The Challenge of the Overactive Bladder: From Laboratory to New Drugs

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1. Introduction

Overactive bladder (OAB) is a complex clinical syndrome that the International Continence Society (ICS) defines as characterised by urgency (sudden, compelling desire to pass urine, which is difficult to defer), urinary incontinence (involuntary urine leakage with or without urgency), frequency, and nocturia (waking to void more than once at night), in absence of genitourinary pathologies or metabolic factors that could explain these symptoms (www.icsoffice.org). OAB may be associated with, but needs to be distinguished from, detrusor overactivity (DO), which refers to an uninhibited, involuntary rise in detrusor pressure during the filling phase of filling cystometry during urodynamic assessment in a conscious cooperative patient.

European and North American surveys reported that OAB is found in about 16% of the general population aged 40 yr and over; one third of patients with a clinical diagnosis of OAB present urgency urinary incontinence [1]. Interestingly, OAB rates are...
similar in men and women. In a cross-sectional population-based survey of adults (>18 yr old), Irving et al reported a 12.2% total prevalence of OAB in four European countries and confirmed that it is common in men and women of all adult age groups [2].

Because OAB-related symptoms are extremely distressing and have a significant negative impact on quality of life and health care costs, treatment and management remain the main challenges for health care professionals [3]. At present, the primary pharmacologic treatment for OAB uses antimuscarinic agents; objective clinical data, systematic reviews, and adjusted indirect comparisons confer a high level of evidence and strong recommendations [4].

Attention should focus on the natural history of OAB, choice of appropriate study design, trial duration, restricted population, economic issues, unrealistic patient expectations, high placebo response rates, and diverse methods of outcome assessment in different trials. Currently there is no consensus on how long patients should be treated, whether treatment should be continuous, intermittent, or on demand, and why only relatively few patients remain on medication for >4–6 mo [5]. Many urologists are systematically searching for appropriate answers to these open questions and looking for more efficacious alternatives to antimuscarinic agents.

This paper discusses the pharmacologic rationale underlying the development of new compounds, provides an update of progress in the search for new therapies for OAB, and tracks their translation into clinical practice.

2. Pathophysiology of the micturition reflex

The lower urinary tract (LUT) serves two main functions: (1) urine storage without leakage (storage phase) and (2) release of urine (voiding phase). These two functions depend on central, peripheral autonomic, and somatic neuronal pathways and local peripheral factors.

During the storage phase afferent impulses, which reach the central nervous system (CNS) from the bladder, send information to the pons. In the pontine tegmentum in animals, positron emission tomography (PET) studies visualised a medial region (M-region), corresponding to Barrington’s nucleus or pontine micturition center, which is involved in micturition reflex coordination, and a lateral region (L-region), which suppresses bladder contractions and improves external sphincter muscle activity during the storage phase [6]. PET and functional magnetic resonance imaging (fMRI) recently detected several suprapontine centers that modulate the micturition reflex in humans [7]. These areas are under the chemical control of different ligands (neurotransmitters) and receptors (Table 1).

The micturition reflex involves the parasympathetic, sympathetic, and somatic peripheral neuronal systems. The parasympathetic system, originating in the spinal cord sacral area (S2–4) controls bladder contractions. It provides an excitatory input to the bladder through post-ganglion nerve terminal release of acetylcholine (ACh), which excites muscarinic receptors (M2, M3) in the detrusor smooth muscle and leads to contraction. The sympathetic system originating in the thoracolumbar cord (Th11–L2) is involved in bladder relaxation and urethral closure through, respectively, post-ganglion nerve terminal release of norepinephrine (NE). NE provides

<table>
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<tr>
<th>Table 1 – Central nervous system ligands and receptors involved in the regulation of micturition reflex</th>
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<tr>
<td><strong>Ligands</strong></td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Glycine</td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>Serotonin</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Glutamate</td>
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<tr>
<td>N/OFQ</td>
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AR = adrenoreceptor; GlyR = glycine receptor; HT = hydroxytryptamine; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; N/OFQ = heptadecapeptide nociceptin/orphanin FQ; NOP = N/OFQ peptide receptor.
inhibitory input to the bladder, which excites β3-receptors in the detrusor body and leads to bladder relaxation. NE provides excitatory input to urethral smooth muscle, which excites α1-receptors in the urethra and leads to a rise in urethral closing pressure. The somatic system provides excitatory input to striated urethral muscle. Motor neurons, located along the lateral ventral horn of the sacral spinal cord (Onuf’s nucleus), release ACh, which acts on nicotinic receptors to induce muscle contraction.

Until recently, all these factors—the complex neurology of the voiding reflex, the simple, “easy-to-accept” idea of antagonistic, parasympathetic cholinergic, and sympathetic adrenergic, control of the LUT, the interrelationship between voluntary somatic and involuntary control of micturition reflex—discouraged extensive research into new drugs for the treatment of OAB. However, in the last two decades LUT neuropharmacology has progressed. Immunohistochemical and morphologic studies of the bladder wall showed that many neuronal terminal endings do not correspond to cholinergic and adrenergic innervation [8]. These nonadrenergic, noncholinergic (NANC) nerves are peptide-containing fibres that are thought to be “silent” in normal conditions but that might play a major role in regulating LUT functions in pathologic conditions [9]. In the neurogenic bladder the NANC primary sensory nerves are up-regulated and they play the main role in the regulation of the micturition reflex in these patients [9]. The NANC-muscular junction is not a “fixed synapse junction,” with prejunctional and postjunctional specialisation [10]. Observing the synthesis and release of multiple neurotransmitters such as monoamines, purines, amino acid, peptides, and nitric oxide was another step forward in understanding the micturitional reflex [8]. Further achievements included accepting the principles of cotransmission (axons release more than one transmitter for each action potential) [11], neuromodulation (locally released agents may modulate the amount of neurotransmitters released prejunctionally) [12], and recognition that a subset of sensory nerves, which are selectively sensitive to capsaicin, the pungent ingredient in red chilli, are of primary importance because they have both afferent and efferent functions [13]. New varieties of receptors in neuronal and nonneuronal tissues were identified as being involved in regulating sensory-afferent nerve conduction [14]. Finally, autonomic nervous system plasticity during development, ageing, and chronic inflammation and after trauma (neuroplasticity) was another fundamental factor in the development of new drugs [15].

Data from several laboratories have recently shown the urothelium and some suburothelial cells have several novel properties. The urothelium is involved in sensory mechanisms (ie, the ability to express sensor molecules or to respond to thermal, mechanical, and chemical stimuli), expresses many different receptor families, and can release neurotransmitters on stretch during the filling phase of the micturition reflex (Table 2). Birder and de Groat suggested urothelial cells might be targets for neurotransmitters released from bladder nerves or that chemicals released by urothelial cells could alter afferent nerve excitability [16]. Finally, some authors have addressed the presence of interstitial cells of Kajal in the bladder as important components of peripheral modulation of the micturition reflex.

Consequently, OAB may result from increased bladder afferent activity, decreased capacity to handle afferent information, or decreased suprapontine inhibition in the CNS and increased peripheral sensibility to mediating transmitters. The CNS as well as the periphery may be targets for a new class of medications against OAB.

3. **Emerging therapies**

In recent years several clinical trials have reported the relative benefits and weaknesses of new drugs for the treatment of OAB. The potential place of many of these drugs within OAB therapy and the probability of their reaching the market in the near future are addressed in the following sections.

3.1. **Drugs targeting the CNS**

CNS transmitter/receptor systems have been investigated as potential targets of new drugs. Table 1 lists the main ligands and receptors involved in regulating micturition control.

In vitro and in vivo evidence confirmed expression of several adrenoreceptors in the brain and spinal cord. Naftopidil, an α-adrenergic receptor blocker, may inhibit bladder activity in rats by targeting the lumbosacral cord. When associated with tamsulosin in an 8-wk crossover study in 96 patients with benign prostatic hyperplasia (BPH), it seemed to improve storage and voiding symptoms [17]. The antidepressant reboxetine [18], a selective NE reuptake inhibitor (selective NRI), which has minimal affinity for muscarinic ACh receptors and therefore causes less dry mouth, is being tested in a phase 2 trial for mixed urinary incontinence by Pfizer and it might be another alternative agent.
The CNS opioid receptor system is a potential target of pharmacologic research because morphine and analogues have profound inhibitory effects on the micturition reflex. Tramadol, a opioid receptor ligand, which inhibits NE and serotonin reuptake, has promising effects on micturition in preclinical studies [19]. In rats it inhibits cerebral infarction-induced detrusor overactivity and counteracts the excitatory effects of apomorphine in other animals [20].

Evidence from laboratory studies on the potential of drugs acting on the serotonin receptor system is controversial. In humans, exposure to selective serotonin reuptake inhibitors (SSRIs) is associated with increased risk of urinary incontinence especially in elderly users of sertraline [21]. Fluoxetine, a widely prescribed SSRI for depression, seems to inhibit detrusor activity. Capeserod hydrochloride, a 5-hydroxytryptamine 4 (5-HT4) receptor agonist, which has been tested as treatment for Alzheimer’s disease, is under investigation by Sanofi-Aventis as therapy for urgency urinary incontinence in humans. To date, no convincing evidence exists to show SSRIs are effective in the treatment of OAB.

Duloxetine, a serotonin-NRI, which is approved by the European Medicine Evaluation Authority (EMEA) for the treatment of female stress urinary incontinence (SUI), was tested in a randomised controlled trial in 306 women with symptoms of OAB. Patients randomised to duloxetine had significant decreases in voiding frequency and incontinence episodes and improvements in incontinence quality-of-life scores compared with patients receiving placebo. The most common adverse events (nausea, dry mouth, dizziness, constipation, insomnia, and fatigue) were the same as those reported by women with SUI and were significantly more common with duloxetine than placebo [22].

Several studies have focused on γ-aminobutyric acid (GABA) and its receptors, mainly in the CNS, as specific targets to inhibit micturition. Baclofen, a GABA agonist, which is used orally and intrathecally to treat spasticity and DO in humans, attenuates oxyhaemoglobin-induced DO, suggesting the inhibitory actions of GABA_B receptor agonists in the spinal cord. It may help control micturitional disorders caused by C-fibre activation in the urothelium or suburothelium [23]. However, even if its effect on the LUT has been demonstrated some decades ago, this has not been successful enough to introduce it into the treatment of OAB. Experimental studies demonstrated that exogenous GABA has an inhibitory effect on micturition. In preclinical studies tigabine, a GABA reuptake inhibitor, blocked the micturition reflex and could be used in refractory DO in humans [24].

Finally, some pilot studies have proposed anticonvulsants such, as gabapentin and retigabine for the treatments of OAB. Kim et al found gabapentin

### Table 2 – Ligands and receptors in bladder urothelium

<table>
<thead>
<tr>
<th>Ligands released by the urothelium</th>
<th>Receptors expressed in the urothelium</th>
<th>Functions</th>
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<tbody>
<tr>
<td>ATP</td>
<td>P2X, P2Y</td>
<td>Autocrine/paracrine signalling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activation primary afferents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regulation micturition reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nociceptive transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activation/inhibition micturition reflex</td>
</tr>
<tr>
<td>NO</td>
<td>M₂-M₅ (muscarinic receptors)</td>
<td>Release of ATP</td>
</tr>
<tr>
<td>ACh</td>
<td>ARs (α, β)</td>
<td>Activation micturition reflex</td>
</tr>
<tr>
<td>Catecholamine (norepinephrine)</td>
<td>ARs (α, β)</td>
<td>Release of ATP and NO</td>
</tr>
<tr>
<td>NGF</td>
<td>P75, TrK-A</td>
<td>Regulation of sensory functions</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>B₁ and B₂</td>
<td>Paracrine signalling</td>
</tr>
<tr>
<td>H⁺ (heat/vanilloids)</td>
<td>TRPV1</td>
<td>Development of sympathetic and sensory nerves</td>
</tr>
<tr>
<td>Antiproliferative factor</td>
<td></td>
<td>Cell growth</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td>Nociception/inflammation</td>
</tr>
<tr>
<td>Prostanoids</td>
<td></td>
<td>Modulation of micturition reflex</td>
</tr>
<tr>
<td>Anandamide (?)</td>
<td>CB₁ and CB₂</td>
<td>(afferent and efferent functions)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nociception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of epithelial proliferation</td>
</tr>
</tbody>
</table>

**Note:** ATP = adenosine triphosphate; NO = nitric oxide; ACh = acetylcholine; AR = adrenoreceptor; NGF = nerve growth factor; TRPV1 = transient receptor potential vanilloid-1.
improved clinical parameters in 14 of 31 patients with refractory OAB [25] and was generally well tolerated. Gabapentin could be considered as an alternative to antimuscarinic agents in selected patients and some evidence has indicated that there may be synergism with oxybutynin.

3.2. Tachykinins

Experimental studies in animals have suggested tachykinins may play a role in the micturition reflex by acting at the level of CNS as well as peripherally [26]. Mammalian tachykinins, such as substance P, neurokinin A (NKA), and NKB, function as sensory neurotransmitters by the activation of specific receptors (NK-1, NK-2). NK-1 receptor antagonists may inhibit sensorial bladder–spinal cord input, thus increasing the threshold for initiating micturition and increasing bladder capacity without blocking the voiding phase. In a double-blind, randomised, placebo-controlled, parallel group pilot study, postmenopausal women with a history of urge urinary incontinence were assigned to receive a 160 mg capsule of aprepitant, an NK-1 receptor antagonist, or placebo once daily for 8 wk [27]. At 8 wk aprepitant significantly decreased the average daily micturitions and episodes of urgency. The average daily episodes of urgency urinary incontinence and total urinary incontinence were also reduced, although not significantly. Aprepitant was generally well tolerated and adverse experiences were generally mild. Although this study by Green et al seems to demonstrate the potential efficacy of an NK-1 receptor antagonist in the management of OAB, results need to be confirmed in powered follow-up studies. New NK-1 antagonists such as casopitant, Sanofi-Aventis SSR 240600, and tanabe TA-5538 are under clinical investigation (phase 2) and preliminary results are expected by the end of 2007 or early in 2008.

3.3. Vanilloid agents

As a potential alternative to current drug therapies, urologists are placing their trust in afferent blockade by targeting afferent nerves that control the micturition reflex because preventing the micturition reflex that initiates OAB seems more desirable than inhibiting detrusor smooth muscle contractions. Modulation of the afferent arm of the micturition reflex emerged from studies on the effect of capsaicin on sensory nerves. Capsaicin targets the transient receptor potential vanilloid-1 (TRPV1), which is expressed on small-to-medium-sized afferent neurons (C-type and, partially, A-δ type). Acute exposure to capsaicin depolarises and excites the sensory fibres expressing TRPV1 receptors. Because excitation is followed by a refractory period, repeated, long-term, high-dose exposure to capsaicin desensitises, defunctionalises, and ultimately damages peripheral terminals, which become unresponsive. In other words, capsaicin exerts long-lasting reversible suppression of sensory nerve activity, which is dependent on dose, exposure time, and interval between instillations. Intravesical instillation of repeated low doses of capsaicin [28] showed inhibitory modulation of urinary bladder afferent nerves and had therapeutic benefit in OAB. At the turn of the century, several independent and sponsored trials were started using resiniferatoxin (RTX), the ultrapotent capsaicin analogue, to treat LUT disorders. The clinical trials were discontinued because a study about the effects of intravesical RTX for the treatment of incontinent patients failed to show a significant improvement of symptoms when data were compared with placebo and because there were problems with the agent sticking to plastic when being given, so variable amounts were administered, negating the accuracy of the studies. Recent papers on the role of TRPV1 in the LUT reported the benefits of intravesical vanilloid instillation as treatment for the painful bladder syndrome and neurogenic and nonneurogenic OAB [29–31]. In an interesting study 54 patients with DO refractory to anticholinergics were randomly treated with 4 weekly intravesical instillations of 10 nM RTX [32] or vehicle. Three months after the treatment cycle, a significantly higher percentage of patients receiving RTX had excellent and improved results; treatment remained effective at 6 mo in 50% of patients. The authors concluded that multiple intravesical instillations of 10 nM RTX improved incontinence in patients with OAB. Interest in these drugs was rekindled, but to date no natural or synthetic TRPV1 agonist/antagonists are available on the market.

3.4. β3-agonists

Two β3-agonists have been under clinical investigation: GlaxoSmithKline solabegron (GW427353) and Astellas YM178. GlaxoSmithKline tested the safety and efficacy of 125 mg and 50 mg solabegron administered twice daily against placebo in reducing OAB symptoms in women. In North America and Europe, Astellas will develop a phase 2 study for YM178, a β3-agonist with activity against OD in rats [33]. The compound had relaxant effects on rat and human bladder strips. An in vivo study demonstrated it
decreased the frequency of rhythmic bladder contractions induced by intravesical filling with saline.

3.5. Nociceptin/orphanin FQ–NOP receptor system

About 10 yr ago, naturally occurring heptadecapeptide nociceptin/orphanin FQ (N/OFQ) was identified as the endogenous ligand of a previously orphan G protein-coupled receptor now named N/OFQ peptide (NOP) receptor. At peripheral levels N/OFQ exerts potent inhibitory effects on primary afferent bladder fibres.

A preliminary report and a subsequent randomised, placebo-controlled, double-blinded study demonstrated that intravesical instillation of 1 μM N/OFQ solution produces an acute inhibitory effect on the micturition reflex in humans. In patients with neurogenic DO, Lazzeri et al observed daily intravesical instillation of 1 mg N/OFQ (but not placebo) is associated throughout the 10-d instillation period with less frequent incontinence episodes, increased bladder capacity, and improved urodynamic parameters [34]. Malagutti et al performed the neurophysiologic assessment of the nociceptive flexion reflex (NFR-RIII) in four healthy subjects and in five patients with LUT symptoms (LUTS) to investigate the N/OFQ neuronal site and functional mechanism of action. N/OFQ seems to selectively inhibit vesical sensory innervation in patients with LUTS [35] as it exerts a tonic inhibitory modulation of the nociceptive reflex, which is mediated by descending pathways. In healthy subjects N/OFQ modulation of the nociceptive reflex is not functionally active. These findings seem to provide evidence that N/OFQ and C-fibres are involved in the pathophysiology of LUTS and make them attractive targets for new therapies.

3.6. Botulinum toxin

Botulinum toxin (BTX) is a complex protein produced by the anaerobic bacterium Clostridium botulinum and was originally known only to cause serious, often fatal paralysis after ingestion in contaminated food. The BTX-linked neuromuscular blocking effect is thought to alleviate muscle spasm due to excessive neural activity of central origin. Local BTX injections are effective in the treatment of muscular disorders and unlicensed BTX has been used to treat LUTS.

BTX is thought to cleave SNAP-25, a synapse-associated protein, thereby blocking presynaptic ACh release at the neuromuscular junction. This leads to temporary chemical denervation and muscle relaxation. In animal models, BTX inhibits abnormal urethral release of adenosine triphosphate (ATP) and calcitonin gene-related peptide (CGRP), reduces capsaicin-evoked detrusor contractions, and inhibits mucosal release of CGRP. Parasympathetic transmission inhibition is not the only mechanism of action of BTX. It also inhibits substance P release and induces a blockade of mechanisms involved in TRPV1 axonal expression. Apostolidis et al investigated the effect of BTX therapy on human bladder afferent pathways and found a progressive decrease in suburothelial fibres expressing P2X3 and TRPV1, which correlated with clinical improvement but no change in urethelial sensory-receptor immunoreactivity [36].

Clinical results have shown BTX is remarkably efficacious in neurogenic DO and OAB [37,38] when given as a single injection dose of 100–300 U Botox® and of 500–1000 U Dysport® (toxin equivalence is 1 U Botox to 3.5–5 U Dysport) in an injection volume ranging from 0.1 to 0.5 ml/injection site. BTX injection is usually performed using 20–40 evenly distributed intramural injection sites, sparing the trigone. However, two recent studies reported successful outcomes using a Botox injection with trigone inclusion. Most studies used 300 U Botox, with isolated studies reporting the effects of 100, 150, or 200 U. Despite similar outcomes the optimal dose has not yet been defined. The clinical benefit of BTX injection seem to last for a mean of 6–9 mo, apparently independently of population and dose. Side-effects have been rare to date. Botox injections were repeated at different intervals of time in almost all studies and efficacy was reported to continue in the majority of patients undergoing repeated injections.

Haematuria and pain are the most frequent symptoms soon after injection. Systemic symptoms such as respiratory muscle weakness, extremity weakness, and hyposthenia have occasionally been reported, but disappear within 4–5 wk. Urinary retention is a main concern when BTX is given to patients with OAB because several authors reported different percentages of urinary retention over different periods of time. Although many studies were small, overwhelming evidence supports the efficacy, safety, and tolerability of BTX, specifically serotype A, in the management OAB. At present BTX is being tested in phase 3 trials in North America and in phase 2 studies in Europe.

3.7. Others

Chapple et al recently reported the first randomised, double-blind, placebo-controlled phase 2 clinical
study administering ZD0947, a potassium channel opener, to patients with OAB [39]. After 12 wk of treatment with 25 mg/d ZD0947 did not emerge as better than placebo in changing frequency and incontinence episodes even though it was generally safe and well tolerated.

Although past clinical studies showed nonsteroid anti-inflammatory drugs (NSAIDs) have potential benefits in treating urinary symptoms associated with OAB, prolonged use is limited by undesired gastrointestinal and cardiovascular effects. NSAIDs inhibit synthesis of prostaglandin/prostaglandin E2, reduce peripheral sensory fibre afferent activation, and decrease glutamate release, thereby reducing afferent signal transmission to the spinal cord and excitability of neurons involved in the micturition reflex. Chemically modified NSAIDs with enhanced safety for gastrointestinal and cardiovascular effects or combining NSAIDs with other compounds for the treatment of OAB will be under clinical study in the coming year.

4. Conclusion

Several implications should be considered when translating basic science into clinical practice. One is creation of potentially unrealistic expectations in patients and clinicians, of the likely benefits of new treatments. The clinical researcher should try to estimate the probability, on average, of a proposed new treatment for OAB being better than antimuscarinic agents. Unfortunately, antimuscarinics remain the only “on-label” medication on the market, and no significant comparison study with new drugs is available even though several have been tested as alternatives for OAB in the past few years. Most urologists have been optimistic about their efficacy and safety but need to be aware that optimism is usually both unwarranted and counterproductive when uncertainty about the long-term effects of treatments can only be resolved in post-marketing phase 4 surveys.

Conflicts of interest

The authors have nothing to disclose.

Acknowledgement

We thank Geraldine Boyd, at the University of Perugia (Italy), who performed the English revision of the manuscript.

References


B. The recognition of capacity of autonomic nervous system to change during development, ageing, and chronic inflammation and after trauma.
C. The recognition of synthesis and release of a multiplicity of neurotransmitters such as monoamines, purines, amino acid, peptides, and nitric oxide.
D. The interrelationship between the voluntary somatic control of micturition reflex and the involuntary components.

4. Desensitisation, which is a mechanism of action of vanilloid agents, results in:
A. Activation of a G-coupled receptor and block of second messenger chain reaction.
B. A long-lasting reversible suppression of sensory nerve activity.
C. A nonreversible block all the primary sensory nerves of the bladder.
D. A long-lasting reversible suppression of parasympathetic activity.

5. Aprepitant, a neurokinin 1 receptor antagonist:
A. Decreases the average daily number of micturitions compared with placebo at 8 wk as well as the average daily number of urgency.
B. Increases the average daily number of micturitions compared with placebo at 8 wk as well as the average daily number of urgency.
C. Increases the daily number of urge urinary incontinence and total urinary incontinence episodes.
D. Improves the cystometric bladder capacity at urodynamic assessment.

6. The mechanism of action of botulinum toxin consists of:
A. Blocking the presynaptic release of acetylcholine at the neuromuscular junction.
B. Inhibiting the abnormal urothelial release of neurotransmitters.
C. Inhibiting the primary afferents nerves of the bladder.
D. All the previous answers.