The overactive bladder: where are we in 2016?

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In this article the authors discuss some of the issues and controversies generated by the development of the overactive bladder symptom complex, the challenges in its clinical application and the current state of play with regards to pharmacotherapeutic management.

Since its inception two decades ago, the symptom complex of the overactive bladder (OAB) has continued to generate a great deal of interest and controversy. Several large epidemiological studies have confirmed the frequency of its occurrence (approximately 10–20% in both sexes), as well as its considerable impact on quality of life. The economic costs related to the care and treatment of patients with urinary incontinence are significant, in addition to costs related to lost productivity in those of working age. Debate continues as to the accuracy and reliability of the definition of OAB, the most recent of which was introduced in the 2002 standardisation document of the International Continence Society (ICS) as ‘urinary urgency with or without urgency incontinence usually accompanied by frequency and nocturia’ .1 The sine qua non of OAB is urinary urgency, described as ‘a sudden and compelling desire to void that is difficult to defer’.1 Voiding frequency of more than eight times a day is regarded as abnormal, although limited evidence was put forward to substantiate this criterion when it was introduced.

DEFINITION AND DIAGNOSIS

The OAB symptom complex was introduced by Paul Abrams and Alan Wein in 1996. Prior to this, terminology in lower urinary tract dysfunction was largely related to pathophysiology and the urodynamic finding of non-voluntary detrusor contractions during bladder filling (Figure 1). This was referred to as ‘detrusor instability’ in idiopathic cases and ‘detrusor hyper–reflexia’ where there was a documented neurological problem.1 These terms were later superseded by idiopathic or neurogenic detrusor overactivity (DO) respectively. The introduction of a symptom complex was driven in part by the observation that in many patients, in particular up to 60% of women complaining of bothersome lower urinary tract storage symptoms, there is no urodynamic evidence of DO.

Figure 1. Urodynamic trace showing detrusor overactivity on bladder filling.
Drug therapy was found to be beneficial in some of these patients, hence the need for an invasive urodynamic study prior to instigating conservative treatment became questionable.²

OAB was proposed as the descriptive term for the complex of symptoms thought to be associated with DO and was particularly attractive due to its simplicity and clarity, especially in relation to patient education and public health measures. Subsequently, OAB became widely accepted within healthcare and the pharmaceutical industry, and by the regulatory authorities. This undoubtedly led to a rise in the awareness of the importance of the storage component of lower urinary tract symptoms amongst the public, as well as an increase in basic and clinical research, leading to the development and introduction of a number of new pharmacotherapeutic agents.

Despite the clear benefits that have arisen as a consequence of the concept of OAB, the current definition lacks universal endorsement. Some have suggested that inclusion of terms such as ‘with or without’ and ‘usually’ introduce a lack of specificity.³ This is compounded by the lack of an evidence base to support the suggested thresholds relating to what can be considered significant urinary frequency, nocturia and incontinence. There has been concern, therefore, that many individuals who have very mild symptoms or who are perhaps on the spectrum of normality are encompassed by the definition. The inference is that some individuals may be overtreated and that the scale of the problem has been overestimated, particularly in light of the fact that most of the epidemiological data are derived from internet- and telephone-based surveys.

The definition of urinary urgency has also been a point of some contention, as arguably a ‘compelling desire to void’ is also felt by individuals with normal urinary function if the bladder is overfull and hence is not necessarily pathological. A ‘fear of leakage’ is probably what truly defines patients with urinary urgency.⁴ Another deficiency lies in the lack of detail as to whether the sensation of urgency can be considered to be discrete or on a spectrum of intensity, analysed to a light switch and dimmer switch respectively. A further important issue is that the word ‘urgency’ is not differentiated from urge in many languages, thus hampering the universal application of the definition.

Should the patient fail to reach the toilet in time, urgency urinary incontinence (UUI) results. Patients who suffer this are further described as having OAB-wet as opposed to OAB-dry. The distinction is important due to the increased anxiety that incontinence produces, coupled with the fact that OAB-wet is more strongly correlated with underlying DO in both men and women. This was clearly shown by Hashim and Abrams, where 69% and 90% of men with OAB-dry and OAB-wet have DO respectively, whilst in women the proportion is 44% and 58%.⁵ Several other studies have supported these findings.⁶,⁷ Work undertaken in Sheffield demonstrated that ambulatory urodynamic studies have a higher sensitivity for the detection of DO, suggesting that DO could be simply missed in a proportion of patients with OAB.⁸

PHARMACOTHERAPY FOR OAB

Over the past two decades, a large number of agents have been developed to treat OAB. Antimuscarinics are the traditional option and a great multitude of placebo-controlled, randomised trials have been published establishing their safety and efficacy. A systematic review and meta-analysis conducted by our group demonstrated a reduction in micturition episodes of 0.5 to 1.3 per day and a reduction in incontinence episodes of 0.4 to 1.1 per day.⁹ As only a few studies have included direct comparisons of different antimuscarinics, a direct meta-analysis was not possible. Nevertheless, it is generally accepted that there is very little difference in efficacy between different agents. The main drawback of antimuscarinic therapy is the incidence of side-effects, particularly with increasing dosages, including dry mouth, heartburn and constipation and cognitive impairment in vulnerable risk groups (eg frail elderly). There is very little high-quality evidence of a difference between agents in terms of these side-effects, with only oxybutynin 10mg conferring a significantly increased risk.¹⁰ An analysis of UK prescription data found that the proportion of patients still on their originally prescribed agent at 12 months ranged from 14–35% for different agents in common use.¹¹ This poor persistence rate is due to a combination of side-effects and lack of perceived efficacy.

For many years, antimuscarinic agents were avoided in men for fear of precipitating urinary retention. Over the past decade, a strong body of evidence has emerged to support the safety of antimuscarinic use in men with post-voiding residuals of 200ml or less, with rates of retention similar to placebo.¹² In addition, when prostate size was measured, it was towards the lower end of the spectrum. Moreover, most studies span three months in duration, which may not be sufficiently long to assess the risk of retention accurately. Consequently, most guidelines do not recommend antimuscarinic use in men with large residuals, large prostates or a previous history of retention.

Mirabegron

Mirabegron has been introduced into practice relatively recently. It is a beta3-receptor agonist and stimulates beta3-receptors in the detrusor muscle, causing relaxation. Mirabegron improves bladder storage without impacting on voiding contraction. The drug has been studied in over 10 000 subjects. Pooled analysis of the pivotal phase 3 studies shows significant reduction in mean incontinence episodes for mirabegron.
50mg (recommended dose) compared to placebo, −1.48 and −1.10 respectively ($p<0.05$). The mean number of micturition episodes also decreased significantly with mirabegron 50mg compared to placebo, −1.75 versus −1.20 respectively ($p<0.05$).

The safety profile of mirabegron appears to be acceptable. The pooled analysis demonstrated the main treatment-related adverse events of nasopharyngitis, hypertension and urinary tract infection occurring at a similar rate to placebo. Importantly, the rate of dry mouth, a common issue with antimuscarinics, was also at placebo level, as were rates of retention. With any agonist working on the sympathetic system there is some theoretical concern over cardiovascular effects. Mirabegron was found to be associated with negligible rises in pulse rate (<1bpm) and blood pressure (<1mmHg).

It is important to note that in the pooled dataset around half of the patients had had prior treatment with an antimuscarinic that was stopped due to lack of efficacy or because of side-effects. Mirabegron was similarly effective in both groups. It remains to be seen whether this efficacy, together with a lower rate of dry mouth, will translate to better long-term persistence rates in real-life clinical practice.

**Botulinum toxin A**

When oral pharmacotherapy fails, the next step in OAB treatment is often intravesical injection of botulinum toxin A (BTX-A) (Figure 2). Botox is the BTX-A product licensed for OAB in the UK. In a systematic review, including a total of 1380 subjects, BTX-A gave a reduction in mean changes in number of micturitions/24 hour of 29% and incontinence episodes of 59%. In terms of urodynamic effects, maximum cystometric capacity increased by 32%, while maximal detrusor pressure declined by 31%. When the two doses of BTX-A (100 and 200 units) were compared, the higher dose was associated with greater improvements in symptoms, but also a greater risk of urinary tract infection and higher self-catheterisation rates. A starting dose of 100 units has therefore been recommended for OAB.

Other formulations of BTX-A are produced by different manufacturing processes and should not be considered as equivalents. The efficacy of BTX-A persists for six to nine months and injections can be repeated as needed. The development of antibodies to BTX-A over time has been observed and has been mooted as a possible cause of loss of efficacy; however, investigators have shown that, with time, further injections have resulted in good outcomes. Biopsies in patients undergoing repeated injections have failed to demonstrate a significant association with inflammation or dysplasia. Although experience with BTX-A has accumulated, questions remain around the optimal volume and number of injections, and the place of trigonal injections.

Finally, the results of a direct comparison of BTX-A with sacral neuromodulation (ROSETTA trial) should shed much-needed light on which option is superior in terms of efficacy, adverse effects and cost. The method of delivery of BTX-A may change in the future, with developments such as electromotive drug administration and liposome instillation having recently been reported in the literature.

**CONCLUSIONS**

OAB is firmly established as a bothersome and treatable symptom complex. It is unlikely that a significant change to its definition will occur in the foreseeable future, although it would certainly benefit from further refinement in terms of the definition of urinary urgency and clarification as to what constitutes significant urinary frequency and nocturia. The advent of mirabegron has provided a further option in pharmacotherapeutic management, while BTX-A continues to be a highly efficacious option in those patients not responding to oral treatment. Sacral neuromodulation is a well-established alternative therapy, albeit with a high initial cost.

**Declaration of interests**

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KEY POINTS

- Overactive bladder (OAB) is a complex of symptoms, not a disease
- It is common in both men and women and increases in prevalence with ageing
- OAB is variably correlated to underlying detrusor overactivity, more so in men than in women
- Antimuscarinic agents remain the mainstay of pharmacological treatment, but are associated with poor adherence and persistence due to side-effects and/or perceived lack of efficacy
- Mirabegron has emerged as an efficacious alternative to antimuscarinics that is not associated with dry mouth
- Intravesical botulinum toxin A is a good option when oral pharmacotherapy has failed to improve symptoms, but carries a risk of urinary retention

REFERENCES