normal micturition cycle and the pathological inflammation process [44]. Some studies have shown elevated levels of urinary prostaglandins in patients with OAB compared with controls [45]; however, there is conflicting data, bringing in to question the usefulness of urinary prostaglandins as a biomarker for OAB.

Cytokines

Cytokines are extracellular messengers involved in a vast array of cellular processes including differentiation, cell division, fibrosis and inflammation [46]. Immunoassays have suggested significant increases in several chemotactic proteins and growth factors in subjects with OAB [47]. Initial studies have suggested potential differences in urinary cytokine expression in those with OAB compared with normal subjects [48]. Research is ongoing, however, urinary cytokines may, in the future, be a useful biomarker for OAB diagnosis and response to treatment.

Management

Most patients can be managed without the need for specialist involvement with conservative management or drug therapy. The principles of treatment are to reduce urinary urgency to subsequently decrease the number of episodes of incontinence and improve urinary frequency, nocturia and voided volumes [49]. There are several published guidelines on the management of OAB including NICE [101] and SIGN [102].

Behavioral and lifestyle techniques involve fluid intake advice, bladder training and timed voiding. Pelvic floor exercises can be used to suppress involuntary detrusor contractions [50].

Patients should be advised to reduce their fluid intake to 1.5–2.0 l per day and to reduce caffeine intake [51]. Carbonated soft drinks may also exacerbate OAB symptoms [52].

Bladder training is aimed at increasing the time between voids and can be an effective treatment for urgency. A key component of bladder retraining is timed and delayed voiding. Voiding intervals and bladder capacity gradually increase over several weeks, and urgency episodes may decrease. Bladder training has been shown to be most effective when combined with oral medication [53].

Pelvic floor training can improve symptoms in patients with OAB if completed regularly [54].

Weight loss may reduce OAB symptoms. A prospective study of women undergoing weight loss surgery showed a significant improvement of urinary symptoms after losing weight [55].

Patients who smoke are more likely to complain of urinary frequency and urgency. Furthermore, those who smoke heavily are more likely to have these symptoms compared with light smokers [56].

■ Pharmacology

Often lifestyle intervention alone is insufficient to treat OAB and pharmacotherapy is necessary to manage the patient's symptoms.

Antimuscarinics

The most commonly used drugs to treat OAB are antimuscarinics. There are several drugs of this class available. The clinical response to these varies and failure of response to one antimuscarinic should not preclude use of another. Dose escalation can improve efficacy in a significant proportion of patients [57]. All antimuscarinics are administered orally with oxybutynin available as a patch or a gel. Antimuscarinics act by antagonizing the effect of acetylcholine, which is the main neurotransmitter within the detrusor.

Acetylcholine attaches to muscarinic receptors causing an increase in intracellular calcium levels and a contraction of the detrusor muscle [58]. There are a number of muscarininc receptor subtypes with anticholinergic medication usually competitively inhibiting the M2 and M3 subtype receptors in the detrusor muscle, interstitial cells, urothelium and presynaptic nerve endings [59]. Medication can be nonselective, such as oxybutynin, or more selective, for example, darifenacin is selective for M3 receptors.

Common side effects from antimuscarinics include dry mouth and constipation with some patients experiencing blurred vision, dizziness and exacerbation of closed-angle glaucoma. In men with outflow obstruction whose residual urine is less than 150 ml, anticholinergics can be used to treat OAB without an increased risk of urinary retention [60].

All antimuscarinics have level 1 evidence with grade A recommendation for use by the International Consultation on Incontinence and European Association of Urology [61].

β-adrenergic agonists

The bladder has three subtypes of β-adrenergic receptors. Stimulation of β1, 2 and 3 receptor leads to relaxation of the detrusor muscle, medicated by the stimulation of adenylcylase and accumulation of cAMP [62].

β3-adrenoceptor agonists, such as mirabegron and solabegron, represent a promising novel treatment for OAB. Animal studies have shown a reduction in resting intravesical pressure and nonvoiding detrusor contractions with no effect on detrusor contraction during micturition [63]. The incidence of dry mouth is lower than with antimuscarinics, however, there is a potential for increased blood pressure or increased heart rate, therefore, caution is advised in patients with known cardiovascular disease [64]. Mirabegron has been licensed for the treatment of OAB in Japan and the USA, with Europe to follow in the near future.

Placebo effect

A 2009 meta-analysis of randomized placebo controlled studies of antimuscarinic medication suggested a significant improvement in frequency, urgency and urgency incontinence in patients who were placed in the placebo group during drug trials for OAB medications [65].

Botulinum toxin type A

Botulinum toxin type A is a neurotoxin produced by the *Clostridium botulinum* bacterium. It prevents acetylcholine release and inhibits cholinergic detrusor contractions. It also reduces urinary urgency by reducing the afferent impulses of the micturition reflex [58]. Botulinum toxin type A is administered through intradetrusor injections at multiple sites in the bladder, sparing the trigone. It has been used successfully to treat OAB [66]. Duration of effect is variable, although improvement in symptoms may be seen for at least 6 months following treatment [67]. Potential problems arising from Botulinum use include need for regular repeat injections and potential unknown, long-term effects on bladder function. There may be an increase in overall bladder capacity and postvoid residuals with 10–20% of patients needing to self-catheterize after treatment [68].

Botulinum toxin type A is currently unlicensed to treat idiopathic DO; however, the US FDA

have recently licensed onabotulinum toxin A for the treatment of neurogenic DO at a dose of 200 units.

Other medication

Vanilloid receptor agents

Capsaicin and resiniferatoxin have been demonstrated to increase bladder capacity and decrease urgency in OAB patients [69]. These may exert their effect by desensitizing C-fiber-afferent neurons [70]. Despite this, several clinical trials using intravesical resiniferatoxin (the ultrapotent capsaicin analog) were abandoned due to difficulties in administering the drug and failure to show improvement in symptoms compared with placebo [71].

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors potential muscle relaxation in the detrusor via generation of cyclic nucleotides and modulation of nitric oxide [72]. There are several studies showing improvements in patients, with some reporting lower urinary tract symptoms in men [73,74]; however, there are few studies involving female OAB patients.

Neuromodulation

Neuromodulation can be used in those whose quality of life is significantly impaired by their symptoms and do not respond to more conservative and medical measures. Sacral, paraurethral, pudendal nerve and tibial nerve stimulation have been used [75].

Sacral nerve stimulation/neuromodulation

Sacral nerve stimulation (SNS) has been demonstrated to be effective in the treatment of DO [76]. An electrode is placed close to the S3 nerve root and continuously stimulates the nerve. This is thought to inhibit the sacral parasympathetic nerves responsible for detrusor contraction [77]. The procedure is usually performed in two stages, the first being a test stage where the electrode is attached to an external stimulator. If this is successful, a permanent stimulator is placed under the skin in the buttock area. A total of 50% of patients with OAB symptoms reported more than 50% improvement after SNS treatment [78].

Posterior tibial nerve stimulation

This involves inserting a fine-needle electrode near the tibial nerve proximal to the medial malleolus. This is attached to an external battery, which delivers electrical impulses to the sacral plexus via the tibial nerve. Stimulation is applied once a week for 12 weeks for 30 min each time, with maintenance treatment following this. The treatment is effective, well tolerated and safe [79]. NICE have approved both posterior tibial nerve stimulation [103] and SNS [104].

Noninvasive external stimulation of the pudendal nerve using a patch applied to the lower back has been shown to reduce urgency episodes and increase voided volumes [80]. It may be a new noninvasive method of neuromodulation, which may prove to be popular in the future.

Surgery for OAB

Surgical interventions have been seen to be beneficial in those with refractory DO. Augmentation cystoplasty is a safe and effective treatment in neurogenic patients with refractory DO [81] and is the most common form of surgical treatment offered. It increases bladder capacity and reduces the amplitude of phasic detrusor contractions. The patient may need to self-catheterize owing to the enlarged reservoir capacity of the bladder and low storage pressure.

Other options include bladder augmentation [82] and urinary diversion [83]; however, these procedures carry a significant risk of morbidity and not all patients with DO will be suitable for surgery.

Future perspective

A reliable and reproducible method for diagnosing OAB still seems to be some way off. Unfortunately, many patients with refractory OAB rely on urodynamic investigations in order to diagnose underlying DO before being able to access more invasive and expensive treatments. There is some promise with new noninvasive physiological measurements, especially functional MRI. Unfortunately, the cost and resources required, at present, mean that this is unlikely to play a significant role in the diagnosis of OAB in the near future.

Urinary biomarkers, in particular urinary cytokines specific to those with OAB, represent an intriguing avenue for further studies.

There are a variety of treatment options for managing the symptoms of OAB. These range from simple lifestyle modifications to reconstructive surgery. There are several promising emerging management options including β3 adrenergic agonists and transdermal

neuromodulation. As we develop a better understanding of the pathogenesis of OAB treatment, options are likely to continue to improve.

Financial & competing interests disclosure

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