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Review Article

Drugs Currently Undergoing Preclinical or Clinical Trials for the Treatment of Overactive Bladder: A Review

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ABSTRACT

Background: Overactive bladder (OAB) is a common clinical condition for which current drug treatment comprises drugs blocking the cholinergic nerve supply, or augmenting the adrenergic nerve supply, to the detrusor muscle of the urinary bladder. Current treatments have drawbacks, including lack of efficacy and the development of adverse effects in some patients. Hence, new and better drugs for treating OAB will be clinically useful.

Objective: This review is meant to provide information on drugs currently undergoing preclinical or clinical trials for the treatment of OAB published in journal articles or elsewhere.

Methods: The cited articles were retrieved from PubMed and Google Scholar from January 1, 1990, to December 31, 2021. The search terms used were *contraction* or *contractility*, *detrusor*, *inhibition*, *isolated* or *in vitro*, *in vivo*, *overactive bladder*, and *relaxant effect* or *relaxation*.

Results: There are 4 classes of new drugs under various stages of development for the treatment of OAB. These are drugs acting on the autonomic nerve supply to the detrusor muscle of the urinary bladder that include the anticholinergics tarafenacin and afacifenacin and the β_3 adrenoceptor agonists solabegron and ritobegron; drugs acting on ion channels in the detrusor muscle (eg, potassium channel openers and calcium channel blockers), drugs acting on cellular enzymes like phosphodiesterase-5 inhibitors and Rho kinase inhibitors, and drugs acting on miscellaneous targets (eg, pregabalin and trimetazidine).

Conclusions: Drugs currently used to treat OAB target only the cholinergic and adrenergic cellular signalling pathways. There are many other drugs under trial targeting other cellular pathways that may be useful for treating OAB. Their approval for clinical use might improve the treatment of patients with OAB. (*Curr Ther Res Clin Exp.* 2022; 83:XXX–XXX)

Introduction

Overactive bladder (OAB) is a common, chronic syndrome that has a major influence on affected individuals. The definition of OAB has changed with time. Currently, OAB is defined as being characterized by urinary urgency, with or without urinary incontinence, usually with increased daytime frequency and nocturia, and with no local pathological factors.[1,2] The pivotal symptom is considered to be urgency, which refers to a sudden and compelling desire to void that is difficult to defer.[2] In many patients with OAB, incontinence, defined as the involuntary leakage of urine, accompanied or immediately preceded by urgency is common.[2] A well-designed and highly cited population-based, cross-sectional survey of close to 20,000 individuals aged 18 years or older conducted in 2005 in 5 European countries found that the overall prevalence of OAB was 11.8%.[3] During 2011, it was estimated that in the United States, there were 34 million community-dwelling men and women with OAB. Further, the costs incurred because of OAB in the United States during the same year were $12.6 billion.[4] Drugs are available for the treatment of OAB. However, the currently used drugs have adverse effects such as antimuscarinic effects like dry mouth that may prompt discontinuation of treatment.[5] Moreover, some patients do not respond adequately to drugs currently used. Hence new and alternative drugs will be useful for the treatment of OAB.[4] Drugs used to treat OAB generally act by preventing contraction, or causing relaxation, of the detrusor muscle of the urinary bladder. To do this, the drugs alter the contractile mechanism of the detrusor, which like all smooth muscles, involves the interaction of the proteins actin and myosin.[2]

This article is a narrative review of the drugs undergoing preclinical or clinical evaluation for the treatment of OAB from a pharmacodynamics point of view. The guidelines of Murphy[6] for writ-

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ing a review were followed. The review does not include drugs undergoing evaluation for treating OAB due to conditions such as benign prostatic hyperplasia because such conditions are better classified as lower urinary tract symptoms.[1,7] The cited articles were retrieved from PubMed and Google Scholar and the period of review of published information was from January 1, 1990, to December 31, 2021. The search terms used were: *contraction* or *contractility*, *detrusor*, *inhibition, isolated* or *in vitro*, *in vivo*, *overactive bladder*, and *relaxant effect* or *relaxation*. Articles reporting preclinical studies using in vivo or in vitro techniques, and both randomized controlled trials (RCTs) and nonrandomized trials were included. Articles reporting preclinical or clinical studies in which OAB was due to urethral obstruction such as benign prostatic hyperplasia were excluded. Non-English language articles, nonpeer-reviewed articles, and case reports were also excluded.

Drug targets for the treatment of OAB

The 2 wings of the autonomic nervous system have opposing effects on many organs they innervate, the urinary bladder being a good example. Contraction of the urinary bladder is mediated by cholinergic neurons acting chiefly on muscarinic M_3 receptors in humans.[8] These receptors are situated postsynaptically on detrusor muscle cells innervated by cholinergic neurons. Relaxation of the urinary bladder is mediated by adrenergic neurons acting chiefly on β_3 adrenergic receptors situated postsynaptically on detrusor muscle cells. Nonadrenergic noncholinergic neurotransmission is also believed to be involved in the regulation of the contractility of the urinary bladder, although its role may be relatively small.[8,9] Nonadrenergic noncholinergic neurotransmission is mediated by adenosine triphosphate (ATP), which stimulates contractility of the detrusor muscle[8]; nitric oxide; and neuropeptides whose functions in the urinary bladder are unclear.[8]

Other drug targets in the urinary bladder to treat OAB include the voltage-gated calcium channels (VGCC)[10] and RhoA kinase protein (also called Rho-associated protein kinase or ROCK)[11] that influence the contractility of the detrusor muscle. The major phosphodiesterase (PDE) in the detrusor, PDE-5, catalyzes the metabolism of cyclic guanosine monophosphate (cGMP). Inhibition of PDE-5 by drugs causes smooth muscle relaxation.[12] Opening of potassium channels causes hyperpolarization of the detrusor muscle cell and smooth muscle relaxation. Several channels of the transient receptor potential (TRP) family have a role in nociception and mechanosensory transduction in the lower urinary tract. A number of these channels like $TRPV_1$, $TRPV_4$, $TRPM_8$,$TRPA_1$, and $TRPM_4$ are associated with urinary bladder contractility. Based on animal studies, there is evidence that many of these channels are suitable targets for drugs to treat OAB.[13]

Pathophysiology and pathogenesis of OAB

OAB is not 1 disorder, but a syndrome, with many types of clinical presentations depending upon underlying mechanisms and predisposing factors.[14,15] Several factors, showing variation between patients, may be involved in the pathogenesis of this condition.[8] A diagnosis of OAB is made when the patient does not have urinary tract infection, metabolic disorders that can influence urination, or urinary stress incontinence caused by effort or overexertion.[5] There are several risk factors that are known to increase the chance of an individual developing OAB.[4] These include advanced age; postmenopausal status in women due to lower levels of plasma estrogen levels; marked obesity in men and women possibly due to mechanical factors; functional gastrointestinal disorders such as irritable bowel syndrome; as well as race and ethnicity, with a relatively high prevalence among African Americans and Hispanics. OAB can also result from structural or functional damage to the brain or spinal cord.[2] Other possible risk factors include sleep apnea, urinary microbiota (the microbial communities in the urinary tract), smoking, increased coffee ingestion, artificial sweeteners, alcohol, spices, and sour drinks.[2]

The pathogenesis of OAB continues to be under investigation, and 4 theories for its pathogenesis have been proposed.[14] According to the neurogenic theory, there is a decrease in the inhibitory neural impulses and an increase in the afferent sensory impulses from the bladder that trigger the voiding reflex. The myogenic theory proposes that the detrusor muscle becomes more sensitive to cholinergic stimulation, leading to increased spontaneous activity of this muscle. According to the autonomous bladder theory, muscarinic stimulation causes alteration or an increase of phasic activity of the detrusor muscle. The afferent signalling theory suggests that spontaneous bladder contraction during filling leads to raised afferent output resulting in an awareness of bladder filling.

Current management of OAB

The first line of treatment for OAB comprises nonpharmacologic treatment.[5] This includes lifestyle changes such as reducing the volume of fluid intake, cessation of smoking, reduction of body weight, increase in physical activity, and reducing intake of coffee and spices. Another nonpharmacological treatment is bladder and pelvic floor muscle training that can help patients reestablish inhibitory control over the storage of urine and enable them to resist and escape urgency episodes. Pharmacologic treatment is only the second line in the management of OAB.

Current drug therapy of OAB

The standard drug treatment of OAB makes use of antimuscarinic drugs.[14] These drugs antagonize cholinergic control over the bladder leading to lowering of intravesical pressure, increase in bladder capacity, and reduction in frequency of contractions of the detrusor muscle.[15] These drugs may also alter bladder sensation during filling.[16] The muscarinic receptor antagonists currently used for treating OAB include oxybutynin, tolterodine, trospium chloride, darifenacin, solifenacin, imidafenacin, propiverine, and fesoterodine.[17] Some clinical trials have demonstrated small but statistically significant differences in efficacy between these drugs, but the clinical importance of these differences is unclear. The major adverse effects of these drugs are the result of muscarinic receptor blockade, such as dry mouth, blurred vision, constipation, and abdominal discomfort.[16] Blockade of muscarinic receptors in the brain can causes drowsiness, dizziness, and confusion.[16] Antimuscarinic drugs cause detrusor muscle relaxation by blocking M_3 receptors in the detrusor, resulting in reduced formation of the second messenger inositol triphosphate, leading to a fall in intracellular levels of calcium ion (Ca^{2+}) and reduced activation of myosin light chain kinase (MLCK) and muscle relaxation (**Figure 1**).

Another way to relax the detrusor muscle is to activate β-adrenergic receptors on the detrusor muscle cell membrane. Of the β adrenoceptors in the detrusor muscle, the β_3 adrenoceptor is predominant and is responsible for detrusor relaxation during the filling phase.[5,17] In this regard, 2 β_3 adrenoeceptor agonists, mirabegron and vibegron, have been approved for clinical use for treating OAB. Although the efficacy of these drugs is comparable to that of antimuscarinic drugs, the adverse effect profile is better.[5] β_3 adrenoceptor agonists are especially suitable when antimuscarinic adverse effects need to be avoided.[18,19] Activation of the β_3 adrenoceptor leads to activation of adenylyl cyclase and increased levels of cyclic AMP (cAMP), which stimulates cAMP-dependent protein kinase protein kinase A, which in turn inhibits MLCK, leading to muscle relaxation (**Figure 1**).

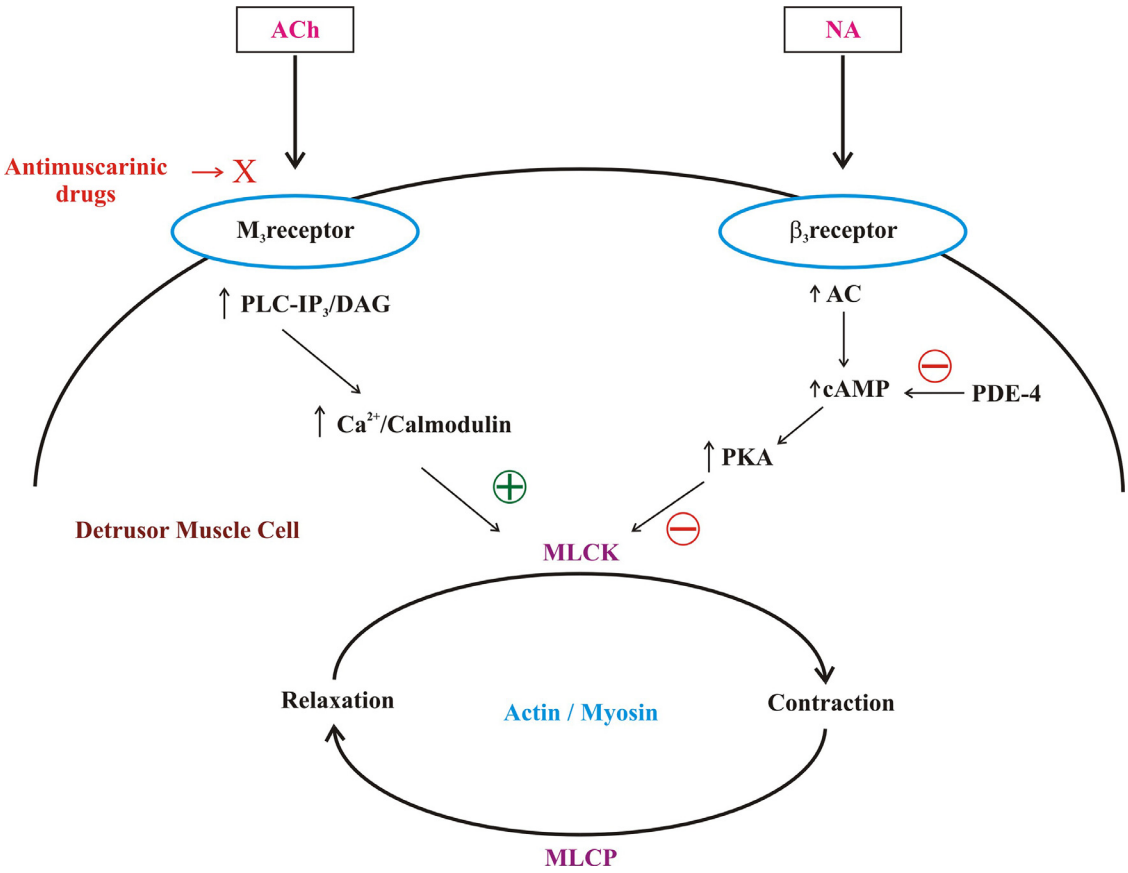

Figure 1. Diagrammatic representation of how activation of muscarinic M_3 receptors stimulates, and stimulation of adrenergic β_3 receptors inhibits, contractility of the detrusor muscle of the urinary bladder. Myosin light chain kinase (MLCK) activity is needed for contraction. Activation of muscarinic M_3 receptors activates phospholipase C (PLC) leading to increased levels of inositol triphosphate (IP_3), which leads to raised levels of Ca^{2+}. Ca^{2+}binds to the protein calmodulin and the Ca^{2+}-calmodulin complex activates MLCK, causing muscle contraction. Stimulation of β_3 receptors activates adenylyl cyclase, which catalyzes the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate, which activates cAMP-dependent protein kinase (PKA). PKA inhibits MLCK leading to muscle relaxation. Phosphodiesterase-4 (PDE-4) catalyzes the metabolism of cAMP. AC = adenylyl cyclase; Ach = acetyl choline; β_3 = beta adrenergic receptor 3 subtype; DAG = diacylglycerol; M_3 = muscarinic 3 receptor subtype; MLCP = myosin light chain phosphatase; NA = noradrenaline. + = Stimulation; − = Inhibition; X = site of antagonism.

Another treatment modality currently used as a second line option to treat OAB is the intravesical administration of botulinum toxin (BTX).[20] BTX is a complex mixture of proteins, containing botulinum neurotoxin and various other nontoxic proteins obtained from the bacterium *Clostridium botulinum* that inhibits acetylcholine (ACh) release from presynaptic cholinergic nerve terminals.[21] This results in an antimuscarinic effect, leading to the relaxation of the detrusor muscle. BTX also potentially affects afferent sensory receptors in the urothelium. There is recent evidence that BTX could also act via neurotransmitters other than ACh. The effect of BTX is long lasting, typically 6 months or more. However, there is evidence that two-thirds of patients discontinue treatment, usually because of tolerability issues.[22]

Antimuscarinic drugs and β_3 adrenoceptor agonists act via different cell signalling pathways (**Figure 1**). Hence, combining these 2 classes of drugs may be useful in OAB treatment.[17] Adding a β_3 adrenoceptor agonist like mirabegron to supplement an anticholinergic has been shown to provide greater efficacy, while at the same time avoiding antimuscarinic adverse effects that could occur with an antimuscarinic dose escalation.[17] After a year of administration, efficacy is still possible. Conversely, adding an antimuscarinic drug like solifenacin or tolterodine when the first drug is a β_3 adrenoceptor agonist like mirabegron has also been shown to provide improved, well-tolerated, and durable effects.[17] A 2021 multicriteria decision analysis model for comparing the benefit-safety profiles of patients with OAB designed to help clinicians better meet their patients' needs, showed that fesoterodine, especially flexibly dosed fesoterodine, is the best anticholinergic available and indeed was better than the β_3 adrenoceptor agonist mirabegron and solifenacin/mirabegron drug combinations.[23]

Some patients with OAB do not respond to currently available drugs and are said to have refractory OAB. This remains a clinical challenge for urologists.[24] Current options for treating refractory OAB include combination therapy with antimuscarinics and β_3 adrenoceptor agonists, and the treatment of underlying disorders like obesity. Third-line options include intravesical BTX, and percutaneous tibial nerve stimulation, and sacral nerve stimulation.[24] In rare cases, more invasive surgical procedures, like augmentation cystoplasty, may need to be considered.[24]

Potential drugs for treating OAB

Drugs acting on the autonomic nervous system

Unapproved drugs acting on the autonomic nervous system that are being investigated for possible use in OAB are listed in **Table 1**. George et al[25] investigated the use of 5 anticholinergics used in the treatment of disorders of the eye (cyclopentolate and homatropine), bronchi (ipratropium), the myometrium (valethamate), or urinary bladder (tolterodine) by inhibiting the ACh-induced contraction of the isolated caprine (goat) detrusor muscle. The authors found that at suitably low concentrations that can be achieved after systemic administration to patients, all 5 drugs inhibited isolated detrusor contractility. Hence the authors suggest that like tolterodine, the other 4 anticholinergics can also be investigated

Table 1
Trials of new drugs for treating overactive bladder acting on the autonomic nervous system.

Drug	Drug class	Phase	Source of tissue	Reference
Cyclopentolate	Anticholinergic	Preclinical	Goat	25
Homatropine	Anticholinergic	Preclinical	Goat	25
Ipratropium	Anticholinergic	Preclinical	Goat	25
Valethamate	Anticholinergic	Preclinical	Goat	25
Tarafenacin	Anticholinergic	Phase IIB	NA	26
Afacifenacin	Anticholinergic	Phase II	NA	27
Solabegron	β_3 agonist	Preclinical	Dog	28
Solabegron	β_3 agonist	Phase II	NA	29
Ritobegron	β_3 agonist	Preclinical	Cynolmolgus monkey	30
Ritobegron	β_3 agonist	Preclinical	Rat	31

NA = not applicable.

Table 2
Trials of new drugs for treating overactive bladder acting on ion channels.

Drug	Drug class	Phase	Source of tissue	Reference
Pinacidil	K^+ channel opener	Preclinical	Rat, guinea pig	32, 33
Minoxidil	K^+ channel opener	Preclinical	Guinea pig	33
Nicorandil	K^+ channel opener	Preclinical	Rat	34
Nicorandil	K^+ channel opener	Preclinical	Human	35
Pinacidil	K^+ channel opener	Preclinical	Human	36
Pinacidil	K^+ channel opener	Preclinical	Pig, human	37
Pinacidil, minoxidil	K^+ channel opener	Preclinical	Pig	38
ZD0947IL/0004	K^+ channel opener	Phase I	NA	39
Iberitoxin, Apamin	K^+ channel opener	Preclinical	Pig	40
NS1608	K^+ channel opener	Preclinical	Guinea pig	41
Nifedipine, nimodipine	CCB	Preclinical	Human	42
Nifedipine	CCB	Preclinical	Mouse	43
Cilnidipine	CCB	Preclinical	Goat	44
SKA-31	SK channel opener	Preclinical	Human	45
NS309	SK channel opener	Preclinical	Rat	46
9-phenanthrol	TRP channel opener	Preclinical	Guinea pig	48
GSK1016790A	TRP channel opener	Preclinical	Guinea pig	49
KPR-5714	TRP channel opener	Preclinical	Rat	50
Diarylpiperazine	TRP channel opener	Preclinical	Guinea pig	51

CCB = calcium channel blocker; K^+ = potassium ion; NA = not applicable; SK = small- conductance Ca^{2+}-activated K^+ channels; TRP = transient reverse potential.

for use in clinical conditions like OAB that require inhibition of the detrusor muscle. Song et al[26] conducted a Phase IIB RCT of a new antimuscarinic drug tarafenacin at daily doses of 0.2 and 0.4 mg for treating OAB. They found that 0.4 mg tarafenacin decreases the incidence of urinary incontinence after 12 weeks of treatment and that the drug was well tolerated.

New β_3 adrenoceptor agonists being developed for treating OAB include solabegron and ritobegron. In a preclinical study using in vitro and in vivo techniques, Hicks et al[28] showed that solabegron caused urinary bladder relaxation and facilitated bladder storage mechanisms. Later, in a multicentre Phase II RCT, it was reported that solabegron significantly reduced OAB symptoms and was well tolerated.[29] Preclinical studies on another β_3 adrenoceptor agonist, ritobegron, conducted in cynomolgus monkeys[30] and rats[31] have shown results suggesting that this drug may be useful for the clinical treatment of OAB. No clinical trials of the use of ritobegron for treating OAB were found in our literature search.

Drugs acting on ion channels

Ion channels are another target for drugs relaxing the urinary bladder detrusor muscle (**Table 2**).[10] Drugs that open potassium ion (K^+) channels are being evaluated for treating OAB. K^+ channel openers relax smooth muscle by opening K^+ channels in the cell membranes of smooth muscle cells, thereby causing exit of K^+ ions and membrane hyperpolarization. This results in closing of membrane-bound VGCC and a fall in intracellular Ca^{2+} levels, which leads to muscle relaxation.[10] Zhou et al[34] showed that the antianginal smooth muscle relaxant nicorandil inhibits the contractile responses to ACh, potassium chloride, and electrical stimulation in the isolated rat detrusor muscle. The inhibitory effect of nicorandil on detrusor contraction due to electrical stimulation was antagonized by glyburide, but not nitroglycerin or apamin, and slightly potentiated by methylene blue.[34] Methylarginine (an inhibitor of nitric oxide synthase) also did not affect the relaxation caused by nicorandil. The level of cGMP was increased by nicorandil and nitroglycerin.[34] Although nicorandil is known to have a dual action (opening of ATP-sensitive K^+ channels and increase of cGMP levels), the authors suggested that, based on their results in the rat detrusor, nicorandil acts by opening ATP-sensitive K^+ channels. Faruqui and colleagues[35] showed that nicorandil relaxes the isolated human detrusor muscle contracted by the addition of potassium chloride. They found that the lowest concentration of nicorandil that would relax the detrusor was 200 μM, a concentration not easily achieved by systemic administration of nicorandil. Hence, the authors suggest that if nicorandil is to be used to treat OAB, it might need to be administered intravesically. Other ATP-sensitive K^+ channel openers that have been shown to relax the detrusor include pinacidil, minoxidil, and ZD0947IL/0004.[36–39]

Another class of drugs that are able to relax the detrusor are calcium channel blockers (CCBs), which block the entry of Ca^{2+} ions into the cell through VGCC from the exterior of the cell. This leads to a fall in intracellular Ca^{2+} levels and muscle relaxation (**Figure 2**). In this regard, Darblade et al[36] showed that the L-type CCB nifedipine abolishes the phasic contractile activity of the isolated human detrusor muscle. Maria[44] found that the CCB cilnidipine at 20, 40, and 80 μM concentrations inhibits the contractility of potassium chloride-induced contraction of the isolated goat detrusor muscle.

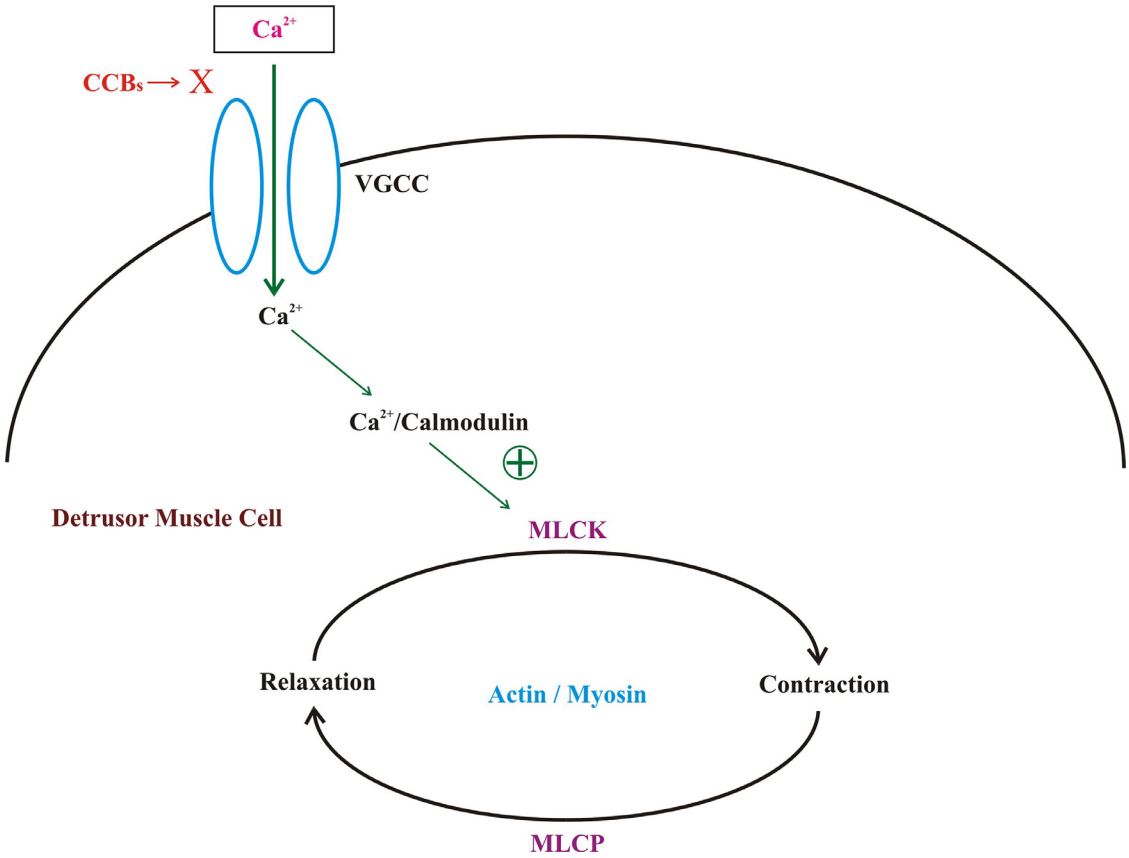

Figure 2. Diagrammatic representation of how blockade of voltage-gated calcium channels (VGCC) by calcium channel blockers (CCBs) can inhibit contractility of the detrusor muscle of the urinary bladder. Normally, when VGCC are activated, calcium ions (Ca^{2+}) pass from exterior into the detrusor muscle cell. Inside the cell, Ca^{2+} combines with the protein calmodulin. The Ca^{2+}- calmodulin complex activates myosin light chain kinase (MLCK), which contracts the muscle. MLCP = myosin light chain phosphatase; + = Stimulation; − = Inhibition; X = site of antagonism.

Table 3
Trials of new drugs for treating overactive bladder acting on enzymes.

Drug	Drug class	Phase	Source of tissue	Reference
Forskolin	AC activator	Preclinical	Rabbit	52
Forskolin	AC activator	Preclinical	Pig	53
Sodium nitroprusside	sGC stimulator	Preclinical	Human	54
Sodium nitroprusside	sGC stimulator	Preclinical	Rat	55
BAY 41-2272	sGC stimulator	Preclinical	Mouse, rat, rabbit	56
Sildenafil	PDE-5 Inhibitor	Preclinical	Human	57
Sildenafil	PDE-5 Inhibitor	Preclinical	Rat	58
Sildenafil	PDE-5 Inhibitor	Preclinical	Spinal cord-injured mice	59
Avanafil	PDE-5 Inhibitor	Preclinical	Goat	60
Tadalafil	PDE-5 Inhibitor	Phase I	NA	61
Tadalafil	PDE-5 Inhibitor	Phase I	NA	62
Tadalafil	PDE-5 Inhibitor	Phase I	NA	63
Roflumilast	PDE-4 Inhibitor	Preclinical	Rat	64
HA-1077, Y-27632	RHO kinase inhibitor	Preclinical	Rabbit	65
H-1152, Y-2763, HA-1077	RHO kinase inhibitor	Preclinical	Rat	66
Fasudil	Rho kinase inhibitor	Preclinical	Pig	67
Y-27632	Rho kinase inhibitor	Preclinical	Rabbit	68
Y-27632	Rho kinase inhibitor	Preclinical	Human	69

AC = adenylyl cyclase; NA = not applicable; PDE-5 = phosphodiesterase-5; sGC = soluble guanylyl cyclase.

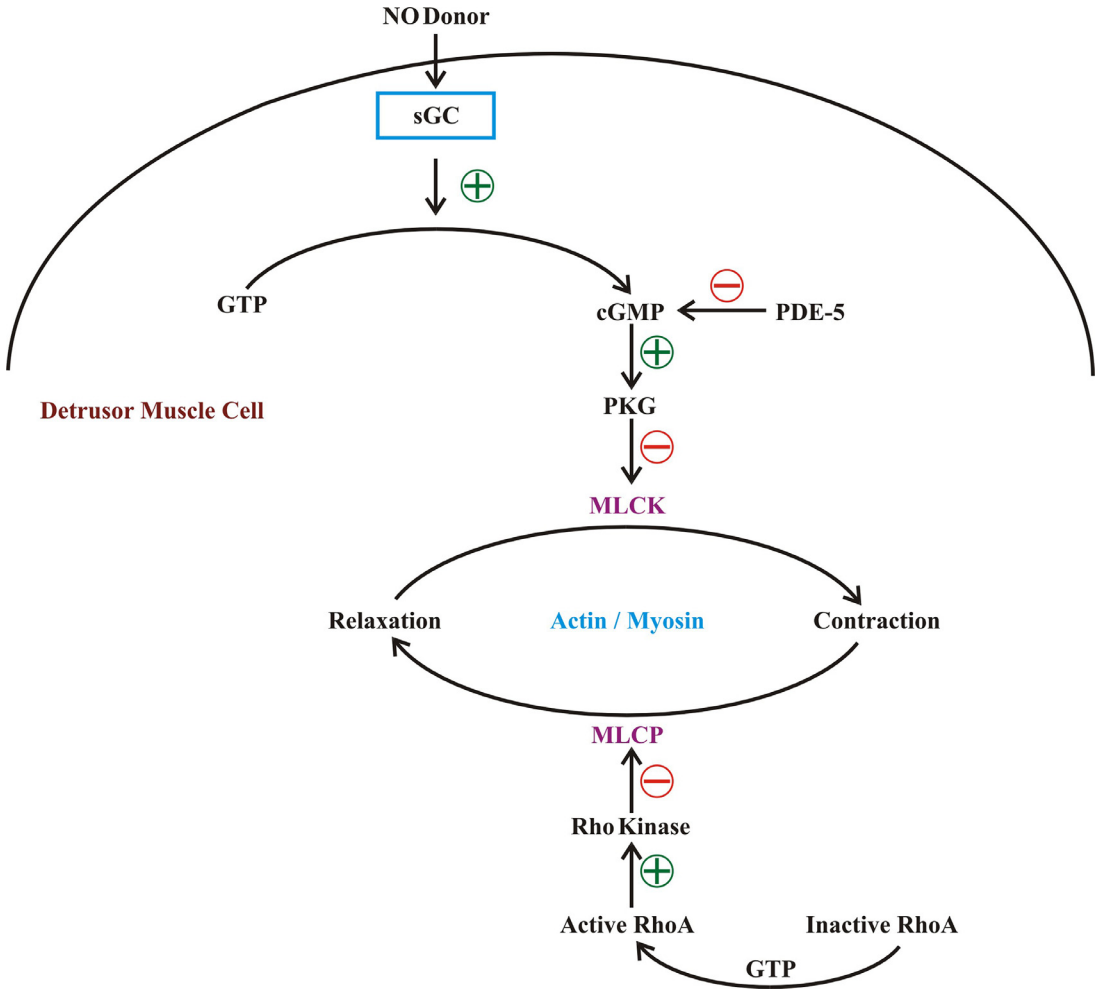

Figure 3. Diagrammatic representation of how activation of soluble guanylyl cyclase (sGC) or inhibition of phosphodiesterase-5 (PDE-5) inhibits contractility of the detrusor muscle of the urinary bladder. Activation of sGC as occurs after addition of nitric oxide (NO) donors catalyzes the metabolism of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) which activates cGMP-dependent protein kinase or protein kinase G (PKG). PKG inhibits myosin light chain kinase (MLCK). Phosphodiesterase-5 (PDE-5) catalyzes the metabolism of cGMP. The RhoA kinase pathway is also involved in smooth muscle contraction. When inactive RhoA is phosphorylated it is activated to active RhoA, which stimulates Rho kinase, a serine/threonine kinase which phosphorylates the myosin-binding subunit of myosin light chain phosphatase (MLCP), thereby inactivating it and promoting muscle contraction. + = stimulation; − = Inhibition.

K^+ channels activated by Ca^{2+} ions are classified as calcium-activated K^+ channels.[45] These channels are divided into 3 main groups, 1 of which is the small-conductance Ca^{2+}-activated K^+ channel (SK channels). Such channels have been shown to regulate the contractility of the detrusor, and are potential targets for treating OAB. Soder et al[45] showed that the SK channel opener SKA-31 induces hyperpolarization and reduces contractility in the human detrusor. Parajuli et al[46] showed that the SK channel opener, NS309, decreases rat detrusor smooth muscle membrane potential and phasic contractions by activating SK3 channels. The TRP superfamily of channels are cell membrane-bound proteins present in the detrusor muscle. They are involved in nociception and mechanosensory transduction.[47] Animal studies suggest that some of these channels are possible targets for the treatment of OAB.[47] Nakanishi et al[50] found that KPR-5714, a novel TRP melastatin 8 antagonist, improves symptoms of OAB via inhibition of bladder afferent activity in rats.

Drugs acting on specific enzymes

A third class of drugs that can inhibit detrusor contractility and could be used to treat OAB are those that act on specific enzyme targets (**Table 3**). One such drug target is the enzyme adenylyl cyclase, which catalyzes the metabolism of ATP to cAMP (**Figure 1**). Truss et al[52] showed that the adenylyl cyclase activator forskolin, which raises intracellular levels of cAMP, significantly relaxes porcine detrusor strips. Another target is the enzyme-soluble guanylyl cyclase, which catalyzes the metabolism of guanosine triphosphate to cGMP, the second messenger that activates cGMP-dependent protein kinase (also called protein kinase G [PKG]). PKG has an inhibitory effect on the activity of MLCK, leading to muscle relaxation (**Figure 3**). The metabolism of cGMP is catalyzed by PDE-5, which is inhibited by drugs like sildenafil, tadalafil, and avanafil which are used to treat erectile dysfunction. Preclinical[54–60] and Phase I clinical trials[61–63] have shown that PDE-5 inhibitors could be useful for treating OAB. Protein kinase A or cAMP-dependent protein kinase, like its counterpart PKG, has an inhibitory effect on the activity of MLCK (**Figure 1**). The counterpart of the enzyme PDE-5, PDE-4, catalyzes the metabolism of cAMP (**Figure 1**). Hence, inhibition of PDE-4 would inhibit the activity of MLCK, leading to muscle relaxation. Ding et al[64] reported that the PDE-4 inhibitor roflumilast prevented the augmented frequency and nonvoid contractions in obesity-associated OAB in rats fed a high-fat diet. The enzyme Rho kinase inhibits myosin light chain phosphatase, thereby favoring smooth muscle contraction (**Figure 3**). Preclinical studies have shown that Rho kinase inhibitors relax the detrusor muscle.[66–69]

Table 4
Trials of drugs for treating overactive bladder acting on miscellaneous targets.

Drug	Drug class	Phase	Source of tissue	Reference
Tramadol	Atypical opioid analgesic	Preclinical	Goat	70
Pregabalin, lamotrigine	Anticonvulsant	Phase I	NA	71
Pregabalin	Anticonvulsant	Phase I	NA	72
Pirt	Endogenous protein	Preclinical	Mouse	73
Trimetazidine	Antianginal drug	Preclinical	Mouse	74
URO-902 (hMaxi-K)	Gene	Phase I	Human	75

NA = Not applicable.

Drugs acting on miscellaneous targets

Kumar et al[70] showed that the atypical opioid analgesic tramadol inhibits the ACh-induced contractility of the isolated goat detrusor in a concentration-dependent manner (**Table 4**). The inhibition was reversed by raising the concentration of ACh. Propranolol but not naloxone reversed tramadol's inhibition of ACh-induced detrusor contractility. These results suggested to the authors that tramadol inhibits ACh-induced detrusor contractility by an indirect anticholinergic mechanism involving the stimulation of β adrenergic receptors. Pregabalin, an anticonvulsant, has been shown by Loutochin et al[71] and Marencak et al[72] to inhibit isolated detrusor contractility and be potentially usable for treating OAB. Engin et al[74] showed that the antianginal drug trimetazidine produces a concentration-dependent relaxation of the isolated mouse detrusor, possibly through its effects on Ca^{2+} and K^+ channels.

Gene therapy, the modification or manipulation of the expression of genes to change the biological properties of cells is also being attempted for the treatment of OAB. The large conductance Ca^{2+}-activated K^+ (also called big potassium [BK_{ca}]) channel is highly expressed on detrusor muscle cells and regulates detrusor muscle contraction. This channel is activated by changes in both voltage and cytoplasmic Ca^{2+} levels. Activation of the BK_{ca} channel may be a therapeutic option for treating OAB.

URO-902 is a plasmid vector that expresses the BK_{ca} α subunit. Rovner et al[75] evaluated the use of URO-902 for treating OAB in female patients in 2 Phase I RCTs. The drug doses were administered and evaluated sequentially (lowest dose first). In 1 RCT, code named ION-02, conducted on patients with OAB using a catheter extending into the lumen of the urinary bladder, 5000 μg URO-902 was instilled in 10 patients, 10,000 μg in 6 patients, and placebo in phosphate-buffered saline–20% sucrose in 5 patients. Study patients were requested to retain the solution in the bladder for at least 2 hours. Of the 10 patients who received 5000 μg URO-902, only 7 completed the study. The other RCT, code named ION-03, was conducted on patients with OAB with injections given directly into the bladder wall using cystoscopy as follows: 16,000 μg URO-902 in 6 patients 24,000 μg in 3 patients, and placebo (as in ION-02) in 4 patients. The study period for both RCTs was 6 months following treatment with URO-902. Posttreatment visits occurred at 1, 2, 4, 8, 16, and 24 weeks.

The safety profile (or tolerability) was the primary outcome measure. The secondary outcome measure was drug efficacy. Among the safety outcomes, there was no dose-limiting toxicity or significant adverse events preventing dose escalation during either RCT and no subject withdrew from the RCT due to adverse events. Regarding efficacy, in ION-02 (n = 21), involuntary detrusor contractions on urodynamics at 24 weeks in patients ($P < 0.0508$ vs placebo) and average urinary incontinence episodes in the 5000-μg group ($P = 0.0812$ vs placebo) showed a trend toward statistical significance. In ION-03 (n = 13), significant reductions compared with placebo in urgency episodes (16,000 μg, $P = 0.036$; 24,000 μg, $P = 0.047$) and number of voids (16,000 μg, $P = 0.04$; 24,000 μg, $P = 0.047$) were observed 1 week after injection. Hence, it has been suggested that there should be further research on larger clinical studies on gene therapy involving the BK_{ca} α subunit.[76]

Conclusions

OAB is a common clinical problem for which currently used drugs either inhibit the cholinergic nerve supply or augment the adrenergic nerve supply to the detrusor muscle of the urinary bladder. These drugs have drawbacks because some patients do not respond adequately to treatment and some drugs have a bad safety profile. As described in this article, there are several drugs undergoing preclinical or clinical drug trials. These include drugs acting on the autonomic nerve supply to the detrusor, ion channels, enzymes, and miscellaneous targets. If 1 or more of these drugs are approved for the treatment of patients with OAB, the treatment of patients with OAB might be improved.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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