Medical Treatment for Overactive Bladder

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ABSTRACT

To research the medical treatment for overactive bladder, a systematic literature search of peer-reviewed papers published through September 2007 was performed. The PubMed databank was searched for original English articles using the following search terms: "overactive bladder (OAB)", "detrusor overactivity", or "urinary incontinence" and "treatment," alone and linked with any potential molecular target or novel drugs cited in the literature. There are 23 papers reviewed in this article. Currently there are medications that are effective in decreasing urinary urgency (> 1 episode/day) and urge incontinence (≒ 1 episode/day) regardless of the antimuscarinics the patient is taking. However, almost all agents are associated with therapy-limiting side effects, such as dry mouth, constipation, and daytime sleepiness. These adverse effects limit the usefulness of these drugs, because patients often take less than the optimal dosage to avoid the side effects or stop taking the medication. More than 70% of patients did not continue therapy beyond 9 months. Though current medications are effective clinically, but alternative OAB medications are needed to increase safety, tolerability, and efficacy profiles. Because patients with OAB have different medical histories, varying comborbid conditions, and may take different concomitant medications, this population will benefit from the availability of OAB medications with varying attributes.
Key words: bladder, overactive bladder, detrusor overactivity, muscarinic receptor, antimuscarinic agent

INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by symptoms of "urgency with or without urge incontinence, usually with frequency and nocturia". Urgency is defined as "the complaint of a sudden compelling desire to pass urine which is difficult to defer" [1]. The prevalence of OAB increases with age and is difficult to determine owing to the attached stigma, which may prevent patients from seeking medical care. OAB is estimated to affect 17% of the adult population over the age of 40 in the United States and is ranked among the 10 most common chronic conditions [2-4].

Muscarinic receptors are involved in both normal and abnormal bladder contractions, and the most commonly used drug treatment of OAB is antimuscarinic drugs [5]. Antimuscarinics block, more or less selectively, muscarinic receptors. The common view is that in OAB, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by acethycholine (Ach), released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, increasing bladder capacity and decreasing urge, and during this phase, there is normally no activity in parasympathetic nerves [6].

The majority of patients with OAB can be successfully treated using a combination of behavioral and pharmacological treatments. Behavioral treatments consist of bladder training, timed voiding, dietary modification, pelvic floor muscle exercises and behavioral modification, such as reduced intake of alcohol, caffeine, fizzy drinks and total fluids [7]. Burgio showed that the combination of behavioral and pharmacological therapy was more effective than either therapy alone [8].

There are a number of pharmacological mechanisms that in theory could reduce overactive detrusor muscle activity. To date, the only approved treatments with Grade A recommendations based on level 1 evidence are anticholinergic drugs [8-10] (Table 1). Many researchers have demonstrated acceptable efficacy, safety and improvements in quality of life in randomized controlled trials for antimuscarinics, such as tolterodine, trospium, solifenacin and darifenacin; as well as drugs with mixed actions, such as oxybutynin and propiverine [10].

CURRENT MEDICAL TREATMENT FOR OAB

Antimuscarinics have been found to be safe and efficacious [7-10]. All antimuscarinics apart from oxybutynin IR were found to be well tolerated. Dry mouth was the most commonly reported adverse event and no drug was associated with increases in any serious adverse events. There were significant differences between the antimuscarinics in rates of withdrawal and ranges of adverse events and efficacy outcomes.

Non-surgical treatment is the mainstay of therapy for OAB and available options include bladder training, biofeedback, medication, and a combination of these options [11]. The principal pharmacological treatment used to improve the symptoms of OAB is based on muscarinic receptor antagonism (antimuscarinics), as well as the local effect of urothelium [12].

All antimuscarinics were found to be efficacious in one or more meta-analyses compared with a placebo [7,8]. Urgency episodes were significantly reduced by more than one episode per day in patients receiving 5 mg solifenacin per day, 10 mg solifenacin per day and 4 mg tolterodine ER per day compared with patients receiving a placebo [7,10,13].

Incontinence episodes were reduced by half an episode or more per day in patients receiving all analyzed doses of oxybutynin, solifenacin and tolterodine compared with those on a placebo [7-9]. The frequency of micturition was reduced in patients receiving all ana-

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lyzed doses of solifenacin, tolterodine and oxybutynin compared with a placebo.

Statistically significant differences in QoL compared with a placebo were reported for tolterodine, trospium, solifenacin, propiverine and oxybutynin [13,14]. The data indicated that antimuscarinics improved several areas of QoL ranging from physical activities, sleep and energy to emotions and relationships. Antimuscarinics are well tolerated and have predictable adverse event profiles with proven efficacy in the treatment of OAB. Some evidence showed that the drugs can return patients to continence. The evidence suggested that there were differences between the drugs, though sensitivity analysis did not show any differences in the results for the different types of drugs.

Compared with patients receiving a placebo, patients treated with oxybutynin (8.8-15 mg/day) had a 40% greater risk of withdrawing from treatment. Unexpectedly, there was a 29% lower incidence of total withdrawals from treatment in patients treated with tolterodine than in patients receiving a placebo. Tolterodine was found to cause fewer withdrawals from treatment due to adverse events than oxybutynin. The most commonly reported adverse event for all the antimuscarinics was dry mouth [7-10]. The majority of antimuscarinic formulations were found to cause significant increases in the incidence of dry mouth compared with a placebo.

ADVERSE EVENTS OF ANTIMUSCARINIC AGENTS

Muscarinic receptors are not only found in the urinary tract, bust also in the salivary glands (subtypes M_1, M_3), gastrointestinal tract (M_2, M_3), eyes (M_3, M_5), heart (M_2) and brain (M_1, M_3, M_4 and M_5). Thus, there are commonly observed side effects including dry mouth, constipation, blurred vision, tachycardia and cognitive problems [10]. These side effects cause poor compliance to medication and keep the compliance rate to as low as 30% [13,14].

FUTURE OPTIONS FOR TREATMENT OF OAB

All of the available anticholinergic agents (oxybutynin, tolterodine, solifenacin, darifenacin, trospium chloride, and propiverine) have been shown in randomized trials to be clinically effective. Unfortunately, these drugs are far from being able to fully control OAB symptoms. In addition, quality-of-life improvement is often modest and the adverse effects significantly impair treatment compliance. Unfortunately, the widespread distribution of muscarinic receptors within the body accounts for the commonly observed side-effects of these agents, including cognitive problems, dry mouth, tachycardia, constipation and blurred vision. However, this creates the opportunity to test novel potential drugs that, if promising, can be offered as second line therapy.

Effective nonantimuscarinic treatments are currently rare, but many new promising compounds are emerging which target key molecular

Table 1. Pharmacological Agents for Treatment of Overactive Bladder

Pharmacology	Tri-cycle antidepressant	Smooth muscle relaxant	Genitourinary smooth muscle relaxant			Bladder urothelium local effect antimuscarinic
Drugs	Imipramine (Tofranil)	Trospium (Spasmex)	Oxybutynin (Ditropan)	Propiverin (Urotrol)	Tolterodine (Detrusitol)	Solifenacin (Vesicare)
Dosage form	Sugar-coated tablets 10 mg/tab	Tablets 5 mg/tab	Tablets 5 mg/tab	Film-coated tablets 15 mg/tab	Sustained-release capsule 4 mg/cap	Film-coated tablets 5 mg/tab
Dosage and Administration	30-50 mg daily Divide to 2 dosage	5-10 mg t.i.d.	5 mg b.i.d. ~ t.i.d	Initial: 15 mg b.i.d.~t.i.d. Titration: 15 mg q.i.d.	4 mg q.d.	5 mg q.d.
Dosage in renal impairment patients	No recommendation	20 mg h.s. for severe renal insufficiency	No recommendation	No recommendation	2 mg q.d.	No dose adjustment is necessary
Dosage in hepatic impairment patients	No recommendation	Caution in moderate or severe hepatic dysfunction	No recommendation	No recommendation	2 mg q.d.	No dose adjustment is necessary in mild to moderate hepatic impairment patients
Side effect	Dry mouth, vertigo, constipation	Dry mouth, constipation, dyspepsia, headache, fatigue, urinary retention, dry eyes	Dry mouth, urinary retention, blurred vision, tachycardia, bradycardia	Dry mouth, blurred vision, disturbance of the GI function	Dry mouth, constipation, abdominal pain, blurred vision	Dry mouth, constipation, blurred vision
Drug interactions	Can not combine with MAO inhibitors	Drug with antimuscarinics may increase both the efficacy and side effects	Drug with antimuscarinics may increase both the efficacy and side effects	The effect of imipramine will increase when combine with tri-cycle antidepressants, tranquilizer, anticholinergics etc	Dosage must decrease to 2 mg q.d. when combine with CY P3A4 inhibitors	Be caution when combine with CYP3A4 inhibitors
Contraindication	1. Glaucoma 2. urinary retention	1. Urinary retention 2. Gastric retention 3. Narrow-angle glaucoma	1. G-I tract symptoms 2. Glaucoma 3. Myasthenia gravis	1. Ileus 2. Myasthenia gravis 3. Achalasia	1. Urinary retention 2. Glaucoma 3. Myasthenia gravis	1. Glaucoma 2. Urinary retention 3. Allergy
EBM recommendation	C	A	A	A	A	A

pathways involved in micturition control [15]. The most promising potential therapeutic targets include; nervous GABAergic, glycinergic, dopaminergic, and serotonergic systems; b-adrenoceptors and cAMP metabolism; nonadrenergic-noncholinergic mechanisms such as purinergic and neuropeptidegic systems; vanilloid receptors; bladder afferent nerves; nonneuronal bladder signaling systems including urothelium and interstitial cells; prostanoids; Rho-kinase; and different subtypes of potassium and calcium channels [16].

Both capsaicin and resiniferotoxin have proven efficacy but are associated with adverse events such as retention, thus, limiting their more widespread applicability [17]. Intravesical botulinum toxin therapy is efficacious, but there is also some evidence for the adverse events and tolerability reported, specifically serotype-A, in the management of OAB and detrusor overactivity [18].

VANILLOIDS

Capasicin, the active component of the capsicum, stimulates nociceptors C-fibers causing pain, inflammation, and eventually desensitization by binding the "transient receptor potential vanilloids 1" (TRPV1). In both humans and animals, capascin-sensitive C-fibers afferents are localized throughout the detrusor, perivascularly, and in a plexus that lies beneath and extends into the urothelium.

A placebo-controlled randomized clinical trial showed that intravesical resiniferatoxin was effective in increasing bladder capacity in spinal induced OAB patients [19]. In 23 patients with refractory urgency, desensitization using resiniferatoxin was shown to be effective in terms of both reduction in urgency episodes number and subjective improvement [20]. In a single center, randomized, double-blind study, there were no significant differences with regard to the benefits or side effects in patients treated with glucidic capsaicin-vs patients treated with resiniferatoxin [17].

BOTULINUM TOXIN

There are seven serotypes of botulinum toxin (BTX), and types A and B are in clinical use in urology. BTX-A, the most used type, acts by inhibiting vesicular release of Ach from presynaptic membranes of cholinergic nerves and providing long-lasting neuronal blockage. The precise mechanism of action of BTX may be on afferent neurotransmission [21]. Remarkable efficacy in terms of improvements of urgency, frequency, and quality-of-life has been demonstrated in the treatment of OAB [22]. Investigating the efficacy of BTX-A in OAB patients, a significant increase in cystometric capacity, decrease in OAB symptoms, and improvements in quality-of-life have been reported in 16 patients compared with the 18 who received a placebo [23]. Although it promises to be a major form of treatment for OAB in the future, one has to be aware that this use of BTX is based on limited clinical trials.

Despite the enormous amount of new biological insight, very few drugs with mechanisms of action other than antimuscarinics have passed the proof-of-concept stage. Further preclinical and clinical studies are urgently needed.

CONCLUSION

Currently, antimuscarinics (anticholinergics) are the only approved drugs for treating OAB. While newer drugs demonstrate improved tolerance in patients, patient compliance remains an issue. Persistence in taking medications is usually poor.

Evidently, the best approach is a combination of behavior and diet modification as well as medication. New compounds (capsaicin, reiniferotoxin, botulinum toxin) for the treatment of OAB are being investigated, and have shown efficacy but have also been associated with adverse events, or lack of large-scale randomized controlled data. The ideal new drugs will be tissue-specific (or organ specific), and improve storage phase dysfunctions without interfering the emptying phase. Further investigations are urgently needed in this field.

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