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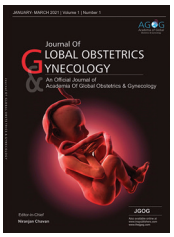
Review Article



The Drug Management of Overactive Bladder

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ABSTRACT

Overactive bladder (OAB) is a condition characterized by a sudden and involuntary contraction of the bladder muscles, leading to an urgency, frequency and sometimes urinary incontinence. The prevalence is seen increasing with age. In women, prevalence ranges from 9–43%. The management of OAB often involves a combination of behavioral therapies, medications, and sometimes surgical interventions.Efficacy of BOTOX injection in treating OAB is exquisite with lower incidence of side effects.

Key words: Overactive Bladder, Botox, Anticholinergic agents

INTRODUCTION

Overactive bladder (OAB) is a condition characterized by a sudden and involuntary contraction of the bladder muscles, leading to an urgency, frequency, and sometimes urinary incontinence. The management of OAB often involves a combination of behavioral therapies, medications, and sometimes surgical interventions.

DRUGS FOR OAB

The International Continence Society defines OAB as a syndrome characterized by urinary urgency, often with urinary frequency and nocturia, in the absence of local pathological factors.[1] The prevalence is seen increasing with age. In women, prevalence ranges from 9% to 43%.[2]

The correct mechanism for drugs used in the management of OAB is:

a. Inhibition of detrusor muscle contraction anticholinergics/ antimuscarinics such as solifenacin
b. Anticholinergics and antimuscarinics like solifenacin work by blocking the action of acetylcholine on the detrusor muscle of the bladder. This inhibition reduces involuntary contractions of the bladder, which are characteristic of OAB syndrome
c. Relaxation of the detrusor muscles is achieved by Beta 3 adrenoceptor agonists like mirabegron
d. Increasing bladder outlet resistance is associated with alpha adrenergic agonists, which are used in conditions like benign prostatic hyperplasia, not OAB
e. Decreasing urine production is the mechanism of action for antidiuretics such as desmopressin, which is used primarily in conditions involving excessive urine production (e.g., diabetes insipidus), not in OAB.

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ANTICHOLINERGIC DRUGS

Anticholinergic drugs indeed remain a cornerstone in the pharmacotherapy of OAB.[3]

The mechanism of action of antimuscarinic drugs in the management of OAB involves blocking the action of acetylcholine on muscarinic receptors[4] particularly M2 and M3 receptors, which are predominant in the bladder's detrusor muscle.

1. Muscarinic receptor types:
   M2 receptors are prevalent within the bladder
   M3 receptors are more active in detrusor muscle function.[5]
2. Antimuscarinic drugs:
   Oxybutynin, tolterodine, fesoterodine, and trospium are antagonists of both M2 and M3 muscarinic receptors. They block these receptors, thereby reducing the bladder's sensitivity to acetylcholine and decreasing involuntary contractions.
3. Solifenacin and darifenacin are selective antagonists of the M3 muscarinic receptor subtype. They specifically target M3 receptors

   Which are primarily responsible for bladder detrusor muscle contraction.

By antagonizing these receptors, antimuscarinic drugs help to alleviate the symptoms of OAB, such as urinary urgency, frequency, and urge incontinence. Selective M3 antagonists such as solifenacin

and darifenacin aim to minimize side effects associated with non-selective antagonism of other muscarinic receptor subtypes.

Antimuscarinic drugs, while effective in treating OAB, are associated with a range of anticholinergic side effects. These side effects occur because these drugs block muscarinic receptors not only in the bladder but also throughout the body, affecting various organ systems.

These are dry mouth, constipation, blurred vision, urinary retention, and confusion and tachycardia.

ANTICHOLINERGIC AGENTS IN SPECIAL CONDITIONS

Women with autonomic neuropathy: These individuals may be more sensitive to anticholinergic effects due to compromised nerve function affecting autonomic responses.

Hiatus Hernia: Antimuscarinics can worsen symptoms related to gastroesophageal reflux disease associated with hiatus hernia.

Hepatic and renal impairment: Caution is necessary in patients with liver or kidney impairment, as these conditions can affect drug metabolism and clearance.

Hyperthyroidism: Antimuscarinics may worsen symptoms associated with an overactive thyroid gland (hyperthyroidism), such as increased heart rate and sweating.

Coronary artery disease (CAD): Anticholinergics can cause tachycardia (increased heart rate) and may exacerbate ischemic heart conditions in individuals with CAD.

Congestive heart failure: These drugs can worsen symptoms of heart failure and may lead to fluid retention or exacerbate arrhythmias.

Arrhythmias: Anticholinergics can increase the risk of arrhythmias due to their effects on heart rate and conduction.

Myasthenia gravis: This autoimmune neuromuscular disease is characterized by muscle weakness and fatigue. Anticholinergic medications can worsen muscle weakness in individuals with myasthenia gravis.

Closed angle glaucoma: Anticholinergics can increase intraocular pressure, which is dangerous in individuals with closed angle glaucoma and can lead to a sudden increase in eye pressure and potential vision loss.

Significant bladder outflow obstruction or urinary retention: Anticholinergics can exacerbate urinary retention in individuals with obstructive uropathy or significant bladder outflow obstruction.

Severe ulcerative colitis: Anticholinergic drugs can worsen symptoms of severe inflammatory bowel disease like ulcerative colitis.

Gastrointestinal obstruction: These medications can further impair gastrointestinal motility and are contraindicated in cases of mechanical gastrointestinal obstruction.

In individuals with these conditions, alternative treatments for OAB should be considered to avoid exacerbating underlying health issues. These contraindications underscore the importance of a thorough medical assessment and individualized treatment planning when managing OAB and other conditions concurrently.

Studies by Akino *et al.*[6] showed that more patients withdrew because of adverse events than lack of efficacy. Hence, when selecting drug treatment for OAB, consideration of adverse events is as important, if not more important, than efficacy.

Hsu *et al.*[7] reported that although fesoterodine 8 mg shows greater improvement in incontinence, urgency episodes, and micturition frequency than tolterodine 4 mg, fesoterodine is associated with a higher incidence of adverse effects like constipation and dry mouth compared to tolterodine.

NICE[8] recommends not offering women flavoxate, propantheline, or imipramine to treat urinary incontinence or OAB, also not to offer oxybutynin (immediate release) to older women who may be at higher risk of a sudden deterioration in their physical or mental health, and offer a transdermal OAB treatment to women unable to tolerate oral medicines.

Frail older women

Antimuscarinic drugs may work differently in frail older women and women with multiple co-morbidities of any age. The varying affinities of these drugs for different antimuscarinic receptors within the brain, as well as their ability to cross the blood–brain barrier, can influence their potential for adverse effects on cognitive function.[8]

Oxybutynin is known to have a higher likelihood of crossing the blood–brain barrier compared to newer agents such as tolterodine and darifenacin. This property of oxybutynin can potentially lead to more significant central nervous system (CNS) side effects, including cognitive impairment.

In contrast, tolterodine and darifenacin have lower lipophilicity, which means that they are less likely to penetrate the blood–brain barrier and therefore may be more suitable choices for older patients or those who are more vulnerable to CNS effects.

Trospium, another antimuscarinic agent used for OAB, is considered to have minimal penetration into the CNS based on studies using neuropsychological and coordination tests. This property makes trospium a preferred option in patients where minimizing CNS side effects is a priority.[9]

COUNSELING FOR WOMEN STARTING ANTIMUSCARINIC TREATMENT FOR OAB

1. Likelihood of success and failure: Patients should be informed about the expected outcomes of treatment, including potential improvements in bladder symptoms and the possibility of treatment not achieving desired results.
2. Known side-effects: Common side-effects such as dry mouth and constipation should be clearly explained. Patients should understand that experiencing these side-effects may indicate that the medication is working as intended.
3. Time to benefit: It typically takes about 4 weeks for antimuscarinic medications to start showing their full therapeutic benefit. Patients should be encouraged to persevere with treatment for at least this duration to accurately assess its effectiveness.

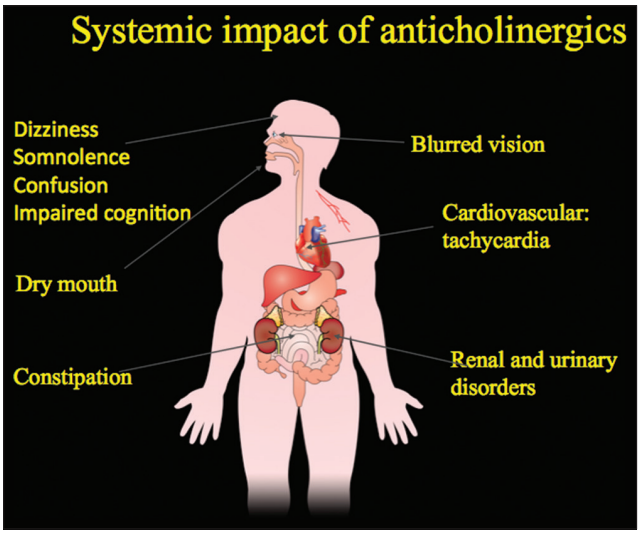

Figure 1: Effect of anticholinergic agents on various systems

4. Monitoring and feedback: Regular follow-ups should be scheduled to monitor treatment progress. Patients should be encouraged to report any limited improvement, lack of improvement, or intolerable adverse effects promptly so that treatment adjustments can be considered.
5. Treatment revisions: If initial treatment does not achieve the desired outcomes or if side-effects are intolerable, adjustments may be necessary. This could involve changing the dosage, switching to a different antimuscarinic drug with potentially different side-effect profiles, or considering alternative treatment options.

Reviewing drugs

A review at 4 weeks after starting a new medicine for OAB and making necessary changes of dose or alternative medicine is advisable.

Mirabegron is recommended as an alternative treatment for OAB symptoms, particularly for individuals who do not respond well to or cannot tolerate antimuscarinic drugs. Several systematic reviews have indicated that mirabegron shows similar efficacy to most antimuscarinic medications in managing OAB symptoms.[10-12]

Mechanism of action

Mirabegron is a sympathomimetic agent that stimulates the β3- adrenoceptors on the detrusor muscle, promoting bladder relaxation during the filling stage.[13]

Side effects

Increased blood pressure, nasopharyngitis, urinary tract infection, and headache are common adverse effects with mirabegron, and dizziness and urinary retention have also been reported.

Drake *et al.*[14] noted that adding mirabegron 50 mg to solifenacin 5 mg improved OAB symptoms when compared with solifenacin 5 or 10 mg, and it was well tolerated in OAB patients. While combination therapy for OAB can offer additional benefits in symptom management, it is important to consider the potential for increased adverse events compared to monotherapy. Several studies have shown that combining different medications, such as an antimuscarinic with mirabegron, may lead to higher incidences of side-effects such as dry mouth, constipation, and others.[7]

Mode of action of OAB treatments [Figure 2]

There are 2 main classes of drugs available to treat OAB: "anticholinergic" medications and "selective beta-3 adrenergic agonists".

Both of these classes of medication are thought to act:

Anticholinergic medications are competitive antagonists of the neurotransmitter acetylcholine at receptor sites within the cholinergic system.

By changing abnormal nerve signalling in the nerve pathways of the bladder and By relaxing the bladder muscle and helping to prevent involuntary bladder muscle contractions.

INVASIVE PROCEDURES FOR OAB

Botulinum toxin type A injection (BOTOX)

NICE recommends injecting bladder wall with botulinum toxin type A to women with OAB caused by detrusor overactivity that fails to respond pharmacotherapy.

Mechanism of action

Botox blocks the presynaptic release of acetylcholine and causes full or partial paralysis and weakening of overactive muscle [Figure 3].

Current evidence

It suggests that Botox may be effective for the symptomatic treatment of OAB. Its use should however be reserved for patients who fail to improve with conservative treatment and medical management with two different anticholinergic drugs.[15]

Drake *et al.*[16] and multiple randomized, placebo-controlled trials have demonstrated that onabotulinumtoxin A (commonly known as botox) is an effective treatment for patients with refractory idiopathic or neurogenic detrusor overactivity (OAB).

Onabotulinumtoxin A provides greater relief of OAB symptoms compared to most other licensed medicines after 12 weeks of treatment. This includes improvements in urinary incontinence episodes, maximum cystometric capacity, and maximum detrusor pressure.

The adverse effects of botulinum toxin A, such as urinary retention and urinary tract infection, were primarily localized to the lower urinary tract.[17]

Nitti *et al.*[18] noted that long-term onabotulinumtoxin A treatment consistently decreased OAB symptoms and improved quality of life.

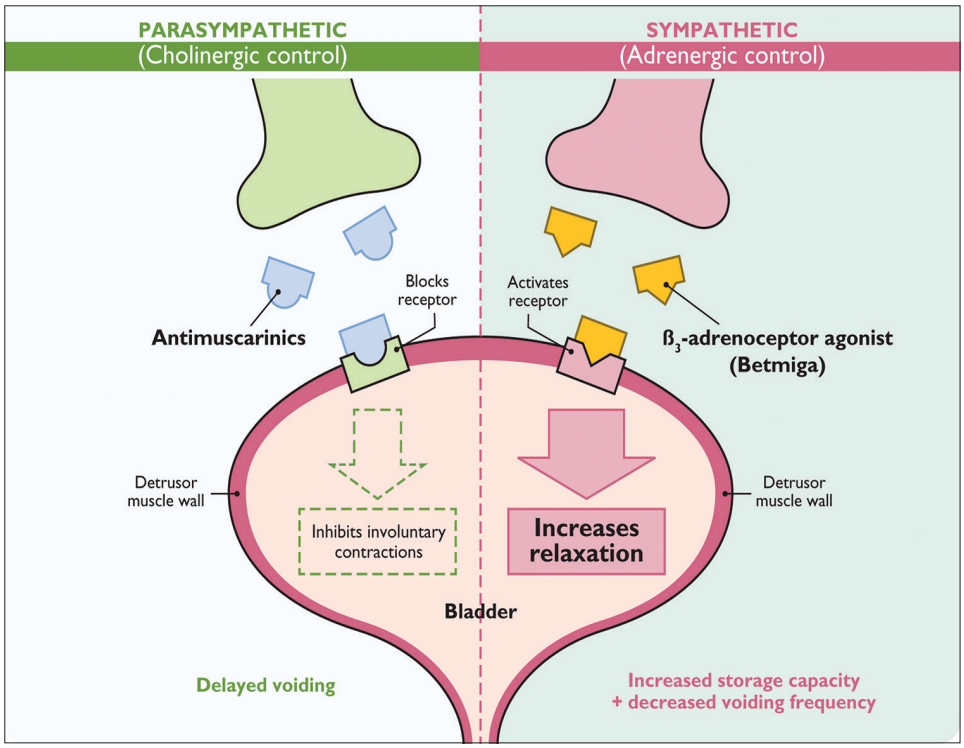

Figure 2: Mechanism of action of antimuscarinic drugs and beta 3 agonists on bladder in the treatment of OAB

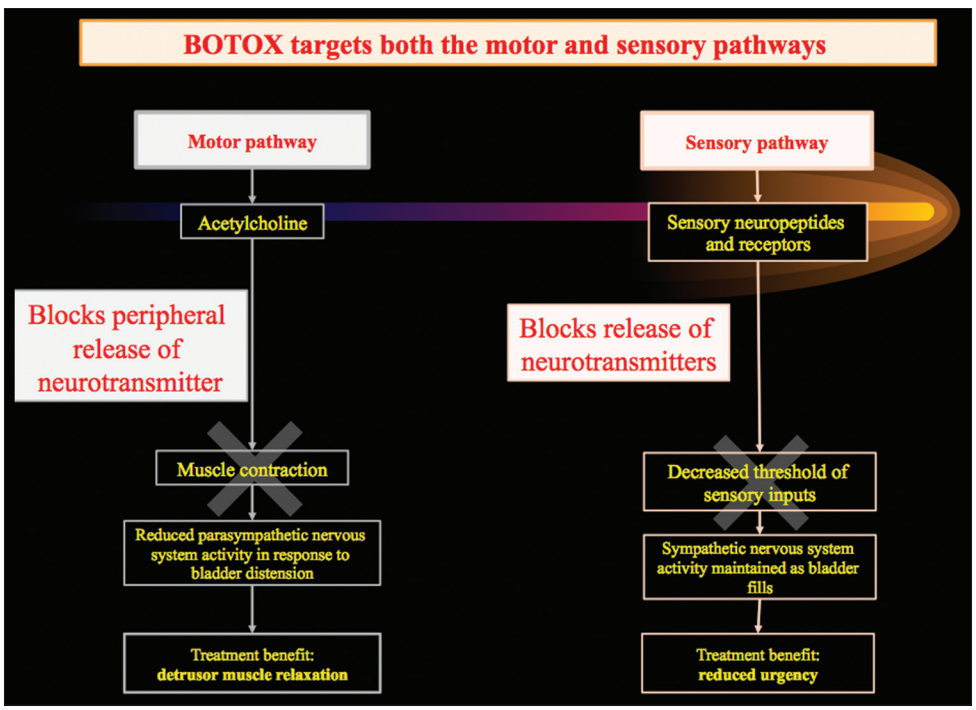

Figure 3: Mechanism of action of BOTOX injection in treating OAB

Precautions and counselling

Patients should be informed about the potential for both complete and partial relief of OAB symptoms following botox injections. There is a risk of developing voiding disorders, such as urinary retention, after botox injections. This may result in difficulty completely emptying the bladder, potentially requiring the use of clean intermittent catheterization to manage urinary voiding and increased risk of urinary tract infection. She should also be

informed that there is no data suggesting long-term efficacy of the injection and their long-term risks.[8]

The procedure is performed under local or general anesthesia using a flexible or rigid cystoscope. BOTOX 100–200 units are dissolved in 10–20 mLs of saline and 1 mL solution is injected at 10–20 sites into the bladder wall, avoiding trigone and ureteric orifices. A post-operative review is required at 3 months and if treatment has been beneficial, then a repeat procedure may be offered with adjusted dose when OAB symptoms recur.

CONCLUSION

Anticholinergic drugs have been the primary treatment for OAB, despite the common issue of side effects leading to patient discontinuation. However, mirabegron has emerged as a well-established alternative to anticholinergics for OAB treatment. Efficacy of BOTOX injection in treating OAB is exquisite with lower incidence of side effects.

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