

PHARMACOLOGICAL TREATMENT USED IN THE MANAGEMENT OF OVERACTIVE BLADDER

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Abstract: *In 2002, the International Continence Society defined the overactive bladder (OAB) as a clinical condition which implies urinary urgency with or without urge incontinence, regularly associated with frequent urination and nocturia. The aim of the study was to realize an update for clinicians that are managing the overactive bladder, with an overview of the current management and also the future perspectives of the therapies used for this disease, including pharmacology, tolerability, side-effects and efficacy. Although anticholinergic drugs will continue to be the gold standard for the pharmacological treatment of overactive bladder, their side effects and limitations urge the necessity of novel drugs.*

Key words: *overactive bladder, antimuscarinic agents, GABA's, botulinum toxin A.*

1. Introduction

In 2002, the International Continence Society defined the overactive bladder (OAB) as a clinical condition which implies urinary urgency with or without urge incontinence, frequently associated urinary frequency and nocturia [63]. The prevalence of OAB, according to different studies is 8-14 %, and increases with age, being more common in women than in men.

The pathophysiology of overactive bladder is still not totally known, being involved multiple, complex and multifactorial mechanisms.

Malfunction of the detrusor muscle, the sensory pathway or the central neural control are the mechanisms involved in the of bladder function. Brading et al [11] proposed the myogenic hypothesis,

concluding that the smooth muscle cells, due to denervation became hyper-excitable. As a consequence, the myocytes show raised electronic coupling, which might result in detrusor overactivity [9].

Another mechanism of the overactive bladder was proposed by Groat [35] et al, the neurogenic one in which it appears at the level of the central neural control a loss of the inhibitory effect.

2. Objective

The aim of the study was to realize an update for clinicians that are managing the overactive bladder, with an overview of the current management and also the future perspectives of the therapies used for this disease, including pharmacology, tolerability, side-effects and efficacy.

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3. Material and method

We searched PubMed and Medline for trials and systematic reviews in adults with overactive bladder and also for meta-analysis of the therapy for overactive bladder, including compliance, efficacy and tolerability. We excluded for the study the pediatric trials.

4. Discussions

The currently used drug classes in the treatment of overactive bladder include: anticholinergic agents (antimuscarinic agent therapy), hormone replacement therapy, desmopressin, tricyclic antidepressive, intravesical Botox and β 3-AR agonist.

4.1. Current overactive bladder pharmacotherapy

Antimuscarinic agents are the first line pharmacotherapy used to treat the overactive bladder. These drugs inhibit the

acetylcholine effects in the central and peripheral nervous system, the mechanism being the blockers of the muscarinic receptors. Muscarinic receptors are found in the smooth muscle, cardiac muscle, central nervous system, and autonomic ganglia, while the nicotinic receptors can be found in the neuromuscular junction in the autonomic ganglia and somatic nervous system [2].

But, antimuscarinic agents cannot always be effective in controlling the overactive bladder symptoms and the most important, the improvement of the quality of life is often limited. Another disadvantage of the use of antimuscarinic agents is the frequent side-effects (as dry mouth, constipation and the adverse effects on the central nervous system), causing poor adherence to the treatment [49].

In *Table 1* it is presented a summary of the antimuscarinic agents used currently in the treatment of the overactive bladder, pointing out the dosage, the mechanism of action, the effects, the metabolism pathways and also the side effects.

Table 1
Summary of the antimuscarinic agents pharmacotherapy for overactive bladder

Medication	Dosage	Mechanism of action	Metabolism	Main side effects	
OXYBUTYNIN	immediate release	2,5-5 mg -Inhibits the effects of acetylcholine on smooth muscle causing relaxation of the detrusor muscle -has no effect at the skeletal neuromuscular junction / autonomic ganglia	Hepatic	-↓ the frequency of involuntary detrusor contraction -↑ bladder capacity -reduces urge incontinence	-Dry mouth (71.4%) - Constipation (15.1%) -somnia (14%) -nausea (11.6%)
	extended release	5,10,15 mg -	Hepatic	↓ the urinary incontinence -reduce the mean voiding frequency -reduce the urgency	Dry mouth (68-72%)

Medication		Dosage	Mechanism of action		Metabolism	Main side effects
	controlled release transdermal patch	3.9 mg/day	-	Reduction in urinary leakage	Gastrointestinal and hepatic	Site pruritus (16.1%) Application site erythema (7.0%), Dry mouth (7%) Constipation 2.1%
Tolterodine tartrate	immediate and controlled release	2,4 mg /day	Competitive muscarinic receptor antagonist	Reduced of leakage episodes, reduced voids in 24 hours	Hepatic	Dry mouth (23%) Headache (6%), abdominal pain (4%)
Fesoterodine fumarate		4-8 mg / day	Competitive muscarinic receptor antagonist	Reduced leakage episodes Reduced frequency Reduced urgency	Hepatic	Dry mouth (19%) Constipation (2%)
Solifenacin		5,10 mg /day	Selectivity for M3 muscarinic receptors	Reduces frequency, urgency	Hepatic	Dry mouth (10.9%) Constipation (5.4%) Blurred vision (3.8%)
Tropium chloride		20 mg		Reduced nocturnal voids, diurnal voids, nocturnal and diurnal urgency and urinary incontinence episodes	Renal	Dry mouth (20.1%) Constipation (5.8%)
Darifenacin		7.5 / 15 mg / day	M3 receptor antagonist			Dry mouth (4.2%) Constipation (14.8%)
Propiverine		30 mg/day	Nonselective antimuscarinic component and calcium channel blocking effects	Reduction in micturition volume, frequency, number of incontinence episodes		Dry mouth Blurred vision constipation

The debate about the clinical use and the pathophysiological rationale of anticholinergic agents remains an unsolved issue [4].

A systematic review conducted by Herbison et al [36], on several placebo-controlled trials (on 6800 subjects), evaluated the treatment of overactive

bladder with antimuscarinic agents versus a placebo therapy. The authors found that the patients with active treatment showed improvement in the symptoms, including reduction of the leakage episode than those on placebo treatment. The most frequently reported side effect was dry mouth but also constipation, cognitive side effects, gastroesophageal reflux, urinary retention and blurry vision.

Only oxybutynin, tolterodine, propiverine and trospium (among the anticholinergic agents), have the highest level of evidence of efficacy and clinical recommendation; tolterodine and oxybutynin being the most studied [25], [83].

Oxybutynin, [86] relaxes bladder muscles, having a local anesthetic, being a nonselective antimuscarinic agent. It can be found in immediate, extended-release forms and transdermal patch. For the treatment of overactivity of the detrusor accompanied by urge incontinence, the immediate-release oxybutynin had been demonstrated in multiple studies to be the most effective, decreasing the incontinence episodes (>50% of the cases) [6], [20-21], [31-32]. But of course the side-effects of the antimuscarinic agents are present also in the case of using oxybutynin: dry mouth, being reported in up to 2/3 of subjects in some clinical trials [3], [10], [12], [29], [59].

Tolterodine is another muscarinic antagonist, available in short-action and also long-action preparations. In multiple trials it was shown that both forms have significant effects on symptoms of overactive bladder [15], [39], [71], [54]. The adverse effects are comparable to

those of short-action oxybutynin, dry mouth being present in 20 to 25 % of patients. In two published studies, that have compared the oxybutynin and tolterodine, it was suggested that the treatments have similar effectiveness and efficacy.

Some other studies showed that another drugs used for the treatment of overactive bladder, such as *propiverine and trospium* are effective for the treatment of urge incontinence and having fewer adverse effects than oxybutynin [42], [47], [52], [53], [55], [57].

Darifenacin, a drug approved in 2004 by Food and Drug Administration, inhibits the M3 receptor in the detrusor, having a reduced M2 inhibition. It maintains the efficacy of the antimuscarinic agents but it had been showed a significant decrease in the appearance of side effects compared to oxybutynin. Being a substrate of several hepatic enzymes, the potential interactions with Cytochrome P450 inducers or inhibitors have to be considered when using this drug [20].

Another antimuscarinic agents *Solifenacin*, which has demonstrated efficacy and tolerability over tolterodine. It was reported in several studies that solifenancin reduces the incontinence episodes and also it has been shown important improvements in the quality of life [15]. The caution of using this drug, like darifenacin is the potential for interactions with inducers and inhibitors of the P450 system [15].

As showed in the *Table 2*, for the treatment of overactive bladder there can be used also some noncholinergic drugs.

Table 2

Summary of the noncholinergic pharmacotherapy used for the treatment of overactive bladder

<i>Medication</i>	<i>Dosage and administration</i>	<i>Mechanism of action</i>	<i>Metabolism</i>	<i>Main side effects</i>
Tricyclic antidepressant	Imipramine 10 mg/day Amitriptyline 10-20 mg/day	Direct action on detrusor Central action (CNS)	Hepatic	Dry mouth, constipation, blurred vision Tremor Arrhythmia nausea
Mirabegron- a β-3 receptor agonist	25-50 mg / day	B3 adrenergic receptor agonist	Hepatic	Hypertension Tachycardia Urinary tract infection Constipation
Desmopresin	0.1-0.2 mg/day	Renal collecting duct /aquaporin 2 mediated	Renal	Hyponatremia Cardiac failure Hypertension
Botulinum toxin A	100-200 U in idiopathic OAB 200-300 U in neurogenic OAB	Presynaptic motor neuron		Urinary retention Hematuria Urinary tract infection

Another drug class used for the treatment of the overactive bladder is the tricyclic antidepressant, the mostly used being imipramine, that has anticholinergic and alpha adrenergic effects. Also it had been demonstrated a possible central effect on voiding reflexes, being recommended for urge-stress incontinence. The common side effects of imipramine are postural hypotension and cardiac abnormalities.

Another treatment used for the symptoms of the overactive bladder, usually for postmenopausal women are the oral or topical estrogen, but there is not relevant documentation on the efficacy of these agents [27], [28], [33], [62], [76],[77].

Recently, it had been identified in the detrusor and urothelium some β -1, β -2 and β -3 adrenoceptors [18], that when are stimulated, they lead to adenylyl cyclase and G protein activation, which results to

an increase in cyclic AMP levels and in consequence a relaxation of the detrusor; Because of the demonstration of this mechanism, it had been developed *Mirabegron*, a β -3 receptor agonist. In case of using this drug, the adverse effects of anticholinergic, such as dry mouth, has a lower incidence, increasing the quality of life [26].

In a important trial that included 2000 patients and evaluated the use of mirabegron vs tolterodine and placebo it had been showed a important reduction in the number of voids and incontinence episodes during 24-h [30], [82]. However, in terms of dry mouth the incidence for placebo, mirabegron 50 mg and mirabegron 100 mg was 2.6%, 2.8% and 2.8%, respectively, in comparison to tolterodine, which was higher at 10.1% [78].

A study by Chapple et al. [17] that included nearly 2500 subjects, compared the safety of mirabegron (50 mg and

100 mg) to tolterodine ER (4 mg). The number of adverse events was consistent across all groups, at 59.7% for mirabegron 50 mg, 61.3% for mirabegron 100 mg and 62.6% for tolterodine ER 4 mg. Adverse events included hypertension, urinary tract infection and nasopharyngitis, and were comparable across all groups. However, in terms of dry mouth, the incidence was 8.6% for tolterodine, whilst for mirabegron 50 mg and 100 mg it was 2.8% and 2.3%, respectively.

In review of the existing data, this therapy appears to be as effective in patients who have failed to respond to antimuscarinic agents or cannot tolerate them, as in treatment naive patients.

If, after a trial of pharmacotherapy, the patient has not had an adequate improvement in symptoms, *Botulinum Toxin intravesical* injection therapy can be offered as the next step. Botulinum toxin contains a heavy chain that binds to the presynaptic terminal of the neuromuscular junction, and this then leads to internalization of the neurotoxic component, which is the light chain. The latter acts by inhibiting the release of acetylcholine from the presynaptic terminal of the motor end plate, that then results in the muscle that is innervated becoming flaccid paralysis. The effect of the toxin is temporary, with a return to function within 6–9 months [19]. Botulinum toxin is also supposed to act on the afferent system, which might be the explanation for the improvement in urinary urgency, which as mentioned previously is a sensory symptom. Other possible mechanisms include inhibiting neurotransmitters (e.g. acetylcholine) from being released by the urothelium.

Botulinum toxin is available in different preparations, each of which is a distinct chemical entity, and the doses and data for each cannot be used interchangeably. Most clinical studies assessing intravesical Botulinum toxin have evaluated the onabotulinum toxin A preparation. There have been significant improvements in the number of voiding episodes over 24 h, incontinence episodes, urodynamic variables and quality-of-life scores [55].

Desmopressin a rapid-acting diuretic it can be used also, especially for reducing the nocturia in both sexes. This symptom reduces the quality of life, being primarily related to detrusor overactivity [51], [56].

4.2. New perspectives for the treatment of overactive bladder

In the past years, it was discouraged, for different reasons, the research on new drugs for the treatment of overactive bladder. The relation between the somatic control of visceral reflex voluntary, the neuropharmacological arrangement of voiding reflex, the parasympathetic cholinergic and sympathetic adrenergic control and the involuntary components were the main limitations [69].

Data from trials are lacking for multiple classes of drugs used to treat other conditions, drugs that have a potential therapeutic value for patients with overactive bladder (prostaglandin synthesis inhibitors, calcium-channel blockers, beta-adrenergic (particularly β_3) agonists, dopamine D1–receptor agonists and γ -aminobutyric acid (GABA) agonists [86].

But there exists several promising directions for the development of medication that can be used to treat overactive bladder (Table 3).

Table 3

Summary of future pharmacological potential drugs for overactive bladder

	Pharmacological target	Localization	Effect on the bladder activity	Potential drugs
MONOAMINES	Serotonergic system	Central Nervous System Bladder	-inhibitory (5HT1a) -stimulatory (5HT2,5HT3,5HT4,5HT7 receptors)	5HT1a agonists, 5HT2,5HT3,5HT4,5HT7 antagonists, SSRI, duloxetine
	Dopaminergic system	Central Nervous System	Inhibitory (D1 receptors) Stimulatory (D2 receptors)	D1 agonists D2-antagonists
	Noradrenaline system	Central Nervous System Bladder	Inhibitory (β receptors) Stimulatory (α receptors)	B3 agonists, PDEI,4.5 inhibitors, α 1 antagonists
GABA system		Central Nervous System Bladder	inhibitory	GABA _A , GABAB agonists
Glutamate system		Central Nervous System	excitatory	N-Methyl-D-aspartate antagonists
Glycinergic system		Central Nervous System	inhibitory	Glycine-receptors agonist
Afferent terminals		Bladder	stimulatory	Vanilloids (capsaicin, resiniferatoxin) TRPV -1 agonists
Prostanoids		Bladder	stimulatory	Cyclooxygenase inhibitors EP1 antagonists
NANC system	Endothelin	Central Nervous System Bladder	Stimulatory inhibitory	ET _A ,ET _B antagonists ECE-inhibitors
	Purinergic system	Central Nervous System Bladder	Stimulatory	P2X antagonists
	Enkephalin system	Central Nervous System Bladder	Inhibitory	Enkephalin-agonists
	Nociceptine	Central Nervous System Bladder	inhibitory	Nociceptin-agonists
	Tachykinins	Central Nervous System Bladder	stimulatory	NK ₁ antagonists NK ₂ antagonists SP-saporin
ION CHANNELS	Potassium channels	Bladder	Inhibitory	Potassium channel openers (KCO) activating BKCa/SKCa opening KCO antagonizing ATP inhibitory subunit (cromakalm, pinacidil, nicorandil) KCO targeting KV: retigabine
	Calcium channels	Bladder	Stimulatory	Calcium L channels antagonists Calcium T channel antagonist
	Sodium channels	Bladder	Stimulatory	ENaC/ASIC blockers

Legend:

5HT-5-hydroxytryptamine; SSRI-Selective serotonin reuptake inhibitor; PDEI-4,5-phosphodiesterase type 4,5 inhibitor; GABA - gamma-Aminobutyric acid; TRPV - Transient receptor vanilloid potential channels; ECE endothelin-converting enzyme; P2X-purinergic receptors; NK-Natural killer, SP-saporin; ENaC/ASIC-epithelial sodium channel/ Acid-Sensing Ion Channels

In the past 2 decades, the treatment of overactive bladder was intensively discussed due to the discovery of the non-adrenergic - non-cholinergic innervation, because of the recognition of some important neurotransmitters such as purines, monoamines, peptides, amino acid, and nitric oxide. Also, the concept of co-transmission and the importance in the control of micturition reflex of some sensory nerves, sensible to capsaicin (pungent ingredient of red chili) were the main advantages gained by the new neuropharmacology. The researchers discovered also of a new variety of receptors that are involved in the regulation of sensory nerves and pointed out that the changes are also occurring after trauma or chronic inflammation (neuroplasticity). All this were the strong points for the development of alternative therapies for the overactive bladder.

Today central nervous system, bladder muscle cells and sensory nerves represents the primary targets of strategy for overactive bladder.

In a study conducted by *Griffiths et al* [34], it was pointed out that in the micturition control are involved some central nervous system transmitters/receptors systems (adrenoceptors, γ -aminobutyric acid (GABA), opioid, dopamine, noradrenaline, serotonin and glutamatergic receptors) [22], [38], [41].

Some different receptors as the one from the CNS have been found also in the spinal cord and brain. (α 1A mRNA in hypothalamic nuclei, α 1A mRNA and α 1B mRNA in raphe nuclei and amygdala) *Andersson et al* [2-4] studied the pharmacology used for the treatment of the overactive bladder showed in his study that α 1 antagonists decreases the detrusor overactivity in rats, tamsulosine has the role to inhibit the micturition reflex (through activation of the spinal receptors) and α 2 agonists by the activation of

supraspinal and spinal receptors, produce the activation of micturition reflex [73], [81]. Another research, conducted on mice pointed out that α 1A-, α 1B-, and α 1D-AR mRNA can be identified in the sacral spinal cord, and showed decreased voiding frequency, a larger bladder capacity and voided volumes.

A randomized study reported the effectiveness of naftopidil and tamsulosin in the treatment of overactive bladder of 96 patients with benign hypertrophy of prostate. The main mechanism of action was the blockage of α -ARs in prostatic muscle, both agents acting on the lumbosacral cord [40], [75]. The authors concluded that naftopidil can be compared in terms of effectiveness and safety as tamsulosin, both drugs being effective in reducing storage and voiding symptoms.

It is known and it had been demonstrated the inhibitory effects that morphine and its analogs have on the reflex of micturition, but despite this, there has been reduced interest in developing drugs that are active on the opioid mechanisms for the treatment of overactive bladder. The micturition control is influenced by opioids at central and peripheral sites, [65] inhibiting the detrusor activity [61].

Tramadol is one of the opioids, an effective and safe analgesic, being a poor μ -agonist. Its metabolites on the other hand, have a potent μ -agonist effect and inhibit the uptake of noradrenaline and 5-HT (5-hydroxytryptamine). However, in some clinical studies conducted on animal models, tramadol, it had been concluded to have positive effects on micturition, because of the inhibition of noradrenaline and serotonin uptake [70]. In a trial that compared tramadol with placebo it had been showed that tramadol had better effects in decreasing the number of incontinence episodes and also it had been showed an improvement of the urodynamic parameters, the main adverse

event being nausea, a frequent side effect found in case of using this drug [72].

Another important role is played by serotonin and its receptors. In a study conducted by *Movig et al* it had been demonstrated that the exposure to SSRIs (selective serotonin reuptake inhibitors) is linked to an increased risk for urinary incontinence [60].

Takimoto et al demonstrated in another study that selective 5-HT₄ and 5-HT_{1A} receptor antagonists (piboserod and ketanserin) can inhibit the micturition reflex [80]. Until now, it does not exist convincing documents whether or not selective serotonin reuptake inhibitors are effective in the treatment of overactive bladder despite positive effects in preclinical models.

Another new treatment that can be used in the treatment of overactive bladder is the Gamma-aminobutyric acid (GABA) [66]. A study conducted on rats, showed that by stimulation of GABA receptors, it can be inhibited the micturition. The antagonism of GABA receptors stimulates micturition, being concluded that the receptors are influenced by tonic GABAergic.

Baclofen has central nervous system inhibitory action of GABAB-receptors agonists, and it had been showed to be useful for controlling the micturition disorders determined by activation in the bladder of the C-fibre [58]. The inhibitory actions in the spinal cord of GABAB receptor agonists can be useful for controlling the micturition disorders in the urothelium, by attenuating the oxyhemoglobin-induced detrusor activity [67]. Some clinical studies suggested a possible role for intrathecal baclofen infusion for the treatment of patients with overactive bladder [74].

Another drug that can be used is gabapentin (an anticonvulsant GABA-mimetic). It had been showed in a study

that gabapentin improved symptoms and urodynamic parameters in patients with overactive bladder. It had been prescribed at antimuscarinic agents-refractory patients with overactive bladder and nocturia, being good tolerated and it had been showed an improvement of symptoms 45% of patients, with fewer side-effects [47].

Several neuropeptide/receptor systems are expressed non-neural components (urothelium). Neurokinin A (NKA) and substance P (SP) have an increased affinity for NK1/2 receptors. It has been proven that the micturition reflex can be modulated by spinal and supraspinal NK receptors [37]. A drug used to treat chemotherapy-induced nausea, *aprepitant* (a central nervous system penetrating NK1-receptor antagonist) had showed good tolerability and reduced the overactive bladder symptoms compared to placebo, in a randomized trial that included menopausal women with urge incontinence [34], [50], [85].

Another new therapy that is under investigation is the nociceptin or orphanin FQ (N/OFQ), an endogenous ligand of opioid-like receptor-4. In some studies, it had been suggested that N/OFQ is acting on the afferent bladder signaling and also on the supraspinal micturition sites, and can inhibit the micturition reflex in animals, increasing the bladder capacity [49].

The main transduction channel for nociception TRPV1 (Transient receptor potential vanilloids 1) is found in the urothelial cells and the C-fibers sensory unmyelinated [79]. An abnormality of the activity of C-fibre may lead to detrusor overactivity. The best known natural TRPV1 agonists, *capsaicin* can cause a desensitization of C-fibers, leading to beneficial effects. *Resiniferatoxin* is another vanilloid, being at least as effective as capsaicin, the main advantage being the absence of the local side-effect [23], [24], [84].

In the detrusor and in the mucosa of the bladder are synthesized also prostanoids (prostaglandins and thromboxane) [45], [46]. It had been also studied the potential role in the preservation of detrusor tonus and also in the modulation of neurotransmission by some prostaglandins [48]. In case of indomethacin, ketoprofen, flurbiprofen and loxoprofen, that are NSAIDs (non-steroidal anti-inflammatory drugs) [7], [14], [13], [43], [80] and act as COX-inhibitors, it had been demonstrated the ability to increase the bladder capacity in animal models, reducing the effects on urinary symptoms [43], [44], [68]. Other studies had shown that the intravesical instillation COX-2 selective inhibitors have potential advantages, if they are used to treat the overactive bladder [5], [46].

Another promising future therapy was suggested by several studies that had evaluated the role of the calcium channel in the activity of detrusor muscle [8]. The detrusor contraction had been demonstrated to be inhibited by the inhibitors of L-type channels, but available data doesn't show that oral therapy with these drugs is effective and safe, especially because the cardiac side effects. The potassium channels opening drugs are another pathway, by reducing the intracellular Ca concentration, that is inducing a relaxation of the detrusor [16]. Recently, the development of a drug bladder-selective KCO that aims to treat the symptoms of overactive bladder without side effects on the heart or vascular system, has been conducted by several drug companies. But even if some data have been published with 1st generation ATP-dependent potassium channels (KATP) openers (such as cromakalim, pinacidil and nicorandil) phase II trial failed to demonstrate superiority of this drugs compared with placebo [1]. Other drugs of this class in different developmental stages (for example ZD6169), have shown favorable effects in rats [64]. A key role in

the smooth bladder muscle excitability is demonstrated to be played by the big calcium-activated potassium channel (BKCa) [39] and by the BKCa channel openers, such as NS-8, having the potential for treating patients with overactive bladder.

5. Conclusion

The antimuscarinic medications have been first line of treatment used for urge urinary incontinence for years. Even if they are effective, the side effects influence the quality of life that is bothersome for patients.

Although anticholinergic drugs will continue to be the gold standard for the pharmacological treatment of overactive bladder, their side effects and limitations urge the necessity of novel drugs. In the last period, several studies shed light on the molecular bases and pathophysiology of OAB, indicating a various number of potential pharmacological targets, important for the development of future medication that can ultimately provide alternative treatment options for patients with overactive bladder. β 3-adrenoceptors agonists and botulinum toxin A promise to become important future treatment options for the overactive bladder several other drugs are in different development stages.

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