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EFFICACY AND SAFETY OF MEDICAL TREATMENTS FOR THE MANAGEMENT OF OVERACTIVE BLADDER: A MINI-LITERATURE REVIEW

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ABSTRACT

Overactive bladder (OAB) is a widespread condition that significantly impairs one's quality of life, yet it often goes undiagnosed and is treated inadequately due to various obstacles such as shame, poor communication, and poor patient compliance. There are several treatment options for OAB, including bladder and behavioural training, medications, and surgical therapies. Oral antimuscarinics are the primary choice for pharmacological treatment of OAB. There are a variety of drugs available to treat bladder storage and voiding issues, and soon, novel compounds with higher specificity for the lower urinary tract receptors will be available. This will help to optimize therapy, reducing side effects and improving adherence, particularly in patients with existing medical conditions and in women. This article provides an overview of the pharmacotherapy of OAB.

Keywords: Efficacy, Safety, Overactive Bladder

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EFIKASI DAN KEAMANAN MANAJEMEN PENGOBATAN MEDIS OVERACTIVE BLADDER: A MINI-LITERATURE REVIEW

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ABSTRAK

Kandung kemih terlalu aktif (OAB) adalah kondisi luas yang secara signifikan merusak kualitas hidup seseorang, namun seringkali tidak terdiagnosis dan diobati secara tidak memadai karena berbagai kendala seperti rasa malu, komunikasi yang buruk, dan kepatuhan pasien yang buruk. Ada beberapa pilihan pengobatan untuk OAB, termasuk pelatihan kandung kemih dan perilaku, obat-obatan, dan terapi bedah. Antimuskarinik oral adalah pilihan utama untuk pengobatan farmakologi OAB. Ada berbagai obat yang tersedia untuk mengobati masalah penyimpanan dan berkemih kandung kemih, dan segera, senyawa baru dengan spesifisitas lebih tinggi untuk reseptor saluran kemih bagian bawah akan tersedia. Ini akan membantu mengoptimalkan terapi, mengurangi efek samping dan meningkatkan kepatuhan, terutama pada pasien dengan kondisi medis yang ada dan pada wanita. Artikel ini memberikan gambaran tentang farmakoterapi OAB.

Keywords: Efficacy, Safety, Overactive Bladder

Introduction

Overactive bladder syndrome (OAB) is a prevalent disorder with a significant impact on quality of life. The estimated worldwide prevalence is approximately 10%, affecting more than 500 million individuals. Despite this high prevalence, there is significant underdiagnosis and undertreatment due to several barriers, including embarrassment, poor communication, and low patient adherence. Benner et al. found that only 45% of people with bothersome OAB symptoms consulted a physician and that less than a quarter ever received treatment for OAB. The strongest predictors of consulting were age and bothersome urinary frequency and urgency.[1] The prevalence of OAB is reported at 11.8% to 17% in women and significantly increases with age. Most women with OAB (96%) report leakage of urine with an overall prevalence of urgency incontinence of 12%.[2] OAB has a greater impact on quality of life than stress urinary incontinence and is responsible for several medical comorbidities. Conservative, pharmacotherapeutic, and surgical interventions are available. This literature reviews these interventions, focusing mainly on pharmacotherapy.[2]

Management of OAB

For conservative management various interventions for managing OAB have been proposed, such as Kegel exercises, electrical stimulation, pessaries, behavioral management, and bladder training. Normal voiding occurs via parasympathetic activation of the M2 or M3 receptors, while the M2 receptors also inhibit sympathetically mediated bladder relaxation. Medications, particularly antimuscarinics, are also used, but they can cause side effects that lead to discontinuation. These drugs work by blocking the response to acetylcholine and other parasympathetic neurotransmitters, thus inhibiting contractions of the detrusor muscle which are normally initiated by muscarinic M2 and M3 receptors. Additionally, M2 receptors inhibit sympathetic bladder relaxation. Anticholinergics block acetylcholine and increase bladder capacity. In 2012, a new OAB medication, the β3 agonist mirabegron, was released. It targets the sympathetic nervous system and the b3-adrenoreceptor, in contrast to antimuscarinics.[1-3]

Pharmacological treatments of OAB

1. Anti-muscarinic

It has been demonstrated by comprehensive studies that anticholinergic drugs, also known as antimuscarinics, are beneficial in a clinical setting. However, there is no definitive proof which antimuscarinic is the most effective for treating symptoms of overactive bladder (OAB) or urinary incontinence (UUI). Information about which anticholinergic is recommended for OAB and UUI use are shown in Table 1.[4]

Table 1 – Overview and characteristics of antimuscarinic drugs for overactive bladder syndrome[5]

Medication	Selectivity	Ability to Cross Blood Brain Barrier
Darifenacin	M3	Low
Fesoterodin	Nonselective	Low
Oxybutynin	Nonselective	High
Solifenacin	Predominantly M3	Moderate
Tolterodin	Nonselective	Moderate
Trospium	Nonselective	Low

a. Solifenacin

Solifenacin has been proven to be highly selective for the bladder M3 receptor, with sustained effectiveness and decreased urgency episodes. Compared to oxybutynin, solifenacin has been found to be more beneficial and cause less dry mouth side-effects than tolterodine. The recommended dosage is 5 mg per day, which may be increased to 10 mg/day if more effificacy is desired, although a higher risk of dry mouth accompanies such an increase. Numerous clinical trials have been conducted to demonstrate the safety and efficacy of solifenacin, with follow-up lasting up to a year. Taking solifenacin has been found to improve the quality of life of those with OAB symptoms and the discontinuation rate at one year is low. Moreover, the incidence of dry mouth in those taking solifenacin is significantly lower than for oxybutynin (35% vs. 83%) and the incidence of constipation is

7-8%. A pilot randomized trial of healthy elderly volunteers also revealed that solifenacin does not adversely affect cognitive function.[2, 4, 5]

b. Tolterodine

Tolterodine has been found to be selective for bladder muscarinic receptors and its metabolite, 5-hydroxymethyl-tolterodine, is thought to significantly contribute to its therapeutic effect. This drug is not very liposoluble, which results in it not being able to cross the blood-brain barrier (BBB). It is available as immediate-release (IR) and extended-release (ER) formulations, with dosing of 20 mg b.i.d. for IR and 60 mg/day for ER. In randomized placebo-controlled trials of 12-week duration, improvements were seen in health-related quality of life and objective OAB parameters in patients taking either IR or ER tolterodine, though greater effects were observed in those with moderate to severe OAB symptoms at baseline. Dry mouth is a common side effect occurring in one-third of patients, but it does not cause discontinuation of treatment. There do not appear to be any adverse cardiovascular or central nervous system (CNS) effects associated with tolterodine.[2, 4, 5]

c. Trospium

Compared to oxybutynin and tolterodine, which are both tertiary amines, trospium is a quaternary amine. Due to its lower rate of hepatic metabolism, it may be a preferred treatment option for patients with comorbidities. Reports from several double-blind, placebo-controlled trials with 12-week follow-up periods have indicated that trospium, both in its IR and XR forms, can improve symptoms of overactive bladder. Adverse effects are more common with the drug than with placebo, though they don't lead to discontinuation of treatment. The XR form has been shown to improve OAB symptoms and condition-specific quality of life. As its CNS penetration is low, it causes fewer CNS side effects than the other tertiary amines. Furthermore, it does not affect cognitive function even when used in conjunction with a cholinesterase inhibitor for Alzheimer's. Trospium is mainly excreted in the urine, and does not have any interactions with medications such as digoxin which are eliminated by the kidneys.[2, 4, 5]

d. Darifenacin

Darifenacin, which was approved by the European Medicines Agency in 2004, has a 5-fold higher affinity for the human M3 receptor when compared to the M1 receptor. It is taken orally with a dosage of 7.5-15 mg/day and studies involving 561 patients with OAB have shown that it can decrease urgency, micturition frequency, incontinence episodes, and increase bladder capacity. It is also well tolerated, with few central nervous system and cardiovascular adverse events being reported. Fesoterodine, which was approved by the EMA in 2007 for OAB, is an antimuscarinic hydrolyzed to 5-hydroxymethyl-tolterodine. Reviews have suggested that it is more effective than tolterodine for reducing urgency, frequency, and leakage episodes in both men and women, however there is a higher risk of adverse events causing withdrawal from the drug. The recommended starting dose is 4 mg per day and can be increased up to 8 mg per day.[2, 4, 5]

e. Oxybutinin

The efficacy of oral oxybutynin has been compared to a placebo, and it has been found to be more cost-effective. However, 80% of patients experience anticholinergic adverse effects, causing 33% to discontinue use. Additionally, oxybutynin may cause cognitive impairment shortly after starting treatment. To mitigate this, two transdermal preparations have been developed – a patch (Oxytrol) and a gel (Gelnique 10%) – which have been found to be more effective than the oral form, with fewer side effects. The patch has been observed to cause application site reactions (such as pruritus and erythema) in 14% of cases, while the gel leads to these reactions in 5%.[2, 4, 5]

f. Atropine Sulfate

Atropine sulphate is not approved by the FDA to treat overactive bladder (OAB). However, some physician may prescribe it off-label to treat OAB symptoms such as an increased urge to urinate and urinary incontinence. Some studies have suggested that atropine sulphate may be effective in reducing OAB symptoms. Possible side effects of atropine sulphate include dry mouth, blurred vision, and confusion. Atropine sulphate has been studied as a potential treatment for neurogenic detrusor overactivity (DO). This antimuscarinic agent has the potential to increase bladder capacity without the systemic side-effects seen with other medications. Initial pilot studies of intravascular formulations of atropine suggest it could be an effective and safe treatment for DO, although further research is needed.[4]

g. Propantheline bromide

From literature searching for randomized controlled trials (RCTs) of propantheline bromide in patients with OAB. The primary outcome was the change in frequency of micturition from baseline. secondary outcomes included changes in urgency, nocturia, and incontinence episodes. The results showed that propantheline bromide significantly reduced the frequency of micturition from baseline (mean difference -1.51, 95% CI: -2.26 to -0.76; $p < 0.001$). It also significantly reduced the number of urgency episodes (mean difference -1.59, 95% CI: -2.41 to -0.77; $p < 0.001$) and incontinence episodes (mean difference -0.55, 95% CI: -0.90 to -0.21; $p = 0.002$). Propantheline bromide has a low bioavailability and its effect on OAB has not been well evaluated in controlled trials, but it can be considered effective and may, in individually titrated doses, be clinically useful. [4]

2. β-Adrenoceptor agonists

Beta-3 agonists may be a potential alternative to other drugs, including antimuscarinics, for the treatment of overactive bladder (OAB) by increasing bladder capacity without changing micturition pressure or residual volume. Examples of such b3-AR selective agonists being tested as treatments for OAB include Mirabegron, which was approved by the European Medicine Agency in 2012. Studies have shown that Mirabegron activates b3-ARs, increasing cAMP activity in cells expressing rat b3-ARs and producing a concentration-dependent bladder relaxation. In addition, it has been shown to increase the amount of urine voided per micturition in infarcted rats. Mirabegron appears to have a good safety/efficacy profile and is well tolerated, resulting in the reduction of incontinence episodes and mean micturition frequency. It may be used as a second-line treatment for OAB

in patients who are poor responders or intolerant to anticholinergics. Clinical trials suggest that Mirabegron is a novel drug for OAB due to its tolerability and lower incidence of side effects compared to antimuscarinics; however, long-term adverse effects have yet to be explored. The recommended starting dose is 25mg once daily. [4, 6, 7]

3. Neurotoxins

Botulinum toxin (Botox) is a neurotoxin often used in patients with neurological problems and bladder storage disorders. It works by injecting the toxin directly into the bladder, which causes the detrusor muscle to relax, increasing the bladder's storage capacity and reducing urinary incontinence. In 2011, the FDA approved Botox injections to treat urinary incontinence in people with neurological conditions such as spinal cord injury and multiple sclerosis, however this treatment is not approved by the EMA. Later in the year, it was approved in 12 European countries for the management of urinary incontinence in those with neurogenic bladder due to those same conditions. Common side effects of the treatment are urinary tract infections and retention, and the recommended dose is 200 units per treatment, not to be exceeded. Furthermore, Mirabegron, a b3-AR selective agonist, was approved by the EMA in 2012 as a potential alternative to other drugs, including antimuscarinics, for the treatment of overactive bladder. Studies have shown that it increases cAMP activity in cells expressing rat b3-ARs, leading to bladder relaxation and an increase of urine voided per micturition. It is thought to be well-tolerated, with a lower incidence of side effects than antimuscarinics, although long-term adverse effects are yet to be explored. The recommended starting dose is 25mg once daily. [4, 8, 9]

Side Effect

Antimuscarinics had a higher risk of side effects compared to placebo, the most common being a dry mouth, itching, and headache; however, there was no link between taking antimuscarinics and the risk of serious side effects, apart from when propiverine ER 30 mg/day was taken. There was a large range of dry mouth cases (4–70%) due to the difference in study protocols and the patients involved. Generally, the same amount of dry mouth occurred when taking ER antimuscarinics and this increased with higher doses. The majority of people who take antimuscarinic medication experience constipation as the most taxing and irritating side effect. Elderly individuals are particularly vulnerable to this, and the potential for constipation to be worsened by the medication is a legitimate concern. Antimuscarinic drugs can lead to adverse effects on the central nervous system, like dizziness, drowsiness, sleeplessness, or mental confusion. These medications have varying abilities to breach the blood-brain barrier due to the difference in their lipophilicity, and therefore, their capability to cause CNS issues. Oxybutynin has the greatest likelihood of entering the blood-brain barrier, while trospium is least likely. Those elderly individuals with cerebrovascular disease or other medical situations that modify the permeability of the blood-brain barrier, limited muscarinic receptor densities in the brain, age-related changes in drug metabolism, or who take multiple medicines, may be in greater danger of CNS adverse events.[10]

Table 2. Muscarinic agonist/antagonist effects and related side effects in different organs.[10]

Muscarinic agonist/antagonist effects and related side effects in different organs.[a]

Organ/system	Muscarinic receptors	Agonist effects	Agonist side effects	Antagonist effects	Antagonist side effects
Heart	M_2	Negative dromotropic, cronotropic and inotropic	Excessive reduction of cardiac contractility	↑Heart rate	Tachycardia (for vagal block); Arrhythmias
Vascular system	M_3 (endothelial)	Vasodilatation	Hypotension	Slightly vasodilation	
Respiratory system	M_1–M_3	Bronchial smooth musculature stimulation; ↑Bronchial secretion	Bronchospasm	Bronchodilation; ↓Bronchial secretion; Prevention of laryngospasm in anesthesia	
Gastro-intestinal Tract	M_1–M_3	↑Tone and muscle contraction; ↑Secretion	Diarrhea, drooling, nausea, sickness, abdominal cramps	↓Motility; ↓Secretion	Dry mouth; Constipation
Exocrine glands	M_3	↑Secretion	Sweating	↓Secretion	
Urinary tract	M_3 (more than) M_2	Contraction of bladder detrusor muscole; ↑Ureters peristalsis; Sphincter relaxation	Urinary retention	↓Tone and Contraction of bladder and ureters; ↓Urination rate	Urinary retention; Difficulty voiding
Eyes	M_3–M_5	Miosis (for contraction of pupillary sphincter muscle); Accommodation lock (for contraction of ciliary muscle); ↓Intraocular pressure	Accommodation problems, lachrymation	Mydriasis; Accommodation lock	Cycloplegia; Blurry vision
CNS	M_1–M_2–M_4–M_5			↓Cognition = sedation, amnesia	Delirium (rare); Hallucination (?); Drowsiness;
Ganglia and autonomic nerves	M_1			Inibition of Slow Postsynaptic Potenzials; ↑Release Ach (for lock of presynaptic receptors)	

Conclusion

Antimuscarinic drugs are medications that work by blocking the action of the neurotransmitter acetylcholine in the body, which is related to muscle movement. These drugs are commonly used to treat overactive bladder (OAB) and are generally well tolerated. Mirabegron is a newer type of drug that works differently from antimuscarinic drugs, by targeting the beta-3 adrenoceptor to relax the bladder muscle and increase bladder capacity. Combination therapy such antimuscarinic drugs and mirabegron can be beneficial in treating OAB, providing increased efficacy and improved patient adherence to treatment. However, patient adherence to OAB medications is still relatively poor. To improve adherence, healthcare providers need to define clear treatment goals, educate patients regarding their medication regimen, and frequently communicate with patients to identify any problems with adherence.

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