Arab Journal of Urology

ISSN: (Print) 2090-598X (Online) Journal homepage: https://www.tandfonline.com/loi/taju20

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To cite this article: Nadir I. Osman & Christopher R. Chapple (2013) Overactive bladder syndrome: Current pathophysiological concepts and therapeutic approaches, Arab Journal of Urology, 11:4, 313-318, DOI: 10.1016/j.aju.2013.07.006

To link to this article: https://doi.org/10.1016/j.aju.2013.07.006

Arab Journal of Urology (2013) **11**, 313–318

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com

VOIDING DYSFUNCTION / FEMALE UROLOGY
MINI-REVIEW

Overactive bladder syndrome: Current pathophysiological concepts and therapeutic approaches

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Received 17 May 2013, Received in revised form 9 July 2013, Accepted 11 July 2013
Available online 18 September 2013

KEYWORDS

Overactive bladder;
Antimuscarinics;
Botulinum toxin;
Mirabegron

ABBREVIATIONS

OAB, overactive bladder syndrome;
DO, detrusor overactivity;
AM, antimuscarinic agent;
ER, extended-release;
BTX, botulinum toxin A;
PTNS, posterior tibial nerve stimulation;

Abstract ***Objectives:*** The overactive bladder syndrome (OAB) is a highly prevalent and bothersome symptom complex. We review contemporary reports to provide an update of the key aspects of its pathogenesis and the therapeutic approaches.

Methods: The PUBMED database was searched for relevant publications in the period from 1 January 1985 to 1 May 2013, using the keywords 'overactive bladder', 'anti-muscarinics', 'β-3 agonists', 'intravesical botulinum toxin', 'tibial nerve stimulation and 'sacral neuromodulation'.

Results: In all, 33 articles were selected for this review. OAB is very common, affecting 10–20% of the population. It is often bothersome and frequently affects the quality of life. The current definition of OAB remains a source of controversy. Anti-muscarinic agents remain the mainstay of pharmacotherapy. The new β-3 agonists have some efficacy whilst avoiding anti-cholinergic effects, and so might benefit patients who are unable to tolerate anti-muscarinic agents. Intravesical botulinum toxin is recommended for patients in whom oral pharmacotherapy fails, although the optimal parameters in terms of dosing, number of injections and injection site are yet to be fully established. Sacral neuromodulation is another option that has a good response in about half of patients.

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Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.aju.2013.07.006

SNM, sacral neuromodulation

Conclusions: OAB remains an incompletely understood problem that presents a significant management challenge. A range of therapeutic options is now available for clinicians managing this problem.

Introduction

The overactive bladder syndrome (OAB) is a common and highly bothersome set of chronic symptoms that often has a significant effect on the quality of life of those affected. OAB affects both men and women equally and becomes more prevalent with increasing age. There is a large economic burden resulting from the problem, on both individuals and society, in terms of the direct care-related costs and lost productivity. OAB comprises storage LUTS and has been defined by the ICS as 'urinary urgency with or without urgency incontinence usually accompanied by frequency and nocturia' [1]. The pivotal symptom which must be present is urinary urgency, defined as 'a sudden and compelling desire to void that is difficult to defer' [1].

Terminology and definitions

The original terminology relating to OAB had its basis in pathophysiology, relying on the finding of non-volitional detrusor contractions during bladder filling, previously termed 'detrusor instability' (idiopathic aetiology) or 'detrusor hyper-reflexia' (neurogenic aetiology) [1]. The term currently recommended for this finding by the ICS is detrusor overactivity (DO). In 1996, Abrams and Wein [2] proposed a shift to a symptom-based definition, as it was clear that patients with bothersome symptoms did not always have DO. Also, it was felt unnecessary to subject all patients with symptoms to urodynamic studies before starting drug therapy. The term OAB was used, as it was deemed to be easier for patients to understand and was subsequently rapidly adopted by the healthcare profession, as well as the regulators and major pharmaceutical companies. The outcome has been an increase in the public profile of the syndrome, the rapid expansion of research into OAB, and growth in the market of agents used in its treatment.

Although there have been clear advantages in developing a symptom-based definition and adoption of the term OAB, OAB continues to generate controversy. Some have argued that the definition of OAB is too vague, with the inclusion of terms such 'usually' and 'with or without', to have sufficient specificity [3]. A further criticism is the lack of standardised outcome measures for symptom severity, e.g., how many voids, the degree of frequency (above the threshold of eight episodes per day) and the degree of incontinence, in the definition. This might result in the inclusion of individuals with mild or occasional symptoms but who might actually be 'normal', albeit on the extreme of a spectrum. Thus the implication is a possible over-medicalisation and an overestimation of the scale of the problem, particularly as the large surveys on the epidemiology reported to date have relied upon rather subjective methods, such as telephone interviews and Internet-based questionnaires.

From a practical perspective the interpretation of urgency, the sensory symptom which must be present, is often difficult. The ICS definition does not describe whether urgency is a discrete or continuous phenomenon, whilst a compelling desire to void is also arguably felt by normal individuals if the bladder is sufficiently full. Some authors have suggested that patients with urgency have a 'fear of leakage' and it is this which truly sets them apart from other individuals [4]. When the toilet is not reached in time incontinence results, termed urgency urinary incontinence, which happens in ≈30% of patients (usually female) with OAB. In men such episodes are highly correlated with underlying DO (in 60–90%) compared to women (in 58%) [5] due to the relatively weaker bladder outlet in women, which means that leakage is more likely to occur. Furthermore, the term 'urgency' is not differentiated from 'urge' in many languages as a specific concept.

Epidemiological aspects

Many epidemiological studies have shown that OAB has a high prevalence worldwide, whilst being a consistent cause of bother and reduced quality of life in both sexes and in all age groups. The largest study was a survey of over 19,000 individuals in four countries across Europe, as well as Canada (the EPIC study), which determined that OAB was present in 10.8% of men and 12.2% of women in the general population, becoming increasingly prevalent in individuals aged >40 years, at 13.1% and 14.6% men and women, respectively [6]. In those with OAB, incontinence was a feature in 28.0% and 44.5% of men and women, respectively. More than half of individuals reported being troubled by their symptoms. Subsequently, the effect of OAB on health-related quality of life has been studied, with the finding that individuals with OAB are more likely than age-matched controls to have depression (11.4% vs. 3.6%) and sexual problems, in addition to being more likely to have work-related impairment (24.7% vs. 12.2%), or be unemployed (42.0% vs. 33.6%) [7].

The economic costs of OAB are legion. The EPIC study found that the total costs related to OAB per country were around US$ 13 billion per year, including nursing-related costs, lost productivity, investigation- and treatment-related expense (including the cost of treating OAB-related depression) [8].

Pathophysiology

Despite intense research, the aetiopathogenesis of OAB in the absence of a neurological cause (e.g. multiple sclerosis) remains incompletely understood. The putative mechanisms might involve aberrations of the detrusor muscle itself, the sensory system and/or the central neural control mechanisms of bladder function, and remain the subject of academic discussion. The myogenic hypothesis, proposed by Brading and Turner [9], asserted that the smooth muscle cells became hyperexcitable due to denervation, or 'denervation hypersensitivity', associated with BOO. Consequently the myocytes show increased electronic coupling, which might result in widespread excitation throughout the detrusor, and thus DO. Whilst traditionally DO was assumed to be the common underlying mechanism, this is clearly not present in all patients with OAB symptoms [10], particularly as obstruction is uncommon in women, suggesting alternative mechanisms.

A neurogenic mechanism was proposed by de Groat [11], based on a loss of the inhibitory effect of the central neural control mechanisms and unmasking of primitive voiding reflexes. Diseases such as stroke and Parkinson's disease can damage the brain, resulting in a loss of suprapontine inhibition on the pontine micturition centre, which might in turn allow primitive reflexes to result in involuntary detrusor contractions. Alternatively, spinal axonal injury can lead to primitive spinal voiding reflexes triggered by C-fibre bladder afferents [10].

A mechanism affecting the afferent system is also possible, especially given that urgency is a sensory symptom. An abnormality in sensory transduction or the central processing of bladder afferent signals might result in some individuals having a heightened perception of bladder filling, and such a mechanism might be particularly at play in those not having DO. Considering that both OAB and DO increase with age it might be that an age-related change in brain/neural function is important.

Recently the urothelium and suburothelium have attracted interest. The urothelium was previously considered to mainly act as a barrier but is now recognised as having a high metabolic rate and subserving an important sensory function in detecting chemical, thermal and mechanical stimuli. The urothelial cells contain several receptors, including those for muscarinic, purinergic and TRPV1 agonists, whilst ATP, nitrous oxide and acetylcholine are released by the urothelium in response to stimuli. The interstitial cells, which have been identified throughout the bladder wall, may also have a role in the urothelium, where they might modulate calcium transmission from smooth muscle cells [12], and in the suburothelial space form networks with gap junctions that might increase the afferent response to stretching [13].

Therapy

The contemporary management of OAB begins with a full assessment of the patient, including a bladder diary, followed by conservative measures encompassing lifestyle adjustments, such as reducing fluid and caffeine intake, weight reduction and behavioural or physical therapies. The next step in the treatment is usually pharmacotherapy, where an antimuscarinic agent (AMs) has traditionally been the agent of choice. A new class of agent, β-3 agonists, has recently become available for use, and the evidence for these will be discussed.

AMs

The muscarinic receptor is known to exist in five subtypes that are distributed throughout the body (e.g., salivary gland M_1/M_3, gut M_2/M_3, brain M_1 and cardiovascular system M_2). In the bladder the M_2 receptors predominate (75%), the exact role of which is not yet known, but it is the M3 receptors (25%) that are responsible for the normal volitional detrusor contraction. AMs have traditionally been viewed as exerting their effect through the blockade of post-junctional muscarinic M3 receptors [14], which normally cause smooth muscle contraction when stimulated [15]. This mechanism is problematic, as in standard doses AMs do not appear to cause any impairment in detrusor voiding function or bladder emptying, whilst at the same time are effective in relieving OAB symptoms. As discussed earlier, the urothelium has been found to contain muscarinic receptors, which have also been found in afferent nerves. This raises the possibility that at lower doses AMs exert their effect through sensory mechanisms, where with higher doses efferent mechanisms operate. This suggestion would explain why individuals with OAB, but not DO, often benefit from AMs.

The evidence base for using AMs for OAB is strong and well established. The common agents in contemporary use (including propiverine, fesoterodine, tolterodine, oxybutynin, solifenacin, trospium and darifenacin) have been subjected to meta-analyses [16,17]. All AMs have been shown to be effective, with a significant benefit over placebo, notwithstanding the accepted high placebo response rate in all studies of OAB therapy [18]. There are clear improvements in frequency and incontinence episodes, in urodynamic variables such as volume at first desire to void and maximal cystometric capacity, and in health-related quality of life.

A common issue with AMs is the poor adherence and persistence with therapy, which can occur due to the side-effects or lack of perceived efficacy. Common side-effects include dry mouth, reported in 30% patients receiving active treatment and in 8% receiving placebo in clinical trials, whilst pruritus occurs in 15% and 5% in the treatment and placebo groups, respectively. Headache, blurred vision, constipation, erythema, urinary retention and fatigue can also occur, but less frequently. Data from marketing studies suggest that up to 70% of individuals discontinue treatment in the first year after starting AMs, which is at odds with open-label studies, which showed discontinuation rates as low as 2% [19].

A strategy that might better balance efficacy and the side-effects of therapy is dose escalation or flexible dosing, whereby patients are given the option of increasing the dosage of the AM until symptomatic improvement is sufficient, whilst adverse side-effects (e.g. dry mouth) are minimised. Using this strategy, those with worse symptoms at baseline showed the greatest benefit [20]. Other factors that might result in variable responses are the route of delivery (e.g., transdermal, oral) and the pharmacokinetics of the agent, particularly how fast the agent is released in the circulation. Particularly, preparations of agents with extended-release (ER) profiles were shown to have a significant advantage over immediate-release preparations in terms of both efficacy and side-effects [17]. The lack of studies of direct comparisons of the different agents at their optimal doses makes it impossible to determine if there is a different efficacy and adverse-event rate across agents. In practice, when a patient has failed to derive therapeutic benefit or failed to tolerate a particular agent it is common practice to try a different agent, although the evidence to support this is lacking.

Mirabegron, the first β-3 agonist

β-1, -2 and -3 adrenoreceptors have been shown to be present in the detrusor and urothelium. When stimulated these receptors lead to G protein and adenyl cyclase activation, which leads to an increase in cyclic AMP levels and relaxation of the detrusor; in man this effect is mediated by the β-3 receptors. Mirabegron, an agent that specifically agonises the β-3 receptor has recently become available for use. Recent phase III trials have been reported that show the efficacy and safety of this agent in patients with OAB. The potential advantage of this agent is the lower incidence of dry mouth and other anticholinergic side-effects that are often bothersome to patients, and can be a reason for discontinuing therapy.

A European and Australian trial including nearly 2000 patients evaluated mirabegron (50 mg and 100 mg) in comparison to tolterodine (4 mg ER preparation) and placebo. There was a significant reduction in the number of voids over a 24-h period, and incontinence episodes, vs. placebo at 12 weeks, at −1.93 vs. −1.34 ($P < 0.05$) and −1.57 vs. −1.17 ($P < 0.05$), respectively [21]. A higher dosage of mirabegron produced no additional benefit. There was a similar ratio of adverse events in all the groups. However, in terms of dry mouth the incidence for placebo, mirabegron 50 mg and mirabegron 100 mg was 2.6%, 2.8% and 2.8%, respectively, in comparison to tolterodine, which was higher at 10.1%.

A study by Chapple et al. [22], that included nearly 2500 subjects, compared the safety of mirabegron (50 mg and 100 mg) to tolterodine ER (4 mg). The number of adverse events was consistent across all groups, at 59.7% for mirabegron 50 mg, 61.3% for mirabegron 100 mg and 62.6% for tolterodine ER 4 mg. Adverse events included hypertension, UTI and nasopharyngitis, and were comparable across all groups. However, in terms of dry mouth, the incidence was 8.6% for tolterodine, whilst for mirabegron 50 mg and 100 mg it was 2.8% and 2.3%, respectively.

Another study from North America also assessed mirabegron 50 mg in comparison to placebo, finding similar decreases in the mean number of voids over 24 h and in incontinence episodes. Furthermore, there were also significant improvements in the levels of urgency and nocturia episodes [23]. In review of the existing data, this therapy appears to be as effective in patients who have failed to respond to AM or cannot tolerate them, as in treatment naive patients.

Intravesical botulinum toxin A (BTX)

If, after a trial of pharmacotherapy, the patient has not had an adequate improvement in symptoms, BTX intravesical injection therapy can be offered as the next step. BTX contains a heavy chain that binds to the presynaptic terminal of the neuromuscular junction, and this then leads to internalisation of the neurotoxic component, which is the light chain. The latter acts by inhibiting the release of acetylcholine from the presynaptic terminal of the motor end plate, that then results in the muscle that is innervated becoming flaccidly paralysed. After 1–3 days the clinical effect becomes manifest, but why there is a delay is not yet understood. The effect of the toxin is temporary, with a return to function within 6–9 months.

BTX is also proposed to act on the afferent system, which might be the explanation for the improvement in urinary urgency, which as mentioned previously is a sensory symptom. A possible mechanism for this might be through a decrease in the number of suburothelial afferent neurones expressing purinergic and vallinoid receptors. Other possible mechanisms include inhibiting neurotransmitters (e.g. acetylcholine) from being released by the urothelium. In addition, a reduction in nerve growth factor has been reported after BTX injection, which might lead to a reduction in C-fibre hyperexcitability.

BTX is available in different preparations, each of which is a distinct chemical entity, and the doses and data for each cannot be used interchangeably. Most clinical studies assessing intravesical BTX have evaluated the onabotulinum toxin A preparation. There have been significant improvements in the number of voiding episodes over 24 h, incontinence episodes, urodynamic variables and quality-of-life scores [24]. The efficacy peaks at ≈4 weeks, with the effect lasting typically up to 9 months, and repeated treatment efficacy has been shown in up to 10 treatment cycles. There is a reduction in episodes of urgency and incontinence by ≈80% and 60%, respectively. Patients should be counselled about the risk of an increased postvoid residual volume, occurring in 20–40% of individuals, and the need to use self-catheterisation, with the attendant risk of UTI (14–40%). The risk of general muscular weakness is considered very rare. In terms of dosage, there are no firm recommendations, but in our practice we would advise a lower starting dose of 100 units of onabotulinum toxin A, based on the currently available research [25]. The disadvantage with higher dosing is the reduction in detrusor voiding pressures and an increased risk of voiding problems, whilst at the same time there is no increased efficacy [26].

Some important issues for further investigation are the injection site, volume and number of injections. Injection at the trigone has been shown not to cause vesico-ureteric reflux and might be a beneficial site to inject in some individuals. Increasing the volume of injections was shown to enhance the distribution of the toxin in the bladder, although whether this leads to clinically increased efficacy in man needs to be established, in addition to the effect of varying the number of injections.

Posterior tibial nerve stimulation (PTNS)

PTNS is a treatment option for individuals with OAB in whom pharmacotherapy has failed. Electrical stimulation of the nerve is given through a needle puncturing the skin above the medial ankle. Treatment sessions usually last about 30 min. The evidence base for PTNS is largely composed of observational studies in patients with OAB in whom drug therapy had failed. There was considerable success, with rates of response of up to 81%. The randomised studies, conducted in women, found a good therapeutic effect [27–29] which was maintained at 12 months [28]. The main limitations of this approach are the need for repeated sessions to sustain efficacy, and the attendant expense that this incurs.

Sacral neuromodulation (SNM)

SNM is a useful treatment option in patients with refractory OAB. It consists of implanting a device that generates electrical impulses that are transmitted to the sacral nerves. These impulses are thought to modulate the neural reflexes that control bladder function. The implantation procedure is most commonly performed over two stages. The lead that transmits the impulses is placed through the third sacral foramen. There was a symptomatic improvement of >90% in about half of the patients [30,31], which was maintained at 3 years [32] and beyond 5 years [33,34]. The main limitations of SNM are the risk of complications, such as migration of the lead, infection and failure of the device, as well as the need for revision in ≈30% of patients.

Summary

OAB is a common problem with a significant personal burden for affected individuals, as well as bearing high healthcare costs, notwithstanding the significant economic costs consequent upon lost productivity. Despite extensive research it is still the case that the pathophysiological basis of OAB is incompletely understood in many patients. Although new therapeutic targets are emerging, the mainstay of pharmacotherapy continues to be AMs, although this might change in the near future with the emergence of β-3 agonists. However, it is clear that the therapeutic plateau for AMs has now been reached. BTX has provided an effective option for patients in whom oral pharmacotherapy has failed, whilst the optimal parameters in terms of dosing, injection, number and site are yet to be fully established. The β-3 agonists are associated with a lower incidence of dry mouth and might provide an option in patients unable to tolerate AMs. SNM offers an option to patients with refractory symptoms.

Conflict of interest

C. Chapple is a Consultant and Researcher to Astellas, Pfizer, Recordati, Allergan, and Lilley.

N. Osman has no conflict of interest.

Source of funding

None.

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