Overactive Bladder

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8.1 Introduction

Overactive bladder (OAB) has been defined by the International Continence Society (ICS)/International Urogynecological Association (IUGA) as urinary urgency with or without urge urinary incontinence, usually accompanied by frequency and nocturia in the absence of a urinary tract infection or other pathology [1]. The symptoms can be distressing affecting all aspects of a woman's quality of life (QoL) including social, work-related, emotional and sexual function [2].

OAB has a reported overall prevalence of 16.9% in women which increases with age. Women under 25 have a prevalence of 4.8% increasing to 30.9% in women over 65 [3]. Prevalence has separately been reported as high as 38% in postmenopausal women [4].

8.2 Pathogenesis

OAB is a symptom-based diagnosis with an aetiology that is still poorly understood. It can be associated with detrusor overactivity which is diagnosed by urodynamic studies. Spontaneous or provoked involuntary contractions of the detrusor muscle during the filling stage of micturition can be observed.

OAB is more prevalent in postmenopausal women with symptoms of genitourinary syndrome of menopause (GSM). Symptoms include vaginal dryness, burning, dyspareunia and urinary tract infections. The aetiology can be linked with genitourinary atrophy which can be attributed to oestrogen deficiency during the menopause with reduced oestrogen receptors in tissues such as vaginal epithelium and the bladder trigone [5]. This is also thought to contribute to urinary symptoms

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F. R. Pérez-López (ed.), *Postmenopausal Diseases and Disorders*,
https://doi.org/10.1007/978-3-030-13936-0_8

because of the increased contact of sensitive nerve endings with urine due to bladder atrophy [6].

There is emerging research suggesting that OAB in some patients may be linked to chronic bladder infection, although the mechanism of how bacterial colonisation causes OAB is unclear. Newer technologies such as RNA sequencing or extended culture techniques have shown different groups of microbiota cultured from patients with or without OAB. This will have an impact on future emerging treatment options [7].

8.3 Assessment of Women

A full clinical history is important to explore factors that can contribute to OAB symptoms and influence ongoing management. Discuss lower urinary tract symptoms divided into storage problems (frequency, urgency, nocturia, incontinence), voiding symptoms (hesitancy, straining, poor and intermittent flow), post-micturition symptoms (sensation of incomplete emptying, post-micturition dribble) and other symptoms (nocturnal enuresis, dysuria). Enquire into menopausal symptoms to explore GSM.

Lifestyle questions exploring fluid intake, type of fluids preferred (e.g. carbonated drinks, caffeinated drinks) and pad usage to assess for modifiable habits and severity of disease.

Past gynaecological and obstetric history is useful to identify if the patient is known to have a fibroid uterus that may compress the bladder causing urinary urgency and frequency or risk factors for vaginal prolapse, for example.

Relevant medical history such as diabetes or neurological symptoms should be assessed to identify co-morbidities that may produce or worsen OAB symptoms. If pharmacotherapy for OAB is being considered, conditions such as prolonged QT interval, uncontrolled hypertension, functional gastrointestinal pathology, myasthenia gravis and uncontrolled narrow-angle glaucoma, as well as renal and liver impairment will influence treatment choice [8].

Previous surgical history, for example, hysterectomy or vaginal prolapse surgery, may have influenced symptoms.

Current medication history may identify medications contributing to worsening of symptoms such as diuretics and sympathomimetics or if any medications will interact with medical treatment of OAB.

Assessment is completed with physical examination. Abdominal examination and bimanual vaginal examination should be carried out to assess for pelvic masses. Vaginal examination is important to assess pelvic organ prolapse (POP) and the integrity of the vaginal mucosa and identify atrophic change. If neurological symptoms are elicited from the history, carry out neurological examination with attention to the sacral neuronal pathways from S1 to S4 with the assessment of perineal sensation, rectal sphincter tone and ability to contract the anal sphincter [8].

8.4 Investigations

8.4.1 Urinalysis and Mid-stream Urine

Urinalysis should be carried out to identify urinary tract infection which may exacerbate symptoms or masquerade as OAB. Overall however urine dipstick analysis has a low sensitivity of 44% and a specificity of 87% for identification of a urinary tract infection when compared to urine cultured from a catheter sample in women with OAB [9]. Detection of blood can suggest infection, stones or cancer. Presence of protein is in keeping with infection or renal impairment; glucose can be identified in patients with diabetes mellitus, especially when not well controlled.

Microbiology culture and sensitivity of a mid-stream urine specimen are recommended for women with symptoms of a urinary tract infection with either a positive or negative urine dipstick or if the urine dipstick test is positive for leucocytes/nitrites. An acute presentation or exacerbation of symptoms may have an infective aetiology.

If urine sampling is consistently positive for blood, cystoscopy and renal ultrasound are indicated.

8.4.2 Bladder Diary

Bladder diary or frequency volume charts can provide an objective assessment of a patient's fluid input and urinary output. It can provide information on a patient's drinking patterns as well as the number of voids and incontinence episodes through the day. This assessment allows review of symptom severity in the everyday situation. Most current practice recommends completing a diary for 3–5 days covering variations in the women's usual activities, such as both working and leisure days.

The bladder diary itself however does not reliably correlate with urodynamic diagnoses [10].

8.4.3 Quality of Life Questionnaire

OAB symptoms are known to have a negative impact on quality of life. Patients with anxiety and depression report a greater severity in their OAB symptoms, poor quality of life and more psychosocial difficulties compared to OAB patients without anxiety [11]. Women with climacteric symptoms (hot flushes, night sweats, vaginal dryness and dyspareunia) are more likely to report anxiety and/or depressive symptoms although a direct causal link between menopause and anxiety and depression has not been clearly found [12].

Clinical trials acknowledge that improvement in quality of life should be considered an endpoint of successful treatment. With a similar principle, routine assessment of OAB symptoms and their impact on QoL can provide women with a manner of tracking their expectations and/or satisfaction with treatment [13].

There are many available validated questionnaires for this purpose. For example, the Overactive Bladder Questionnaire (OAB-q) includes an 8-item symptom bother scale and 25 quality of life items. It is a validated disease-specific questionnaire that assesses symptom bother and health-related quality of life (HRQL) in people with OAB [13]. The King's Health Questionnaire is also widely used and translated patient acceptable and valuable disease-specific questionnaire designed to assess the impact of urinary incontinence on quality of life (QoL) in women through 21 questions [14]. The Bristol Female Lower Urinary Tract Symptoms (B-FLUTS) assessment and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) are alternatives.

8.4.4 Urodynamic Investigation

Urodynamic studies describe several investigations that allow functional assessment of the bladder and urethra. It allows abnormalities of storage and voiding to be identified and detrusor overactivity or concomitant stress urinary incontinence to be confirmed. It is recommended in the investigation of OAB after unsuccessful conservative treatment.

Uroflowmetry is the measurement of urine flow rate. The patient is asked to void onto the flow metre with a comfortably full bladder. This part of the study excludes outflow tract obstruction or a hypotonic bladder.

Multichannel cystometry or subtracted cystometry allows measurement of rectal pressure to represent intra-abdominal pressure and intra-vesical pressure to calculate the detrusor pressure. Cystometric bladder capacity, contractility, compliance, presence of provoked or unprovoked detrusor activity or urodynamic stress incontinence can be determined by this investigation. Sixty-four percent of patients with OAB symptoms have detrusor overactivity detected by urodynamic studies. Conversely 84% of patients with urodynamically proven detrusor overactivity have symptoms of OAB [15].

8.4.5 Cystoscopy

Cystoscopy allows direct visualisation of the bladder using a flexible or rigid cystoscope under local or general anaesthesia, respectively. It can be considered after failure of medical management of overactive bladder or where there is a history of haematuria or recurrent urinary tract infections. Biopsies can be taken to investigate pathology as needed.

8.5 Management

The aim of OAB treatments is to improve control of micturition (behavioural and lifestyle interventions) or to modify detrusor contractility (pharmacological and surgical treatments). There are a variety of treatments available for OAB showing that

none are universally successful. We discuss treatments specifically for OAB further.

To note women with coexisting pelvic organ prolapse and OAB symptoms who undergo surgical correction of prolapse experience improvement in OAB symptoms after surgery in 60–80% of cases. Women with more severe prolapse however may be at a higher risk of persistent frequency or urge incontinence [16].

8.5.1 Lifestyle Modifications

Lifestyle modifications with avoidance of tea (including green tea), coffee, alcohol, carbonated drinks (particularly diet soft drinks) and smoking and dietary advice to avoid constipation are recommended. Following a healthy lifestyle with weight loss encouraged in those who are overweight is the advice of the ICI guidelines [17].

8.5.2 Bladder Retraining

Behavioural modifications include bladder retraining. Bladder retraining focuses on timed voiding aiming to lengthen the intervals between voiding. Patients are asked to void every hour at the start, even if no desire to void, and then progressively increase the voiding interval each week. Bladder retraining is effective for both overactive bladder symptoms and mixed urinary incontinence symptoms. A cure on improvement in symptoms in 59% of women has been reported in a retrospective study [18] of few adverse side effects. It is therefore recommended as first-line therapy with lifestyle modifications.

8.6 Pharmacological Management

Most medications prescribed to treat OAB have anti-muscarinic effects. However antidepressants, vasopressin analogues and alpha-adrenoceptor antagonists and beta-adrenoceptor agonists are also used. There is no ideal medication and treatments can be limited by side effects.

8.6.1 Anti-muscarinic Drugs

Detrusor contraction is mediated by the neurotransmitter acetylcholine binding to muscarinic receptors. Anticholinergic medication targeting M2 and M3 receptors has been the traditional first-line pharmacological treatment. The medication blocks the parasympathetic acetylcholine pathway to reduce the intensity of detrusor muscle contraction. Action via the sensory pathway allows the anticholinergic agent to modulate afferent innervations in the urothelium, thereby altering sensory feedback during filling phase [19].

Popular agents include oxybutynin, tolterodine, trospium, solifenacin, darifenacin and fesoterodine. All agents have shown a statistically significant improvement in OAB symptoms when compared to placebo.

Anti-muscarinic medication, however, can lack bladder specificity with muscarinic receptors in other organs such as the exocrine glands, the nervous system and the heart also interacted with. The most common side effect as a result is dry mouth in 16–28% of patients and as high as 80% with unmodified oxybutynin. Blurred vision, constipation, tachycardia and drowsiness can also occur. Use of extended-release preparations of oxybutynin, tolterodine and fesoterodine or patch or gel formulation of oxybutynin can lower the incidence of dry mouth and constipation [20]. Solifenacin and darifenacin are M3-selective receptor antagonists, in theory more bladder-specific with reduced tendency for anticholinergic side effects, however higher incidence of constipation (9–14%).

Adverse central nervous system side effects include disorientation, hallucinations, convulsions and cognitive impairment. These side effects can be compounded by the total anticholinergic burden contributed to by other regular medication taken by patients, for example, antispasmodic, antipsychotic and tricyclic antidepressants and anti-Parkinson medication [19]. Such side effects limit compliance as well as limit treatment availability for older women with established cognitive impairment.

Contraindications for anti-muscarinic use include hyperthyroidism, myasthenia gravis, narrow-angle glaucoma, hiatus hernia with reflux oesophagitis, heart failure and tachyarrhythmia.

It is good practice to advise patients prior to prescribing this medication of common side effects and that full benefits may take 4 weeks. Prescribe the lowest recommended dose of the medication, and ideally review in 4 weeks to assess symptoms and acceptability of treatment [21].

8.6.2 β3-Adrenoceptor Agonist

Mirabegron, the first β3-adrenoceptor agonist to enter clinical practice, is a selective β3-adrenoceptor agonist. In the human lower urinary tract, β3-adrenoceptors can be found in the bladder detrusor but also in the urothelium. Stimulation of β3-adrenoceptors leads to detrusor relaxation and increased bladder capacity. Mirabegron is a well-tolerated new medication associated with significant improvements in incontinence episodes and micturition frequency. Benefits of treatment were observed in patients with no previous pharmacotherapy for OAB as well as women who have previously trialled and discontinued anti-muscarinic treatment [22].

Combination therapy of mirabegron with solifenacin has also demonstrated significant improvements in mean volume voided (primary endpoint), micturition frequency and number of urgency episodes, without increasing the bothersome adverse effects associated with anti-muscarinic therapy (with the possible exception of constipation).

Reported adverse side effects include hypertension, nasopharyngitis and urinary tract infection. Contraindications to the medication include severe uncontrolled hypertension, severe renal impairment (i.e. GFR 15–29 mL/min/1.73 m^2) or in those with moderate hepatic impairment.

8.6.3 Desmopressin

Desmopressin is a synthetic analogue of vasopressin. Used at night it can reduce nocturnal urine production by up to 50% and can be used to treat nocturnal enuresis or nocturia in adults or children. The drug should be used with care in the elderly however due to a risk of hyponatraemia [23].

8.6.4 Oestrogen

Although oestrogen deficiency has been implicated in the aetiology of OAB by epidemiological studies, the role of oestrogen replacement treatment remains controversial. A Cochrane review has found low-quality evidence that intra-vaginal oestrogen preparations can improve the symptoms of vaginal atrophy and urinary incontinence in postmenopausal women when compared to placebo [24, 25]. It is widely thought that local oestrogen therapy for OAB however may be of benefit.

A randomised placebo-controlled trial (*n*-1612) reports 25 μg of micronised 17beta-oestradiol administered locally improved maximal cystometric capacity (290 mL vs. 200 mL, $P = 0.023$) and volume at which there was a strong desire to void (170 mL vs. 130 mL, $P = 0.045$) with a decrease in uninhibited bladder contractions from baseline pretreatment values [26]. There was no reported endometrial thickening or rise in serum oestrogen level as a result of treatment. Evidence supports a subjective improvement in symptoms of OAB with a better quality of life as assessed by short form-36 [27].

Conversely studies with higher doses of oestrogen, e.g. 25 mg oestradiol implants, have shown adverse effects such as vaginal bleeding with need for investigation and treatment including hysterectomy [28]. Systemic therapy with unopposed or combined hormone treatment has been shown to worsen urinary incontinence and frequency symptoms at 1 year [24] and should not be recommended for lower urinary tract symptoms.

8.6.5 Tricyclic Antidepressants

Although these agents are sometimes used for the treatment of OAB, they are not approved for this indication, nor is there any clinical trial evidence supporting this use [20]. Tricyclic antidepressants (TCAs) are potent inhibitors of muscarinic, a-adrenergic and histamine H1 receptors and inhibit norepinephrine and serotonin

reuptake at nerve terminals. Imipramine or amitriptyline is the most commonly used and may be useful for patients particularly bothered by nocturia or bladder pain [29].

The side effects of TCAs predominantly reflect their anti-muscarinic properties. Caution should be exercised in the context of combination therapy with anticholinergic agents, due to the risk of cumulative side effects, for example, urinary retention, confusion or QT prolongation [23].

8.7 Refractory OAB

Despite conservative and medical management, treatment outcomes may not provide optimal improvement in symptoms for 25–40% of patients [30], and second-line therapies may be sought. Although no standardised definition exists, we describe this as refractory OAB. Treatment options include intra-vesical Botox injections, neuromodulatory treatments or surgery. Before further invasive therapy, it is good practice to discuss the patient with a multidisciplinary team and explain the advantages and disadvantages of all treatment options.

8.7.1 Intra-vesical Treatment with Botulinum Toxin

Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum*, of which seven (A to G) serotypes have been identified. The use of botulinum A toxin (Botox) to treat a neurogenic OAB was first described in 1999 by Schurch et al. [31]. Injection of botulinum toxin acts presynaptically and prevents fusion of neurotransmitter-containing vesicles, leading to a decrease of acetylcholine release across the neuromuscular junction. The resultant muscle paralysis with a likely additional effect on the sensory afferent pathway mediates an improvement in OAB symptoms [32].

The botulinum toxin product is administered via cystoscopic injection using either a flexible or rigid cystoscope with local or general anaesthesia. There are no current recommendations for standardised administration and dose of the toxin or long-term safety data; however few side effects or complications are reported. Urine retention and the need to carry out clean intermittent self-catheterisation (ISC) have been reported as 5–15% with a risk of urinary tract infection as 5–31% [32, 33]. The risk of urine retention can increase with age and could develop as late as 2 weeks following injection. As such it is recommended that all women should be taught to carry out ISC prior to the procedure and followed up at 2 weeks following the procedure to assess post-void residual volumes.

8.7.2 Neuromodulation

Neuromodulation aims to achieve inhibition of detrusor activity by continuous neural stimulation through peripheral (via the posterior tibial nerve) or central (dorsal sacral nerve roots S2, 3, 4) nerves.

Posterior tibial nerve stimulation (PTNS) is the least invasive method of neuromodulation. It can be carried out in the outpatient setting, usually with 12 weekly sessions. This nerve has mixed fibres originating from L4 to S3 spinal cord segments, in common with bladder and pelvic floor innervation. The technique, first described in 1983, involves passing an electrical current through a 34-gauge needle electrode placed next to the PTN approximately three finger breadths cephalad to the medial malleolus. Subjective improvement in OAB symptoms occurs in about 60% of the patients with 47–56% improvement in frequency voiding charts [34].

The treatment is safe with few side effects (bruising, discomfort, slight bleeding); however without top-up treatments, effectiveness may decrease over time [34]. In a small study, 77% of patients maintained a moderate to marked improvement in their OAB symptoms after 3 years. It is recommended when intra-vesical botulinum A toxin injection treatment to the bladder or sacral neuromodulation is not acceptable or suitable for patients [35].

Central neuromodulation can be carried out using an implantable, programmable medical device with a tined lead electrode that is typically passed through the S3 sacral foramen to lie next to the sacral and pudendal nerves. The battery device delivers continuous electrical stimulation. Originally designed to treat neurogenic bladder disease, the treatment has been shown to be effective in treating overactive bladder, neurogenic bladder symptoms, urinary retention as well as faecal incontinence and chronic pain.

Insertion of the device requires a two-stage procedure. The first implants an external device with a wire or tined electrode for 2 weeks to ensure effectiveness of the product before a subcutaneous permanent device is inserted with a tined electrode. Studies have shown a reduction in improvement in incontinence episodes, leakage severity, voiding frequency and pad use with treatment benefits persisting in 68% of patients at 5 years [33].

Adverse effects must be discussed when offering this treatment modality. The procedure has an overall reported reoperation rate of 33% for pain, lead migration or infection at the implant site or battery change after 5–7 years depending on the device and usage settings. Nine percent of patients required complete removal of the device [36].

Miniature wireless implant devices for pretibial nerve stimulation and rechargeable devices for sacral neuromodulation are currently being developed and trialled for the treatment of OAB which may provide promising treatment alternatives for the future.

8.8 Surgery

Surgical treatment for OAB remains a last resort for those who have failed the above treatment modalities or find them unacceptable. Patients often have a low-capacity, poorly compliant bladder with refractory OAB symptoms. The two most commonly carried out procedures include clam ileocystoplasty or urinary diversion. Both are considered major and complex surgical procedures, and patient selection and comorbidities need to be considered before offering this treatment. The traditional approach to this surgery is through open abdominal surgery; however through

equipment advances, laparoscopic and robotic methods can also be employed in experienced hands [37].

8.8.1 Clam Cystoplasty

Clam cystoplasty aims to turn a high-pressure system into a low-pressure one through the anastomosis of a bowel segment to the bladder. The most commonly used intestinal segment is the ileum in an ileocystoplasty. Bladder capacity is therefore increased, detrusor pressure is reduced, upper tracts are protected and any concurrent ureteric reflux can resolve. Satisfactory outcomes from this procedure are reported in up to 88% of patients.

Common side effects or complications long term include the need to carry out ISC for 10–75% of patients. Metabolic disturbances can contribute to vitamin B12 deficiency and hyperchloraemic acidosis with resulting bone demineralisation with osteoporosis. Others include bacteriuria, urinary tract stones (15–40% of patients), mucous retention in the bladder, spontaneous bladder perforation, incontinence and carcinoma. The chronic exposure of the ileal mucosa to urine can lead to malignant change in 1.2% of patients. As a result, long-term yearly cystoscopic and biopsy monitoring after 10 years post-procedure is advised [37, 38].

8.8.2 Urinary Diversion

As a last-resort treatment modality who cannot carry out ISC, with uncompromised renal function, a urinary diversion to an ileal stoma or various segments of the intestinal tract (most commonly the appendix or ileum) creates a continence reservoir that requires catheterisation to empty the urine. Low incontinence rates of 2–16% [38] have been reported following this procedure.

Key Points

- Overactive bladder is prevalent in postmenopausal women and prevalence increases with age.
- OAB can have a significant impact on quality of life, improvement of which is considered a treatment outcome.
- Lifestyle changes and medical management remain first-line treatment options.
- Treatment with topical oestrogen may be of benefit, although synergistic benefits with pharmacotherapy are unclear.
- Refractory overactive bladder symptoms can occur in 25–40% of patients.
- Multidisciplinary management with patient counselling of treatment options and expected outcomes with written information is essential in the management of refractory OAB.
- Intra-vesical botulinum A toxin injections, posterior tibial nerve stimulation (PTNS) or sacral neuromodulation can provide effective second-line treatment.

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