Overactive Bladder: A Review

Reviewed by:

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Introduction

Overactive bladder (OAB) syndrome has been described as a condition of urinary urgency often associated with frequency and nocturia, where urgency incontinence may or may not be there, when there is no infection or clear pathological condition.[1,2]

This chronic condition has a considerable impact on the patient's quality of life.[2,3] The condition affects both men and women,[2] with a rise in incidence with age.[4] It has been reported that OAB more frequently affects women.[4]

Symptoms include urgency, frequency, nocturia, and urgency incontinence, with urgency incontinence believed to be more prevalent among females, while males more commonly experience urgency and frequent urination.[3] Nocturia is the symptom that troubles patients the most and has been linked to poor sleep quality and reduced quality of life.[2]

Risk factors for OAB

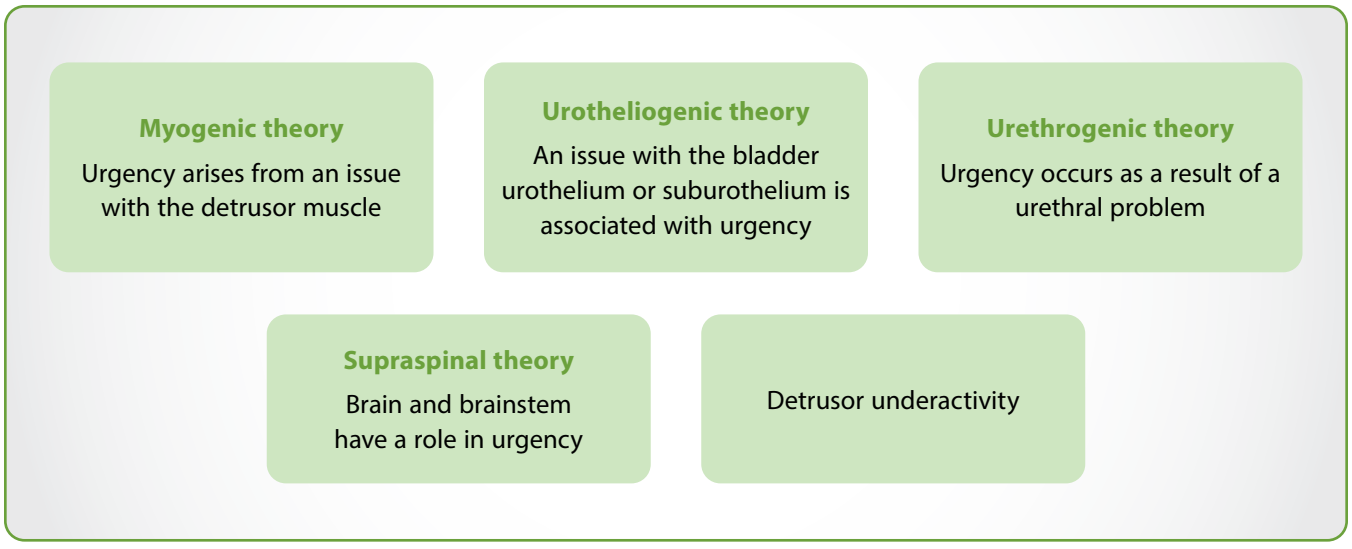
Several factors have been reported to be associated with the risk of developing OAB.[2,3]

- Age—OAB more frequently affects patients above the age of 40 years; children and young adults can also be affected
- Gender—Postmenopausal status with decrease in estrogen levels leads to a higher prevalence of symptoms
- Race—African-American and Hispanic patients have been reported to have a greater OAB prevalence
- Genital prolapse—It has been linked to a heightened risk of OAB
- Surgery for stress urinary incontinence
- Body mass index (BMI) of over 30 kg/m^2
- Affective disorders
- Functional gastrointestinal disorders
- Dysfunction of the autonomic nervous system
- Urinary microbiota
- Smoking and alcohol consumption
- Spices and sour beverages, use of artificial sweeteners
- Sleep apnea
- Increased coffee intake.

Pathophysiology of OAB

While the cause of OAB still remains unclear, the theories proposed revolve around the concept of detrusor overactivity.[2,3] As the bladder's sensory mechanisms are impacted, there is a sense of urgency to void at smaller quantities than usual. A complex interaction between the central and peripheral nervous systems maintains bladder function.[3]

The theories suggested for factors associated with OAB include the following:[3]



Management of OAB

Management of OAB involves non-pharmacological and pharmacological treatment approaches.

Non-pharmacological treatment

It forms the first line of therapy for OAB. This includes behavioral therapy and bladder training. Changes are introduced in the patient's lifestyle, such as quitting smoking, losing weight, changes in diet and fluid intake, and avoiding the intake of coffee, alcohol, spices, and sour beverages. The patient may be advised not to take any fluids 2 hours before going to bed. Regulating the bowels and increasing exercise are also part of non-pharmacological treatment.[2,3] Fluid intake should be restricted to 1 to 1.5 liters in a day.[4]

Bladder training has been reported to have favorable effects in OAB. Under this, the patient passes urine at regular intervals which may begin with intervals of 30 minutes, gradually increasing to 3-4-hour intervals.[2,3]

Pelvic floor muscle training (PFMT), via a reduction in detrusor contractions, can help decrease the episodes of urgency and incontinence. Pelvic floor exercises include Kegel exercises, pelvic floor exercise with biofeedback, vaginal weight training, and pelvic floor electrical stimulation.[2,3]

Pharmacological treatment

Pharmacological treatment forms the second line of therapy for OAB. Antimuscarinic or anticholinergic agents can play a role in relaxing the detrusor muscle. These drugs have been reported to be effective and safe and improve the patient's symptoms as well as their quality of life.[3,4] However, their use is plagued by various side effects, including dryness of mouth and eyes, constipation, cognitive impairment, arrhythmia, etc.[3] Hence, the discontinuation of these agents by the patients.[3]

Therefore, one should begin with small doses and observe the patient for the effectiveness and adverse effects of the agent. The drug can be titrated accordingly.[2,3]

Beta $(\beta)_3$-agonists are also used to manage OAB. Mirabegron, a β_3-adrenoceptor agonist, has been shown to have positive effects on OAB symptoms. It is tolerated well and appears to be similar to antimuscarinic agents in effectiveness.[3] However, it has been known to cause hypertension.[2]

Patients who do not respond to monotherapy may be given a combination of antimuscarinic and β_3-agonist.[4]

Third-line therapy is needed in patients refractory to antimuscarinic agents or β_3-agonist. Third-line treatment includes the use of peripheral tibial nerve stimulation (PTNS), temporary chemical denervation of the detrusor muscle with botulinum toxin A, or sacral neuromodulation. Surgery constitutes the fourth line of therapy and is needed in patients not responding to any other treatment. This includes augmentation cytoplasty and urinary diversion.[3]

Role of flavoxate in OAB

Flavoxate became the first medication that received the Food and Drug Administration (FDA) approval for the treatment of OAB in the year 1970.[5] This drug has been used by urologists for several years.[6] Flavoxate hydrochloride is a spasmolytic agent and acts as a potential smooth muscle relaxant.[7]

Mechanism of action of flavoxate

Figure 1 summarizes the mechanism of action of flavoxate. Acting centrally, flavoxate inhibits the micturition reflex. It also enhances bladder capacity and inhibits rhythmic bladder contractions. In humans, flavoxate has been reported to directly inhibit the detrusor muscle and leads to its relaxation by blocking voltage-dependent L-type calcium channels.[5] It does not have the usual anticholinergic effects.[7]

Clinical efficacy of flavoxate

Several studies have shown the beneficial effects of flavoxate in symptoms of urgency and incontinence. An observational study was conducted by Fehrmann-Zumpe and colleagues on flavoxate for urge incontinence. In a subgroup of patients with no urinary tract infections or benign prostatic hyperplasia, investigators noted a 37% decrease in dysuria, a 53% reduction in nocturia, a 61% reduction in daytime urge and a 69% decrease in nighttime urge. Additionally, bladder volume at first urge sensation was found to be increased by 36%. The drug was found to be effective and was tolerated well.[8] Gu and colleagues noted a complete cure in symptoms of urgency/incontinence in 67% of the patients with flavoxate while 20% showed improvement. Additionally, the drug was noted to be effective in 77.4% of the patients who did not respond to prior anticholinergic therapy. Adverse events were noted in just 1.3% of the patients.[9]

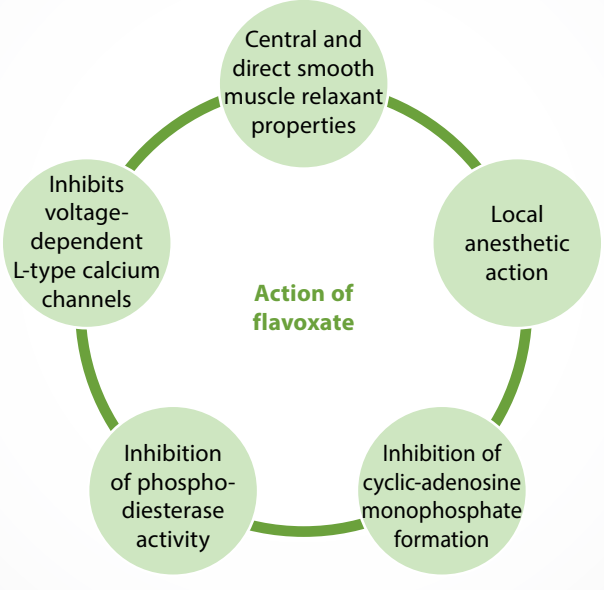
Oxybutynin is a commonly used drug to treat urge incontinence. A study by Milani and colleagues found that the efficacy of flavoxate was equivalent to oxybutynin for the relief of urge syndrome in women. Of note, flavoxate had lesser and milder adverse effects.[10]

A meta-analysis by Sweeney and colleagues evaluated the efficacy and safety profile of flavoxate in the symptomatic management of OAB. The meta-analysis revealed better efficacy with flavoxate in comparison with placebo, propantheline, emepronium, and phenazopyridine. The drug was found to be effective and well-tolerated and the adverse effects were minimal.[6]

Adverse effects with anticholinergics vs. flavoxate

Flavoxate has only slight affinity to the muscarinic receptors while anticholinergic agents like oxybutynin have a strong affinity to these receptors.[7] In a crossover

Figure 1. Action of flavoxate

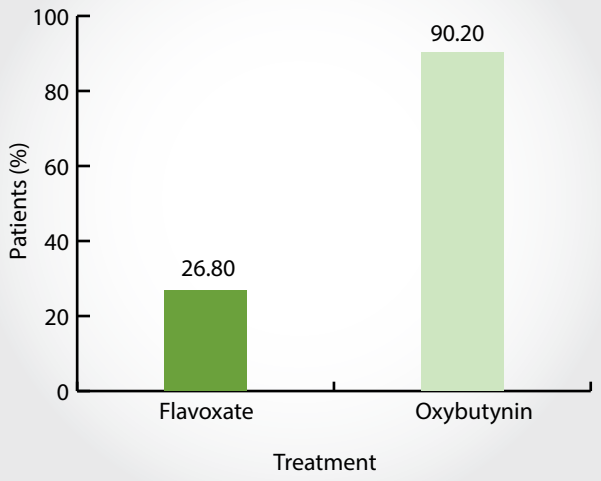


comparison study of flavoxate and oxybutynin, adverse effects were evident in only 26.8% of the patients with flavoxate compared to 90.2% of the patients with oxybutynin (Figure 2). None of the patients interrupted treatment while on flavoxate while 5 patients stopped the treatment owing to side effects on oxybutynin therapy.[10]

Other treatments

Other treatment options, being investigated, that may have a role in OAB, include alpha-adrenoceptor antagonists, neurokinin receptor antagonists, inhibitors of nerve growth factor, gene therapy, stem cell therapy, capsaicin, and vaginal estrogen.[2,3]

Figure 2. Proportion of patients experiencing adverse effects with flavoxate vs. oxybutynin



Conclusion

Overactive bladder is a prevalent and chronic condition significantly impacting patients' quality of life, manifesting through symptoms such as urgency, frequency, nocturia, and urgency incontinence. The management of OAB requires a multifaceted approach, beginning with non-pharmacological interventions, like behavioral therapy, lifestyle modifications, and PFMT. These initial strategies aim to alleviate symptoms without the adverse effects associated with medications.

When non-pharmacological methods are insufficient, pharmacological treatments, primarily antimuscarinic agents and β_3-agonists, are employed. Although effective, these treatments often come with significant side effects, leading to poor adherence and discontinuation by patients. Flavoxate emerges as a valuable alternative, offering symptom relief with a more favorable side effect profile compared to traditional anticholinergic agents. Clinical studies have demonstrated flavoxate's efficacy in reducing symptoms such as urgency and incontinence while maintaining a higher tolerance among patients.

As research progresses, newer therapeutic options and novel treatments continue to be explored, potentially expanding the arsenal for managing OAB. Ultimately, the choice of treatment should be individualized, considering the patient's specific symptoms, preferences, and response to previous therapies. Flavoxate's unique mechanism of action and a favorable safety profile position it as a prudent option in the pharmacological management of OAB, contributing to improved patient outcomes and quality of life.

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