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REVIEW

CURRENT MANAGEMENT AND FUTURE PERSPECTIVES OF OVERACTIVE BLADDER (OAB) PHARMACOTHERAPY

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Abstract: Overactive bladder (OAB) is a condition characterized by urgency with or without urgency incontinence (UI), usually with increased daytime frequency and nocturia, which affects even 8–14% of adult population. The gold standards of OAB treatment are antimuscarinics, although this clinical entity is often poorly controlled with these agents. Thus, a progress in OAB pharmacotherapy is expected and takes place. The purpose of this article is to short review the present management of the overactive bladder with paying special attention on development of new drugs indicated for OAB treatment.

Key words: overactive bladder, OAB current pharmacotherapy, antimuscarinics, OAB future pharmacotherapy

ABBREVATIONS
Ach – acetylcholine, AE – adverse effect, ASIC – acid sensitive ion channel, BKCa – large-conductance, calcium activated potassium channel, BPH – benign prostatic hyperplasia, BTX-A – botulinum toxin A, DRG – dorsal oot ganglion, ENaC – epithelial sodium channel, ICS – International Continence Society, IKCa – intermediate-conductance, calcium activated potassium channel, KCO – potassium channel openers, LUT – lower urinary tract, NANC – non adrenergic non cholinergic, NMDA – N-methyl-D-aspartic, OAB – overactive bladder, PAG – periaqueductal grey nucleus, PDE – phosphodiesterase, PMC – Pontine Micturition Center, PSC – Pontine Storage Center, RyRs – ryanodine-sensitive calcium channel, SKCa – small-conductance, calcium activated potassium channel, SNRI – selective noradrenaline reuptake inhibitors, SSRI – selective serotonin reuptake inhibitors, TAD – tricyclic antidepressant, TRPV1 – transient receptor potential vanilloid subfamily 1, VDCaC – voltage dependent calcium channel

Basic Overactive Bladder definition and pathophysiology

The common OAB definition was given in 2002 by the International Continence Society (ICS) as urinary urgency with or without urge incontinence, usually associated with frequency and nocturia, in the absence of proven pathological or metabolic disorders (such as: lower urinary tract (LUT) infection, bladder cancer, benign prostatic enlargement) or other obvious pathology (1). However, the last reviewing in the ICS 2002 terminology report, published in 2006, recommends replacement of current terms in the definition given above. "Urge incontinence" is suggested to be replaced with "urgency incontinence" to underline that incontinence is due to urgency and not urge (understood as a "desire"). According to 2006 update, the word "frequency" should be substituted by the term "increased day time frequency". Thus, the reviewed OAB definition is urgency with or without urgency incontinence (UI), usually with increased daytime frequency and nocturia (2).

OAB is common clinical entity, with global prevalence ranging 8–14% according to different studied populations, depending on sex, age and differences in accepted OAB definition. Generally, OAB occurrence increases with age and is more common in women than men. Selected reports describing OAB prevalence in western countries are given in Table 1 (3).

Urinary bladder plays a role in urine storage and voiding. Its functioning is regulated by the

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Table 1. Selected studies reporting overactive bladder prevalence in Western countries (3).

Study year	Age of respondents	Prevalence in men population [%]	Prevalence in women population [%]	Both genders prevalence [%]	Reference
2001	≥ 40	15.6	17.4	16.6	(45)
2003	≥ 18	16.0	16.9	16.5	(46)
2004	≥ 35	14.8	21.2	18.1	(47)
2005	≥ 40	17.4	25.6	21.5	(48)
2005	21–91	10.2	16.8	13.5	(49)
2006	≥ 18	10.8	12.8	11.8	(50)
2007	18–79	6.5	9.3	8.0	(51)
2007	≥ 18	13.1	14.7	13.9	(52)
2008	≥ 18	NA	13.0	13.0	(53)

NA – not available

peripheral and central nervous system. At least two types of afferent neurons innervate the urinary bladder. One of them are mechanosensitive, myelinated Aδ fibers, activated by both low, non-nociceptive and high-nociceptive intravesical pressure. The other ones are C-fibers which respond to many chemical irritations. These fibers are suspected to be mostly implicated in OAB pathogenesis. During filling (storage phase), an activation of afferent Aδ fibers takes place due to bladder distention and urothelial signals. The impulses pass the dorsal root ganglion (DRG) and are conveyed *via* pelvic nerve (some of them also *via* hypogastric one) to periaqueductal grey nucleus (PAG) and then to suprapontine regions, which temporally inhibits voiding, deciding of voluntary control of micturition. PAG, in turn, communicates with the pontine tegmentum. One can distinguish two different pontine regions: dorsomedially located M region (Barrington's nucleus), which is said to be a pontine micturition center (PMC) and more laterally located L region, which is regarded to be pontine urine storage center (PSC), responsible for suppressing bladder contractions. The efferent arm of the micturition (emptying phase) reflex starts in PMC; the impulses are conveyed to the sacral S2-S4 spinal parasympathetic nucleus. This nucleus contains preganglionic nerves which project to the bladder. Detrusor contractions are initiated *via* acetylcholine (Ach) and some non-adrenergic non-cholinergic (NANC) neurotransmitters release from postganglionic fibers. Bladder is also innervated with sympathetic nerves, originating from the intermediolateral nuclei in the thoracolumbar region (Th10-L2) of the spinal cord. Sympathetic signals are conveyed *via* both pelvic and hypogastric nerves. Physiologically, during storage phase, no spinal parasympathetic activity and bladder contractions occur and increased sympathetic discharge contributes to bladder relaxation with urethral smooth muscle and urethral and pelvic floor striated muscles keeping the outflow closed. On the other hand, during voiding, the decreased sympathetic activity contributes to bladder outflow opening which, in connection with increased parasympathetic input, lead to bladder contractions and emptying (4, 5).

Concerning the physiological implicates, two main pathophysiological theories have been proposed – neural and myogenic ones. The first one focuses on both central and peripheral innervation disturbances. OAB may result from a lack of central nervous inhibition of voiding (in cerebrovascular diseases, multiple sclerosis, Parkinson's disease, spinal cord injuries). This clinical entity can also occur as a result of sensitization of afferent nerves together with abnormal urothelium activity. These local mechanisms seem to be especially interesting targets for future OAB pharmacological agents. Factors which may be involved in neurogenic OAB pathomechanism are: bradykinin, catecholamines, substance P (SP), calcitonin-gene related peptide (CGRP), vasoactive intestinal peptide (VIP), tachykinins, enkephalins, vanilloids, prostanoids, nerve growth factor (NGF) and many others. There are also evidences that chronic inflammatory bladder is characterized by overexpression of nitric oxide synthase and NO release form capsaicin-sensitive afferents. NO is a molecule relaxating smooth muscles around the bladder outlet and thus contributing to urethral pressure drops that precede involuntary bladder contraction. VIP seems to be an inhibitory agent in efferent parasympathetic pathways and – together with SP – an excitatory factor in bladder afferents. It was discovered that VIP con-

centration in overactive bladder smooth muscles is reduced when compared to normal bladder leading to the conviction that loss of its inhibitory impact may promote bladder overactivity. These findings also hold promise for future therapies ameliorating OAB. The role of calcium influx in unstable myocytes is also emphasized. Apart from neurotransmitter disturbances mentioned above, poor calcium and potassium ion regulation is proposed as another potential mechanism leading to increased cells depolarization and detrusor instability, thus agents affecting calcium influx are also expected to be introduced in the future OAB treatment. The important role in bladder overactivity is attributed to C-fibres, which may be overresponsible to many chemical stimuli. Moreover, abnormal spontaneous bladder activity called "micromotions" may arise from enhanced muscarinic receptors stimulation by acetylocholine released in inadequate amount in basal conditions (1, 4, 6, 7).

OAB pathogenesis, according to myogenic theory, may be also associated with bladder wall rebuilt and reduced compliance and abnormal electrical cells excitation. In the normal bladder, foci of electrical activity spread across small number of coupled neighboring cells. Thus, physiologically, excitatory nerve input must be delivered to a large number of smooth cells to trigger an organized bladder contraction. In OAB muscle, dysfunctional electrical coupling between smooth muscle cells enables small foci of electrical impulses to be propagated beyond their normal range. As a consequence, it may be concluded that normal bladder is characterized by scattered contractions which appear locally,

Table 2. Pharmacological agents used for OAB treatment, assessed by the International Consultation on Incontinence, Paris, 2001 (9, 10).

Class	Agent	Level	Grade
Antimuscarinic	Darifenacin	1	A
	Solifenacin	1	A
	Tolterodine	1	A
	Trospium	1	A
	Atropine	3	C
	Hyoscyamine	3	C
	Propantheline	2	B
Mixed action drugs	Dicyclomine	3	C
	Flavoxate	2	D
	Oxybutynin	1	A
	Propiverine	1	A
Antidepressant	Imipramine	3	C
Vasopressin analogue	Desmopressin	1	A
α-Adrenergic antagonists	Alfuzosin	3	C
	Doxazosin	3	C
	Tamsulosin	3	C
	Terazosin	3	C
β-Adrenergic agonists	Clenbuterol	3	C
	Salbutamol	3	C
	Terbutaline	3	C
Cyclooxygenase inhibitors – prostaglandin synthesis inhibitors	Flurbiprofen	2	C
	Indomethacin	2	C

Level 1 – recommendation based on randomized controlled clinical trials.
Level 2 – recommendation based on good quality prospective studies.
Level 3 – recommendation based on retrospective case-control studies.
Level 4 – recommendation based on case series. Grade A – highly recommended – based on level 1 evidence. Grade B – recommended – based on level 2 or 3 – evidence. Grade C – recommended with reservation – based on level 4 evidence. Grade D – not recommended – based on evidence inconsistent/inconclusive.

while in overactive bladder these local activities are more prone to global spread. The electrical abnormalities may be due to altered bladder wall structure (1, 2).

Summarizing, bladder contractions are under complex neural control and drugs targeting afferent or efferent arms of micturition arc, reducing or blocking locally released various neurotransmitters or directly affecting bladder smooth muscles are regarded to be effective in bladder overactivity treatment.

Non-pharmacological OAB management

Treatment options of OAB involve both non-pharmacological, such as behavioral and psychological training and pharmacological interventions, based on the OAB etiological theories mentioned above. Other clinical OAB implications concern neuromodulation and surgery, although the initial, first-line therapy is a combination of lifestyle modification, pelvic floor muscle exercises, bladder training and antimuscarinic drugs administration.

The goal of OAB non-invasive treatment is to increase urine volume triggering micturition, reduction of urinary frequency and nocturia, decrease urgency and urgency incontinence episodes (3, 8).

Lifestyle intervention should be introduced in each OAB patient and involve fluid limitation, avoiding both high water-containing foods (fruits and vegetables) and fluid input in the evening hours before going to bed, stopping smoking, caffeine reduction and body mass decrease. The bladder training results in bladder capacity increase and voiding intervals extension with overactive bladder contractions, urgency and urge episodes reduction because of increased feedback inhibition. Bladder exercise is usually accompanied by pelvic floor muscle training (PFMT) in which patient is taught to tight the pelvic floor when an involuntary contractions start. The same mechanism – contracting the pelvic floor led to a detrusor decline and urethral pressure increase occurs in electrical stimulation. Additionally, some positive effects of hypnotherapy and acupuncture were reported although they play only marginal role and their effectiveness is not long-term mantained (3, 8).

Current OAB pharmacotherapy

In the past, agents used in OAB treatment included "old" antimuscarinics (such as propantheline, methantheline, emepronium, dicyclomine, terodiline), spasmolytics (such as flavoxate), tricyclic antidepressants (imipramine), prostaglandin synthesis inhibitors (such as indomethacin, flurbiprofen). However, these agents are not commonly used because of lack of their efficacy and/or poor tolerability. At present, several classes of drugs have been approved in OAB treatment. They are presented in Table 2 (9, 10).

Only for a limited number of these agents acceptable efficacy and safety were demonstrated in randomized clinical trials. Thus, they have been found to fulfill the criteria for level 1 evidence and have been given A grade of recommendations by the International Consultation on Incontinence. These values were given parasympathycolytics (antimuscarinic; anticholinergic) drugs, which are nowadays the mainstream of OAB treatment (9, 10).

The rationale for using of these agents comes from physiological findings concerning voiding reflex. As it was mentioned above, acetylcholine released from efferent nerve endings stimulates muscarinic receptors, located on detrusor smooth muscles leading to contraction and micturition. It seems thus simplest to block muscarinic receptors to reduce detrusor abnormal contractility. Moreover, as if OAB background is associated with enhanced "micromotions", these agents exhibit particularly valuable properties. The main problem associated with antimuscarinics use is a lack of their absolute selectivity. Ach is released not only in the bladder but also in other organs, reacting on five (M_1–M_5) subtypes of muscarinic receptors. Therefore, antimuscarinic usage in OAB treatment could have side effects all over the body. In the detrusor, urothelium, interstitial cells and nerve fibers, the predominant muscarinic receptor is M_2 one, but activation of M_3 receptors (which account for one-third) are responsible for direct bladder contraction. The pharmacological studies suggested that M_3 receptors primarily mediate direct contractile response to Ach and other agonists. Formerly it was thought that this action was a result of intracellular calcium release after phospholipase C activation and inositol phosphate synthesis. Nowadays it is regarded that human bladder contraction depends on extracellular calcium entry through L-type calcium channels with subsequent Rho kinases system activation. Interaction of calcium ions with calmodulin activates myosin light chain kinase resulting in contraction. The M_2 receptors seem to mediate indirect contractile response by abolition of relaxative effect, mediated through stimulated β-adrenoreceptor. It was discovered that β-agonists cause an increase of intracellular cAMP, which activates phospholipase A, diminishing calcium level and leading to smooth muscle cell relaxation. On the contrary, M_2 receptor activation leads to the adenylate cyclase inhibition and a decrease of cAMP (5, 8).

Ach may be also released from nerve endings, affecting the subtype unknown muscarinic receptors located on urothelium, causing ATP release, which in turn affects afferent activity *via* purinergic P2X3 receptors and other factors release which can modulate indirectly detrusor contractility. Thus, urothelium and suburothelium that was traditionally viewed only as a passive barrier separating intravesical lumen from the internal bladder layers, nowadays is regarded to participate in sensory bladder functioning by release of many neurotransmitters and various receptors expression. Thus, urothelium and its modulatory effects also seem to be interesting pharmacological targets in novel OAB pharmacotherapy (7).

As it was mentioned, selectivity towards Ach receptors is the one of the main problem associated with antimuscarinic drugs use in OAB therapy. These drugs may affect other than M_2 and M_3 receptors or bind at more than one muscarinic receptors; furthermore these drugs may block these receptors outside of bladder. The restrictions decide of their adverse effects (AE). Blockade of M_3 receptor located in the salivary glands, lower intestinal tract and ciliary and iris smooth muscles in the eye are reported to be most frequent AE, clinically expressed as dry mouth, constipation and blurred vision. Moreover, especially in the elderly population, cognitive impairment during antimuscarinic therapy is observed in some patients. All five muscarinic receptor subtypes are present in central nervous system. M_1 one, located in hippocampus and cortex, is attributed to play an important role in memory. Thus, the affinity of antimuscarinics for the M_1 subtype contributes to the probability of cognitive impairment during therapy. Additionally, elderly patients are more predisposed to such kind of side effect because aging is associated with progressive decrease in central cholinergic activity and with reduction in the density of functioning muscarinic receptors. Thus, muscarinic blockade achieved with drugs together with physiologically observed diminished cholinergic activity result in increased likelihood of cognitive disturbances during therapy (5, 8, 11).

The last essential AE, which is related to antimuscarinic use is the risk of cardiac AE, particularly with the increased of heart rate through blockade of inhibitory input. Thus, cardiac tachycardia and arrhythmia are one of the precautions given in the individual antimuscarinic compound clinical characterization. On he other hand, studies concerning the essential tachycardia or other arrhythmias in patients treated with tolterodine, trospium, solifenacin and darifenacin did not reveal serious arrhythmia. Antimuscarinics are also suspected to induce QT prolongation leading to the polymorphic ventricular tachycardia (torsade de pointes), although QT prolongation and its consequences are not related to muscarinic receptor blockade but rather linked to inhibition of some potassium channels. Results of cardiac electrophysiological study of patients receiving tolterodine showed no QT interval prolongation. Similar results were obtained for trospium and darifenacin. Summarizing, there is little evidence that antimuscarinic drugs used in OAB treatment increase the risk of cardiac AE, when administrated in recommended therapeutic doses (5, 8).

The short pharmacokinetic and pharmacodynamic description of currently used antimuscarinic agents is given in Table 3 (5, 12–21).

Future approaches of OAB treatment

As it was described above, micturition process involves complex peripheral and central mechanisms, which seem to be potential places of novel pharmacological agents' action. Thus, it should be expected that future OAB drugs will be focused on various neurotransmission which organize micturition on different stages.

Up to now, there is no drug affecting the voiding which acts centrally, although in both spinal and supraspinal mechanisms there are many neurotransmitters receptors which may be the target for central drugs aimed at the micturition control. Glutamate, glicyne, GABA, serotonin, noradrenaline, dopamine, and enkephalines are examples of potential sites of therapeutic intervention. Moreover, agents influencing these chemicals and other: tachykinins, vanilloids, prostanoids released peripherally in bladder, as well as factors acting *via* different neuronal and smooth muscle ion channels are of special interest.

Glutamate and glycinergic systems

Glutamate is one of the most important excitatory neurotransmitters in central nervous system. It has also been found in efferent arm of voiding reflex, between the PMC and the preganglionic neuron. Antagonists of NMDA (N-methyl-D-aspartic) glutamate receptors were given in stroke-mediated OAB rats and they diminished urodynamically measured bladder overactivity. However, important factor limiting the NMDA antagonists using are the findings that glutamate is a key neurotransmitter in brain, regulating most of its function. Thus, usage of agents targeted in glutamate system must be associated with undesired influence of many other central

Table 3. Selected average pharmacokinetic and pharmacodynamic properties of antimuscarinic agents used in the OAB treatment (5, 12–21).

	Oxybutynin	Propiverine	Solifenacin	Darifenacin	Tolterodine	Fesoterodine	Trospium
Relative lipophilicity	lipophilic	NA	highly lipophilic	highly lipophilic	slightly lipophilic	NA	hydrophylic
Metabolizing enzymes and route of elimination	CYP3A4 hepatic	CYP2D6 CYP3A4 hepatic	CYP3A4 hepatic	CYP2D6 CYP3A4 hepatic	CYP2D6 CYP3A4 hepatic	CYP2D6 CYP3A4 hepatic	Ester hydrolysis by nonCYP450 renal
Metabolites contributing to clinical effect	N-desethyl-oxybutynin	N-oxide-propiverine	4-hydroxy-solifenacin	NA	5-hydroxy-methyltolterodine	5-hydroxy-methyltolterodine	none
Mean half life [h]	2 – for IR form 13 – for ER form 7–8 – for TDS form	15	49	12	2 – for IR form 8 – for ER form	7.3	20
C max [ng/mL]	1.1 (dose 10 mg *p.o.*, q.i.d.)	60 (dose 20 mg *p.o.*, b.i.d.)	40.6 (dose 10 mg *p.o.*, q.i.d.)	5.8 (dose 15 mg *p.o.*, q.i.d.)	1.9 (dose 4 mg ER form *p.o.*, q.i.d.)	1.9 (EM)–3.5 (PM) (4 mg *p.o.*, o.d.)	2.3 (dose 20 mg *p.o.*, b.i.d.)
AUC [ng × h /mL]	18	NA	749	88.9	16.9	21.2 (EM) 40.5 (PM)	17,7
Protein binding [%]	99	90	98	98	96	50	50
Affinity (Ki in nM) for receptor: M_1 M_2 M_3 M_4 M_5	 1.0 6.7 0.67 2.0 11.0	 6.58 5.79 6.39 6.46 6.43	 26.0 170.0 12.0 110 31	 7.3 46.0 0.79 46.0 9.6	 3.0 3.8 3.4 5.0 3.4	 8.0 7.7 7.4 7.3 7.5	 0.75 0.65 0.50 1.0 2.3
Licensed dose	ER form: 5–20 mg o.d. TDS form: 1 patch twice weekly	15 mg o.d.–q.i.d. ER form: 30mg o.d.	5–10 mg o.d.	7.5–15 mg o.d.	1–2 mg b.i.d. ER form: 4 mg o.d.	4–8 mg o.d.	20 mg b.i.d.
Brand name	Ditropan Driptane Uroton	Detrunorm Detrunorm XL	Vesicare	Emselex	Detrusitol Detrusitol XL Uroflow	Toviaz	Regurin Spasmo-Lyt

Abbreviations: NA – not available, IR – intermediate release, ER – extended eelease, TDS – transdermal system, AUC – area under curve, EM – extensive metabolizer, PM – poor metabolizer, o.d. – once daily, b.i.d. – twice daily, q.i.d. – four times daily

mechanisms and so far are used only in experimental models.

Contrary, an important inhibitory effect on the spinobulbospinal and spinal micturition reflexes may exert glycinergic neurons. Serum glycine level was lower in patients with spinal cord injury, suffering from neurogenic OAB. Thus, similarly to glutamate system, glycinergic one also seems to be central target for novel OAB medicines development. However, glycinergic neurons are also widely involved in lot of spinal pathways, thus introduction of glycinergic agents selectively affecting micturition to OAB therapy appears to be very laborious and uncertain.

It must be emphasized that taking the essential role of both neurotransmitter systems in various central functions into consideration, the development of selective acting agents targeting only neuronal bladder controlling up to now is only hypothetical (4, 22).

GABA-ergic system

The next central compound, identified as the most important inhibitory neurotransmitter is GABA. There are three GABA receptors, labeled as $GABA_A$, $GABA_B$ and $GABA_C$. The predominant brain receptors are $GABA_A$ and $GABA_B$, while in spinal cord $GABA_A$ receptors are more numerous.

It was discovered that GABA-type interneurons play an important inhibitory role for both bladder and especially central efferents. On the other hand, $GABA_B$ receptor agonist – baclofen – administered intrathecally in oxyhemoglobin induced detrusor overactivity showed the inhibitory action, suggesting that spinal $GABA_B$ agonists may be useful for controlling micturition disturbances caused by C-fibers activation in urothelium. There are also clinical evidences demonstrating baclofen efficacy in patients with neurogenic OAB, secondary to spinal lesions, although the desired effects were accompanied by high incidence of intolerable adverse effects, which made patients to decline therapy. Summarizing, blockade of $GABA_A$ and $GABA_B$ receptors lead to micturition stimulation, thus activation of these receptors may be co-responsible for inhibition of micturition reflex. Similarly, inhibition of GABA-breakdown or GABA reuptake also produces an inhibitory effect on micturition and agents acting *via* this mechanism may be considered as potentially useful in future OAB pharmacotherapy (4, 22).

Serotonin and serotonin receptors

The neurotransmitter, which is widespread in central regions, where afferent and efferent impulses from and to LUT are conveyed, is serotonin. According to chemical structure, signaling pathways and pharmacological effects, the serotonin receptors are usually divided into seven classes ($5HT_1$–$5HT_7$) with some subtypes. All of these receptors are G-protein coupled, except $5HT_3$ ones which are ligand-gated ion channels.

Depending on receptor type and its localization, serotonin may exhibit either inhibitory or excitatory effects on micturition. However, the existence of the descending, inhibitory pathway with serotonin as a key neurotransmitter is unchallenged. De Groat gave the model explaining the serotonin role in the LUT. According to it, raphe nucleus neurons release serotonin at several lumbosacral levels. The fundamental role in LUT serotoninergic system play inhibitory $5HT_{1A}$ receptors, located on preganglionic parasympathetic neurons, neurons conveyed afferent impulses to the brain and on interneurons providing an inhibitory impact on motoneurons projecting the striated urethral sphincter. The neurons of raphe nucleus also express inhibitory $5HT_{1A}$ autoreceptors. Thus, blockade of these receptors would bring increased serotonin release and augmentation of spinal inhibitory system towards the bladder. It is in accordance with the experimental observations that electrical stimulation of raphe nucleus causes inhibition of bladder contractions. The main disadvantage of the proposed theory are the unexpected and sometimes opposite effects arising from serotonin and its agonists influence on other serotonin receptors. For example, experimental intrathecal serotonin administration increased micturition volume but blockade of spinal $5HT_2$ and $5HT_3$ decreased bladder capacity (4, 22, 23).

Apart from limitations underlying complicated and still undiscovered pharmacological networks and effects between various serotonin receptors, blockade of central $5HT_{1A}$ receptors represents a possible target for micturition control in OAB.

In the light of serotonin important role in voiding process, there is a question how drugs interfering with serotonin reuptake, are affecting the bladder functioning. The serotonin deficiency is observed in depression and probably in OAB. Studies are needed to explore if the antidepressants focused on serotonin mechanisms are effective in micturition control in depressed patients only or in all OAB patients. This problem has not been absolutely explored so far. Moreover, some studies are contradictory – there are evidences that some selective serotonin reuptake inhibitors (SSRI), such as citalopram, did not alter bladder contraction. Combined noradrenaline and serotonin reuptake

inhibitors (SNRI) – e.g., venlafaxine, increased bladder capacity. On the other hand, imipramine (Tricyclic Antidepressive Drug – TAD) depressed rat bladder activity. Thus, pharmacotherapy with SSRI, SNRI or TAD may affect voiding process. Among all agents acting *via* monoamine reuptake inhibition, duloxetine is the most studied compound. This drug was demonstrated in animal model to increase neural activity to the striated urethral sphincter and to increase bladder capacity through its effect on the central mechanisms. Beneficial effect of duloxetine was revealed in clinical study in female patients with OAB ("wet OAB") and without ("dry OAB") urinary incontinence. Thus, the concept is enforced that duloxetine may have the potential for OAB treatment (4, 22, 23).

Dopamine and dopamine receptors

Similarly as in the case of serotonin pathways, central dopamine paths exist, exerting both inhibitory and stimulatory effects on bladder function. Experimental studies revealed that activation of D_1 receptors represses micturition while D_2 ones activates micturition. Consistently, D_1 receptors blockade stimulates but D_2 ones inhibits or has little effect on the bladder. Thus, D_1 receptors are regarded to tonically inhibit the voiding reflex while D_2 receptors contribute to the voiding reflex. The indirect evidence that dopamine and dopamine receptors take part in voiding physiology and pathophysiology are findings that patients with Parkinson's disease often suffer from OAB symptoms. Since the pathogenesis of Parkinson's disease is associated with destruction of striatal, dopaminergic neurons, it may be concluded that loss of D_1 receptors is responsible for OAB development in Parkinson's disease patients.

The clinical therapeutic opportunities focused on dopamine system involve highly selective D_1 receptor agonists development; although this area is still poorly explored and further studies are required. Especially that levodopa – the most clinically used in the Parkinson's disease treatment dopamine precursor, has been described to worsen OAB symptoms, probably due to its unselectively influence of all dopaminergic receptors. Similar observations were done in experimental administration of apomorphine or bromocriptine (4, 22).

Noradrenaline and noradrenergic receptors

Noradrenaline neurons originating from the locus coeruleus also seem to be co-responsible for supraspinal control of micturition. Especially α_1 receptors seem to be engaged in the sympathetic neural control of LUT, although only their selected subtypes modulate of reflex bladder activity. The idea of application agents acting *via* α adrenoreceptors arises from the clinical observations, that α_1-adrenoreceptors antagonists used in the treatment of benign prostatic hyperplasia (BPH), inhibit smooth muscle contractions and reverse not only the obstructive symptoms associated with bladder emptying but also relieve the irritative BPH symptoms (frequency, nocturia, urgency). It is regarded that blockade of α_{1A} subtypes ameliorate prostate hyperplasia and smooth muscle contraction while α_{1D} ones mediate the bladder irritative symptoms. It is consistent with the findings that tamsulosin, a blocker of both α_{1A} and α_{1D} receptors reduces overactive bladder symptoms in men. The postulated mechanism of α_1 antagonists in bladder function improvement is unclear, however, α_1 receptors are expressed on bladder sensory neurons and their activation may contribute to enhancement of signaling of irritative and nociceptive responses. Tamsulosin was also proved to have an inhibitory effect on C-fibers urethral afferents *via* TRPV1 receptors (24).

β-Adrenoreceptors are also found in the bladder with the predominant β_3 subtype (they account up to 95% of all β-receptors). In experimental studies relaxation of bladder body after terbutaline, salbutamol and clenbuterol was demonstrated, thus β_3-receptor selective agonists have been studied for years as a potential OAB modern drugs. These kinds of drugs would produce fewer if any cardiovascular adverse effects than β_1- or β_2-agonists, thus they would be safe agents. The detrusor relaxation after β-agonists is mediated mostly *via* increasing intracellular cAMP level although the activation of large-conductance Ca-activated K (BK) channels seems to be also possible. The other therapeutical option resulting in the same effect (an increase of cAMP) is phosphodiesterase (PDE), an enzyme degrading cAMP blocking. There are six isoforms of PDE, found in bladder smooth muscles: PDE1-5 and PDE9. PDE1 inhibitor – vinpocetine, PDE4 inhibitor – rolipram and PDE5 one – vardenafil exhibited in clinical trials efficacy in ameliorating irritative LUT symptoms. Further studies are required to establish the optimal doses, precise indications and patient population. As it was mentioned, the main target of β_3-agonists is detrusor smooth muscles, although lately it has been suggested that urothelial β_3-receptors are also presumed pharmacological goals. Stimulation of these receptors results in urothelial nitric oxide (NO) release, which modulates afferent nerves activity. Moreover, hypothetical urothelial derived inhibitory factor, which is not

identified with NO is released, that inhibits smooth muscles contractions (4, 22, 24).

Nonadrenergic-noncholinergic system: enkephalins, purinergic system, endothelins, tachykinins, nociceptin

Enkephalins – endogenous opioid peptides are widely distributed in the brain, including areas involved in micturition (PAG, PMC, spinal parasympathetic nucleus). Usually, three opioid receptors are distinguished: μ, δ and κ, which bind morphine and other opioids, mediating the inhibitory effects on micturition. It was experimentally and clinically demonstrated that morphine increased bladder capacity and blocked bladder contractions when administrated intravenously, intraperitoneally or intrathecally. Moreover, naloxone – an μ opioid antagonist abolished the effects mentioned above. These findings suggest that μ receptors may perform an inhibitory control of the micturition and it brings another therapeutic approach. However, μ-receptor agonists are not expected to be introduced in OAB therapy due to their adverse effects, such as nausea, respiratory depression, constipation, pupillary contraction and others. Among opioid agents, tramadol – with combinatory effect on opioid receptors with inhibition of serotonin and noradrenaline reuptake seems to be attractive because of its fewer adverse effects. It seems possible that tramadol may be used in treatment of OAB. Similarly, after administration of partial μ-receptor agonist and κ-antagonist – buprenorphine, an improvement in micturition manifested as increased bladder capacity and decreased micturition pressure were observed. Thus, the most probably is that apart from μ receptors, stimulation of other ones is engaged in micturition (4, 22).

The next important transmission in NANC system is purinergic one, with ATP as a main molecule. There are several receptors for ATP: metabotropic P2Y and ionotropic P2X1–7 families. Detrusor muscle cells possess P2X1, P2X2, P2X4 subtypes, bladder nerves are supplied with P2X1, P2X2, P2X3 and P2X5 ones while urothelial cells express P2X2, P2X3 and P2X5 receptors. Purinergic transmission is regarded to affect both afferent and efferent endings. ATP is a molecule being co-responsible for afferent sensitization and neurogenic inflammation development. Moreover, there are evidences suggesting ATP role in the bladder contraction *via* P2X1 and that ATP is released from urothelial cells playing an autocrine and paracrine role. Experimental studies suggest that P2X channels blockers offer the next novel therapeutical option, although these studies are still early and need to be advanced (22).

Another chemicals involved in bladder controlling are endothelins (ET1–3), showing affinity to ET_A and ET_B receptors. Endothelins are attributed to have a regulatory role of detrusor tone and a modulatory impact on detrusor neurotransmission. Moreover, ET also exerts strong mitogenic effect on smooth muscle cells, thus antagonization of ET activity is expected to prevent detrusor hypertrophy and would be of special interest in obstructive and diabetic OAB patients. It is consistent with the experimental findings revealing higher ET receptors density amount in obstruction-induced OAB. The predominant endothelin type is ET1, which mediated *via* ET_A receptor slowly developing bladder contraction. Thus, selective ET_A receptor blockade could be an effective treatment for OAB. The next therapeutic approach seems to be endothelin converting enzyme inhibitors – during endothelin synthesis an enzymatic cleavage of proendothelin occurs, similarly to angiotensin II synthesis from its precursor angiotensin I with angiotensin converting enzyme. Endothelin converting enzymes inhibitors are also considered to be promising novel OAB drug candidates (22).

An important physiological and pathophysiological role in central and peripheral bladder function controlling plays a tachykinin system. Tachykinin family involves several peptides, including substance P (SP), calcitonin gene-related peptide (CGRP) and neurokinins A (NKA) and B (NKB), which possess the affinity for NK_1, NK_2 and NK_3 receptors, respectively. These receptors were demonstrated in various brain regions, including those ones which take part in micturition. Tachykinins acting *via* central and peripheral mechanisms facilitate the micturition. When administrated SP-saporin conjugate (SP-SAP – a conjugate of substance P (SP) to saporin, a ribosome inactivating protein from *Saponaria officinalis*), an improvement in overactivity symptoms was observed. SP-SAP has been shown effective in destroying neurons expressing the neurokinin-1 receptor (NK_{1R}) in the striatum and lamina I of the dorsal horn of the spinal cord. Tachykinins released peripherally from urothelial cells and capsaicin-sensitive afferents contribute to local and spinal micturition reflexes. Increased tachykinins release is suspected to be involved in OAB pathogenesis, and NK_2 antagonists were effective to reduce experimental detrusor hyperactivity in the rat. Moreover, these compounds influence vascular tone and permeability being co-responsible for neurogenic inflammation development. Tachykinins and their pathophysiological role in OAB are widely studied in experimental models

nowadays. There is also randomized, controlled clinical trial of women with urge urinary incontinence, showing that aprepitant – NK_1 antagonist were effective in ameliorating their OAB symptoms. These all findings support the idea that counteracting effects of tachykinins may be an interesting pharmacological tool in future OAB treatment (22, 23, 25).

There is also another molecule arousing the interest in searches novel OAB treatment options. Nociceptin – orphanin FQ (N/OFQ) was discovered to be endogenous agonist of opioid-like receptor-4 (NOP receptor). Nociceptin inhibits micturition by blockade of afferent C-fibers discharge in rats. In experimental studies this compound was also demonstrated to have central inhibitory effect, affecting supraspinal micturition centers. There are also preliminary clinical studies confirming the nociceptin efficacy (although the studied OAB population was relatively small and the large clinical trials are needed). Several selective NOP receptor agonists were also synthesized making this receptor a realistic new target for OAB drug design (22, 26).

Vanilloid receptors and primary afferent nerves

As it was mentioned above, there are two main afferent pathways carrying the impulses from the bladder to central nervous system. The major pathway is composed of myelinated Aδ fibers but in addition to this dominant route there are also unmyelinated C-fibers, conveying afferent impulses mostly in response to chemical irritants (e.g., inflammation mediators). These fibers are said to be capsaicin-sensitive afferents – it means that after initial stimulation with capsaicin, subsequent long term desensitization occurs.

C-afferent fibers are located in the detrusor, perivascularly and in the intramural bladder plexus extending to urothelium and contain tachykinins, which may be released from their endings, contributing to neurogenic inflammation. Under physiological conditions, these neurons transmit nociceptive and thermoceptive information to the central nervous system and regulate homeostatic reflexes, such as bladder microcirculation. These afferents are also involved in OAB pathophysiology, convey pain sensation and provoke neurogenic inflammation, which destabilizes resting bladder activity and affects complex interactions between all bladder structures (afferent/efferent innervation, detrusor smooth muscles, urothelium and others) (7, 22, 23). Capsaicin, stimulatory agent for C-fibers is a neurotoxin, belonging to the group of vanilloids, together with resiniferatoxin and their analogues because these compounds share a common structural element – a homovanillyl group. Thus, capsaicin-sensitive neurons are also called vanilloid-sensitive ones to underline that these fibers are either activated or inactivated by vanilloids in a receptor-mediated way.

Capsaicin is the active ingredient of the hot chili pepper (*Capsicum annuum*), isolated for the first time in 1846 and completely synthesized in 1930. Resiniferatoxin was obtained from the cactus-like *Euphorbia resinfera* in 1975 and in 1989 it was recognized as more potent analogue of capsaicin. Both capsaicin and resiniferatoxin affect the vanilloid receptors located on afferent neurons, thus being exogenous ligands. These receptors are presently known as transient receptor potential vanilloid subfamily 1 – TRPV1 and some endogenous agonists were also found: protons, N-arachidonoyl-ethanolamine (anandamide), N-arachidonoyl-dopamine, N-oleoyl-dopamine, eicosanoid acids and lipooxygenase products (22, 23, 27, 28).

TRPV1, formerly known as vanilloid receptor type 1 is a non-specific ion channel, stimulated by heat (> 43^{o}C), low pH and exogenous (vanilloids) and endogenous agonists mentioned above. This receptor represents TRP family of ion channels, also called "thermo-TRP" class. Usually, four heat-sensitive channels, including TRPV1–4 and two "cold-sensitive" TRMP8 (currently identified with cold menthol receptor CMR1) and TRPA1 have been distinguished. Moreover, the TRP family was broaden of two thermal-nonsensitive channels TRPV5 and TRPV6. It must be emphasized that sensitivity to vanilloids has been demonstrated for TRPV1 subtype so far and the influence of vanilloid compounds on other TRPV subgroups remains still controversial and requires further studies. It seems that TRPV1 channels play essential role in OAB, resulting from pathological excitation C-afferents. The frequency of bladder contractions in chronically inflamed rat urinary bladder (cyclophosphamide inflamed rat bladder) is increased and capsaicin administration reduces the bladder motility in this OAB experimental model. Under physiological conditions, the TRPV1 role in regulation of normal bladder activity is regarded to be of less meaning (29, 30).

Chemical denervation of C-vanilloid afferents after intravesical administration of capsaicin binding TRPV1 was showed to be effective in overactive bladder disturbances treatment. Most clinical studies suggest that after this procedure, in 60% OAB patients urodynamic improvement was achieved 1–2 months after capsaicin instillation with long-lasting effect, even up to one year in some patients. This compound is difficult to dissolve therefore ethanol-

saline solutions must be used (mostly 30% ethanol). Acute pain after capsaicin administration on bladder mucosa and its irritation limit common clinical use of the agent (although burning sensation was also noted when administered was 30% ethanol with no capsaicin). Apart from this phenomenon, most of patients reported initial worsening of OAB symptoms during first few days up to even two weeks after capsaicin solution instillation. These adverse effects are more seldom observed after resiniferatoxin, which is estimated to be a thousand times more selective and potent than capsaicin – this compound is active at concentrations 100–10000 times lower than capsaicin. It enables thus dose lowering and showing fewer adverse effects. It is commonly believed that resiniferatoxin favors desensitization of C-fibers while capsaicin causes an initial excitation, which then turns to C-fibers silence. It is unknown if there are different mechanisms by these compounds produce their effects, however, in both cases strong role of single TRPV1 is emphasized. The possible explanations are that resiniferatoxin has a higher molecular weight than capsaicin and is more lipophilic, thus has slower tissue penetration after administration on mucosa. Secondly, it seems that capsaicin after binding TRPV1 stimulates rapid in onset but brief in duration inward ion current. Contrary, resiniferatoxin induces slowly rising but more sustained currents. These findings make resiniferatoxin an interesting alternative to capsaicin in therapeutic OAB efforts. What is surprising from the clinical point of view, resiniferatoxin administered intravesically had variable efficacy – it increased cystometric bladder capacity (in part of OAB patients of 31–136% and it was even reported of 500%!!!), with no warm or burning sensation, but this compound produced effects lasting only from 4 to several weeks, in dependence on the used resiniferatoxin concentrations (22, 23, 28).

Summarizing, vanilloids are effective agents in suppressing detrusor hyperreflexia, affecting the afferent innervation of the bladder. However, the precise role of C-fibers and their interactions between bladder urothelium in normal and pathophysiological conditions must be still evaluated.

Prostanoids

Prostanoids are heterogeneous group of molecules derived from arachidonic acid in enzymatic process of cyclooxygenation. This group includes prostaglandins (PG) and thromboxanes (TX), synthesized by cyclooxygenase (COX). It is known, that there are at least two COX izoforms: COX-1, responsible for the normal, physiological prostanoids biosynthesis and COX-2, activated in response to various pathophysiological stimuli, especially mediators of inflammation.

There are several prostanoid receptors: DP, EP1–EP4, FP, IP and TP, which bind preferentially PGD_2, PGE_2 and TXA_2. Prostanoids are synthesized locally both in the detrusor and mucosa. PGE_1, PGE_2 and $PGF_{2\alpha}$ cause sluggish detrusor contraction. Moreover, these compounds are regarded to elicit bladder afferent activity, contributing to hypersensitization (31).

Nonsteroidal antiinflammatory drugs (NSAID) are COX inhibitors, which were found to improve OAB symptoms (increase bladder capacity and prolonged micturition intervals). The common NSAID adverse effects (nephrotoxicity, antiplatelet and ulcerogenic properties) limit their clinical usefulness. Thus, an increasing interest in prostanoid receptors antagonists development is observed. It was demonstrated in experimental model of rat obstructive-derived OAB that one of the EP_1 receptor antagonists showed beneficial effects, thus these kind of agents may also have potential as a treatment of OAB in humans (22, 32).

Ion channels – calcium channels

There are also efforts of introducing to OAB pharmacotherapy agents directly affecting smooth muscle contractility through the influence on smooth muscles electrical properties. The action potentials have different phases due to the coordinated action of several ionic conductances. The depolarization spike is a result of extracellular calcium entrance through the voltage-dependent L-type calcium channels (VDCaC) with subsequent calcium release from sarcoplasmic reticulum through ryanodine-sensitive calcium channels (RyRs). The participation of T-type Ca channels is also considered, as calcium influx through these channels may account for prolonged depolarization. The repolarization phase results from the activation of both voltage-dependent potassium channels KV and large-conductance, calcium activated potassium channels (BKCa). Then hyperpolarization occurs, mediated through the small-conductance, calcium-activated potassium channels (SKCa) and likely KV channels, restoring the potential to the initial value. There are also ATP-dependent potassium channels which are suspected to be involved in detrusor hyperpolarization and its relaxation (22).

The studies targeting the agents affecting detrusor smooth muscles action potentials focused on the VDCaC antagonists, thus agents preventing the depolarization phase. Nifedipine was shown to have strong inhibitory effect on isolated bladder

Table 4. Summary of the potential targets for novel OAB pharmacotherapy (22).

Pharmacological target		Localization	Effect on bladder activity	Potential drugs
Glutamate system NMDA receptors		CNS	excitatory	NMDA antagonists
Glycinergic system glycinergic receptors		CNS	inhibitory	Gly-receptors agonists
GABA system $GABA_A$, $GABA_B$ receptors GABA-transaminase		CNS, bladder	inhibitory	$GABA_A$, $GABA_B$ agonists
Monoamines	**Serotoninergic system** descending inhibitory pathway with $5HT_{1A}$ autoreceptors $5HT_2$–$5HT_7$ receptors	CNS bladder	inhibitory ($5HT_{1A}$) stimulatory ($5HT_2$, $5HT_3$, $5HT_4$, $5HT_7$ receptors)	$5HT_{1A}$ antagonists $5HT_2$, $5HT_4$, $5HT_7$ antagonists SSRI, duloxetine
	Dopaminergic system D_1 and D_2 receptors	CNS	inhibitory (D_1 receptors) stimulatory (D_2 receptors)	D_1-agonists D_2-antagonists
	Noradrenaline system α_1- and β_3-adrenoreceptors	CNS, bladder	inhibitory (β receptors) stimulatory (α receptors)	β_3-agonists PDE1,4,5 inhibitors α_1-antagonists
NANC system	**Enkephaline system** ENK receptors (μ, δ and κ)	CNS, bladder	inhibitory	ENK-agonists
	Purinergic system (P2Y1–8, P2X1–7 receptors)	CNS, bladder	stimulatory	P2X antagonists
	Endothelins ET_A, ET_B receptors ECE	CNS, bladder	stimulatory inhibitory	ET_A, ET_B antagonists ECE-inhibitors
	Tachykinins NK_{1-3} receptors	CNS, bladder	stimulatory	NK_1-antagonists (aprepitant) NK_2 antagonists SP-saporin
	Nociceptin NOP receptor	CNS, bladder	inhibitory	NOP-agonists
Afferent terminals TRPV1and other channels		bladder (C-fibers)	stimulatory	desensitization: vanilloids (capsaicin, resiniferatoxin), TRPV-1 agonists
Prostanoids DP, EP, FP, IP, TP receptors; COX		bladder	stimulatory	COX-inhibitors EP1-antagonists

Ion channels	**Calcium channels** L-type, T-type	bladder	stimulatory (L-type-neurogenic contraction); T-type-myogenic contraction)	Calcium L-channels antagonists Calcium T-channels antagonists
	Potassium channels Calcium activated: BKCa, SKCa, IKCa ATP-inhibitory KATP Direct KV	bladder	inhibitory	KCO activating BKCa/SKCa opening KCO antagonizing ATP inhibitory subunit: cromakalim, pinacidil, nicorandil, KCO targeting KV: retigabine
	Sodium channels ENaC, ASIC	bladder	stimulatory	ENaC/ASIC blockers
	Botulinum toxin		inhibitory	BTX-A

Abbreviations: NMDA – N-Methyl-D-aspartic acid receptor. GABA – γ-Aminobutyric acid. NANC – non adrenergic non cholinergic. CNS – central nervous system. SSRI – Selective serotonin reuptake inhibitors. ECE – Endothelin converting enzyme. TRPV1 – Transient receptor potential vanilloid subfamily 1. COX – Cyclooxygenase. KCO – Potassium channel openers. ENaC – Epithelial sodium (natrium) channels. ASIC – Acid sensitive ion channels. Other explanations given in the text.

smooth muscles, but clinical studies investigating the VDCaC antagonists are scarce, especially due to their cardiovascular adverse effects. Thus, the local use of the potent Ca-antagonists might be an interesting therapeutic approach. Moreover, taking into consideration the T-type calcium channels role in depolarization, it seems that pharmacological manipulation of T-type Ca channels would be another future target in OAB treatment (33–35).

Ion channels – potassium channels

Potassium channels can be distinguished into some subtypes, including: K ATP channels, KV channels and large (BKCa), intermediate (IKCa) and small (SKCa) conductance calcium-activated channels, all expressed on bladder smooth muscles. The key role seems to play BKCa channels, being responsible for repolarization phase and opposing both cholinergic and purinergic excitability of detrusor. The confirmation of the role BKCa channels in OAB pathogenesis gave experimental studies with mice with deletion of gene encoding a subunit of BKCa channel. In this animal model, a rapid urodynamic OAB features were developed. Thus, a calcium activated potassium channel opening drugs – "Potassium Channels Openers, KCO", might have the potential for treating OAB patients. One of them, labeled as NS-8, undergoes preclinical studies demonstrating suppression of micturition in rats. Apamin, a selective SKCa blocker, was shown to enhance bladder phasic contractions in animals. Thus, these channels and agents opening SKCa can be next interesting targets for drugs aiming to control micturition (22, 36, 37).

K ATP channels are composed of K channel pore and ATP regulatory subunit. This subunit may be a place of another KCO group action that promotes channel activity by antagonizing ATP-induced ion exchange inhibition. There are evidences that administration of "old" KCO targeting ATP subunit – cromakalim, pinacidil and nicorandil lead to detrusor relaxation in human. The similar effects were demonstrated when these agents were given to rats with obstructive OAB or in rats with spinal cord injury. Several studies are ongoing being aimed at finding more selective "new" KCO affecting ATP regulatory subunit (22, 38).

KV channels play an important role in the regulation of basic electrical activity of the detrusor. There are evidences that agents opening these channels may be promising targets of future OAB treatment. Retigabine is an antiepileptic drug that opens KV channels. After *i.v.* and intracerebroventricular administration of retigabine in rats, an increase of the

micturition volume and voiding intervals were observed. The major disadvantage of KV openers is their widespread and not predictable effects with markedly pronounced blood pressure reduction, arising from KV openers nonselectivity. The cardiovascular restrictions made rationale to study the effects of KV openers administrated locally and there are animal studies focused on the effects of agents affecting KV channels, however, so far no KV opener has passed to further stage of studies (22, 39).

Ion channels – sodium epithelial channels

The sodium epithelial channels – (ENaC, also called "degenerin/epithelial sodium channels" – Deg/ENaC) family was discovered in early 1990s. The summary name of this group of receptors is derived from protein "degenerin" identified in *Caenorhadbitis elegans* in which mutation of deg1 gene resulted in sensory neurons, involved in touch perception degeneration. These channels are blocked by amiloride and activated by mechanical stimuli, low temperature, pH drop and still unidentified chemical ligands (30, 40). ENaC were found in kidneys, distal colon, secretory glands and respiratory airways, playing a key role in epithelial sodium absorption.

Recently, ENaC have been also found in lower urinary tract (LUT) epithelia (renal pelvis, ureter, urinary bladder) and in suburothelial afferent nerves (30, 41). The subgroup of epithelial sodium channels, which are proton-gated and especially often found in the urothelium and detrusor muscles, is acid sensing ion channels (ASIC). The precise physiological role of these channels remains unknown; however, their disruption changes due to mechanical influences. It seems that ENaC and ASIC have the ability to change its sodium influx in dependence on hydrostatic pressure – an increase in intrabladder pressure may initiate activation of these channels and trigger afferent endings. Thus, this mechanism is of special interest in obstructive OAB model. It is consistent with the observations that in human bladder the expression of ENaC is low but it markedly rises in patients with obstructive bladders and OAB symptoms. Thus, agents blocking ENaC/ASIC might be considered as next hypothetical target for future agents effective in OAB treatment. However, the studies on ENaC/ASIC LUT selectively agents are still elementary and poorly developed (30, 42).

Botulinum toxin (Botox)

Botulinum toxin (BTX), derived from *Clostridium botulinum* acts by decreasing acetylcholine release from presynaptic endings of cholinergic nerves and provides long-lasting neuronal blockade. BTX is expected to cleavage SNARE (Soluble NSF Attachment Protein Receptors) protein SNAP-25, responsible for the exocytosis of neurotransmitters. There are seven subtypes of BTX and mostly used is BTX-A. Taking into consideration the cholinergic mechanism of efferent bladder supplying, the ability of BTX-A to prevent acetylcholine release with subsequent decreased bladder contractility made this compound an interesting approach to OAB future treatment. The produced chemical denervation is reversible as axons regenerate in 3–6 months. Botox does not cross the blood-brain barrier thus has no central effects. Moreover, it has recently been postulated that BTX-A also affects afferent neurotransmission (22). The mechanism of BTX-A action seems to be not only associated with efferent endings blocking but also with inhibition of release of tachykinins from afferents together with downregulation of purinergic (P2X3) and TRPV1 receptors expression (27).

There are several clinical reports showing BTX-A efficacy in improvement of OAB symptoms and decrease of involuntary detrusor contractions. Repetitive injections of BTX-A resulted in persistent significant therapeutic effect although optimal doses, precise route of administration and fully elucidating the BTX-A mechanism of action remain for further studies. Despite the incomplete knowledge, BTX-A promises to become one of the major future treatment for OAB (43, 44).

CONCLUSIONS

Current options for pharmacotherapy of overactive bladder are unfortunately scanty and insufficient. Increasing understanding OAB pathophysiology enables development of new agents, selectively targeting the OAB pathomechanisms, both central and peripheral. Thus, it should be expected that in close future the OAB pharmacotherapy will be more effective and safer. The aim of this article was to give rationale for searching other therapeutical approaches. The main directions in novel OAB pharmacotherapy are summarized in Table 4.

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