Current Pharmacologic Treatment of Lower Urinary Tract Symptoms

13

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Introduction

The function of the lower urinary tract (LUT)—to store and release urine—is dependent on the co-ordinated activity of smooth and striated muscles in the bladder, urethra, and pelvic floor. These structures form a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors [24, 52, 203, 277; see 46]. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of voiding/emptying. Failure to store urine may lead to various forms of incontinence (mainly urgency and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence. A disturbed filling/storage function can, at least theoretically, be improved by agents decreasing detrusor activity, increasing bladder capacity, and/or increasing outlet resistance [810].

Many drugs have been tried, but the results are often disappointing, partly due to poor treatment efficacy and/or side effects. The development of pharmacologic treatment of the different forms of urinary incontinence has been slow, but several promising targets and drug principles have been identified [31, 34, 67, 133, 181].

This chapter is an update of the report from Committee 8 of the fifth International Consultation on Incontinence held in Paris, February, 2012 [40].

Pathogenesis of Bladder Control Disorders

Bladder control disorders can be divided into two general categories: disorders of filling/storage and disorders of voiding [810]. Storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence. Failure to store also occurs if the bladder is overactive, as in the overactive bladder syndrome (OABs). The prevalence varies with the criteria used for diagnosis, but according to Irwin et al. [392], using the International Continence Society (ICS) definition of 2002 [4], the overall prevalence of the OABs, based on computer-assisted telephone interviews (the EPIC study) was 11.8 %; rates were similar in men and women and increased with age [392]. A similar study based on a cross Canada telephone survey found the prevalence of OABs to be 13 % in men and 14.7 % in women [355]. In a Finnish study, taking into account bother, the prevalence of *clinically meaningful OABs*, was much lower than reported in these studies [786].

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OABs (symptomatic diagnosis) is often assumed to be caused by detrusor overactivity (DO; urodynamic diagnosis), even if this does not always seem to be the case [19, 220, 344, 382]. Only 1/3 of patients with OABs are incontinent, suggesting that the bladder may not necessarily be the source of the dysfunction, but that the problem in OABs with or without incontinence is at the level of the central nervous system (CNS), and that possible treatments for these conditions should target the micturition pathways at that level [369].

OABs/DO is multifactorial and can occur as a result of sensitization of afferent nerve terminals in the bladder or outlet region, changes of the bladder smooth muscle secondary to, e.g., denervation, or consequent upon damage to the (CNS) inhibitory pathways, as can be seen in various neurological disorders, such as multiple sclerosis, cerebrovascular disease, Parkinson's disease, brain tumors, and spinal cord injury (SCI) [48, 76, 606, 811].

Bladder Contraction

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle [32, 52]. Atropine resistance, i.e., contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species, but seems to be of little importance in normal human bladder muscle [24, 79]. However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused mainly by adenosine triphosphate (ATP) [24, 52, 79, 440, 595]. A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders and has been reported to occur in hypertrophic bladders [703], interstitial cystitis [609], neurogenic bladders [802], in the aging bladder [834], and in females with overactive bladder [595]. The importance of the NANC component to detrusor contraction in vivo, normally, and in different micturition disorders, remains to be established [30].

Drugs Used for Treatment of Overactive Bladder Symptoms/ Detrusor Overactivity

It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence, and an abundance of drugs has been used for treatment (Table 13.1). Helfand and coworkers showed that in a cohort of 7,244,501 patients over 45 years with an OABs diagnosis, 24.4 % of these were treated mainly with antimuscarinic agents; 75.6 % went untreated. Only 25.6 % of those treated were men [348]. Drugs may be efficacious in some patients, but they do have side effects, and frequently are not continued indefinitely. Hence, it would be worth considering them as an adjunct to conservative therapy.

Specific aspects of drug treatment of LUTS in the elderly can be found elsewhere [40].

Antimuscarinic (Anticholinergic) Drugs

Mechanism of Action

Antimuscarinics block, more or less selectively, muscarinic receptors irrespective of location [2, 33] (Fig. 13.1). The common view is that in OABs/DO, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by ACh, released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity, and during this phase, there is normally no parasympathetic input to the LUT [2, 33]. Furthermore, antimuscarinics are usually competitive antagonists. This implies that when there is a massive release of ACh, as during micturition, the effects of the drugs should be decreased, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinics can produce urinary retention in humans, but in the dose range used for beneficial effects in OABs/DO (Fig. 13.2),

Table 13.1 Drugs used in the treatment of LUTS/OABs/DO

	Level of evidence	Grade of recommendation
Antimuscarinic drugs		
Atropine, hyoscyamine	3	C
Darifenacin	1	A
Fesoterodine	1	A
Imidafenacin	1	B
Propantheline	2	B
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D
Drugs acting on membrane channels		
Calcium antagonists	2	D
K-Channel openers	2	D
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
Alpha-AR antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Silodosin	3	C
Naftopidil	3	C
Beta-AR antagonists		
Terbutaline (beta 2)	3	C
Salbutamol (beta 2)	3	C
Mirabegron (beta 3)	1	B
PDE-5 inhibitors[a]		
(Sildenafil, Taladafil, Vardenafil)	1	B
COX-inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)[b]	1	A
Botulinum toxin (idiopathic)[b]	1	B
Capsaicin (neurogenic)[c]	2	C
Resiniferatoxin (neurogenic)[c]	2	C
Other drugs		
Baclofen[d]	3	C
Hormones		
Estrogen	2	C
Desmopressin[e]	1	A

Assessments according to the Oxford system (modified)
[a]Male LUTS/OABs
[b]Bladder wall
[c]Intravesical
[d]Intrathecal
[e]Nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!

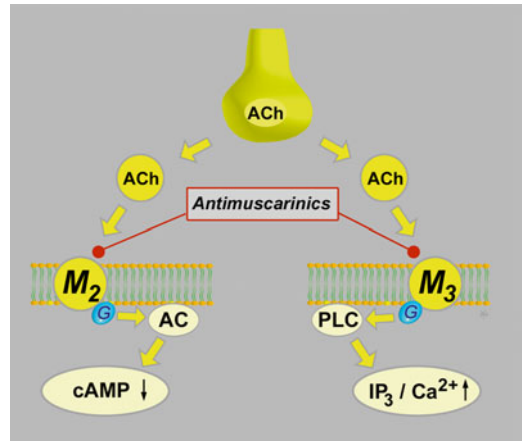

Fig. 13.1 Acetylcholine (ACh) activates all types of muscarinic receptor. The two types of muscarinic receptors dominating in the bladder contribute to bladder contraction in different ways: M3 (contraction) and M2 (inhibition of relaxation). Both subtypes of receptor are blocked by antimuscarinics

there is little evidence for a significant reduction of the voiding contraction [271]. However, there is good experimental evidence that the drugs act during the storage phase by decreasing the activity in afferent nerves (both C- and Aδ-fibers) from the bladder [206, 387] (Fig. 13.3).

Muscarinic receptors are found on bladder urothelial cells where their density can be even higher than in detrusor muscle. The role of the urothelium in bladder activation has attracted much interest [90, 91], but whether the muscarinic receptors on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues [836, 838, 839] found that there is

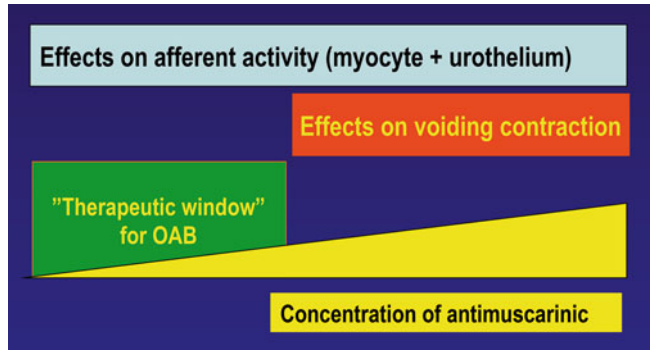

Fig. 13.2 Rationale for use of antimuscarinics for treatment of OABs/DO. Blockade of muscarinic receptors at both detrusor and nondetrusor sites may prevent OAB symptoms and DO without depressing the contraction during voiding. The "Therapeutic window for OAB" can be obtained in most patients with recommended doses of antimuscarinics

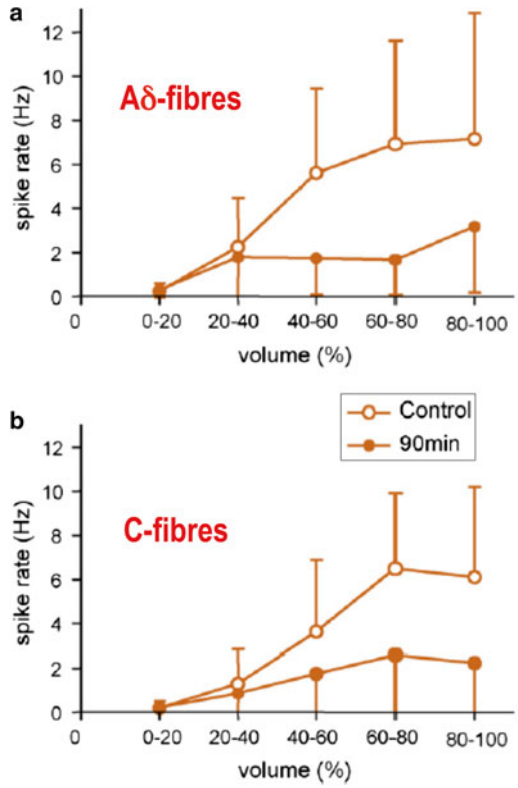

Fig. 13.3 Influence of darifenacin on volume-related nerve activity in A**δ** afferents (**a**) and C afferents (**b**) in the rat pelvic nerve. From Iijima et al. Eur Urol. 2007 Sep;52(3):842

basal ACh release in human bladder. This release was resistant to tetrodotoxin and much diminished when the urothelium/suburothelium was removed; thus, the released ACh was probably of non-neuronal origin and, at least partly, generated by the urothelium. There is also indirect clinical evidence for release of ACh during bladder filling. Smith and coworkers [706] found that in patients with recent spinal-cord injury, inhibition of ACh breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch et al. [840] inhibited ACh breakdown with edrophonium in a series of patients with disturbed voiding or urinary incontinence. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly decreased detrusor compliance in 78 % of the patients with the symptom pattern of overactive bladder, but in no patients without specific complaints suggesting DO. Thus, during the storage phase, ACh and ATP may be released from both neuronal and non-neuronal sources (e.g., the urothelium/suburothelium) and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor (Fig. 13.4). These mechanisms may be important in the pathophysiology of OABs/DO and represent possible targets for antimuscarinic drugs.

Pharmacologic Properties

Generally, antimuscarinics can be divided into tertiary and quaternary amines [2, 334]. They differ

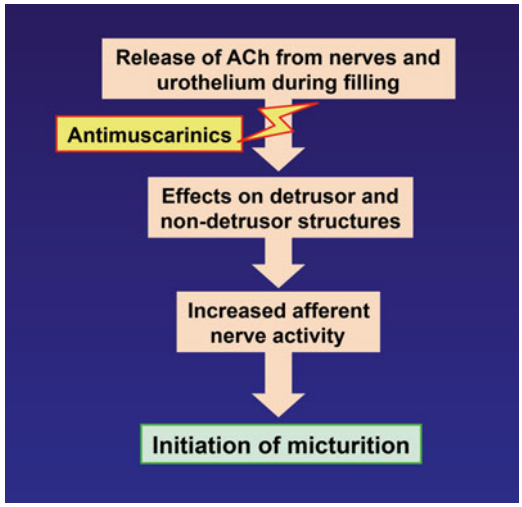

Fig. 13.4 During filling it can be assumed that acetylcholine is released from nerves and urothelium, an effect enhanced in OABs/DO. This release is reduced by antimuscarinics

with regard to lipophilicity, molecular charge, and even molecular size, tertiary compounds generally having higher lipophilicity and molecular charge than quaternary agents. Atropine, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl-tolterodine), oxybutynin, propiverine, solifenacin, and tolterodine are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the CNS, dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood brain barrier, but in some cases, such as darifenacin, that is compensated by active transport out of the CNS by the product of the MDR1 gene [112]. Quaternary ammonium compounds, like propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects [114, 142, 334, 796]. They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, increases in heart rate, and dryness of mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites [334]. The most commonly involved P450 enzymes are CYP2D6 and CYP3A4. The metabolic conversion creates a risk for drug–drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration/effect of the antimuscarinic and/or interacting drug. Antimuscarinics secreted by the renal tubules (e.g., trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism. Some antimuscarinics and their active metabolites are excreted in urine in amounts that may affect the mucosal muscarinic receptors from the luminal side. This has not yet been demonstrated to imply superior clinical efficacy [42].

Antimuscarinics are still the most widely used treatment for urgency and urgency incontinence [29, 39]. However, currently used drugs lack selectivity for the bladder, and effects on other organ systems (Fig. 13.5) may result in side effects, which limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained, if the subtype(s) mediating bladder contraction, and those producing the main side effects of antimuscarinic drugs, were different. Unfortunately, this does not seem to be the case. One way of avoiding many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical only in a limited number of patients.

Individual data on most of the antimuscarinic drugs currently used clinically are given in the "Appendix."

Clinical Use of Antimuscarinics

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned [352]. However, large meta-analyses of studies performed with the currently most widely used drugs [152–154, 161, 162, 594] clearly show that antimuscarinics are of significant clinical benefit. It was recommended that since the pharmacological profiles of each drug (see "Appendix") and dosages differ, these factors should be considered in making treatment choices.

The durability of the effects of antimuscarinics is not known and the relapse rate of symptoms after discontinuation of treatment has not been

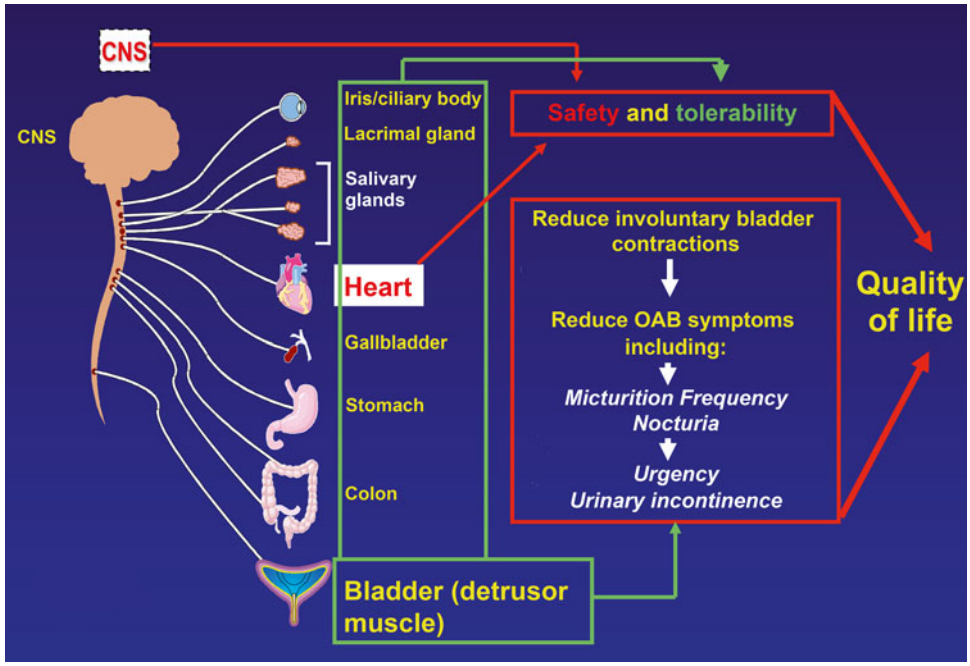

Fig. 13.5 Important sites of action of antimuscarinics. During bladder filling, there is normally no parasympathetic nervous outflow to the bladder and no release of acetylcholine (ACh). The sympathetic nervous system is active and releases noradrenaline (NA) that via β_3 adrenoceptors stimulates adenylyl cyclase (AC) and generation of cyclic AMP (cAMP) which mediates relaxation of the bladder. In addition, β_3-adrenoceptor stimulation activates K^+ channels, stimulating outflow of K^+, which causes hyperpolarization and inhibition of Ca^{2+} inflow

systematically studies. In 173 women with OAB symptoms for >6 months, Lee et al. [480] studied in a prospective, randomized, open-label, trial what happened 3 months after the patients had been successfully treated for 1, 3, or 6-months. The relapse rate was 62 %, and the request for treatment was 65 %, indirectly suggesting an efficacy of treatment.

None of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine, or trospium) is ideal as a first-line treatment for all OABs/DO patients. Optimal treatment should be individualized, implying that the patient's comorbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration [153, 162].

To compare the effects of different antimuscarinic drugs for OAB symptoms, Madhuvrata et al. [508] analyzed 86 trials, 70 with parallel and 16 with cross-over designs (31,249 adults), drawing attention to the significance of the adverse effect of dry mouth. They concluded that when the prescribing choice is between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. Also extended release (ER) preparations of oxybutynin or tolterodine might be preferred to immediate release preparations because there is less risk of dry mouth. Comparing solifenacin and immediate release tolterodine, solifenacin might be preferred for better efficacy and less risk of dry mouth. Fesoterodine might be preferred over ER tolterodine for superior efficacy, but has higher risk of withdrawal due to adverse events in general, but in particular a higher risk of dry mouth.

Several studies have documented that the persistence with prescribed antimuscarinic therapy for overactive bladder is low [78, 436, 684, 795]. The most common causes seem to be lack of efficacy and adverse effects. However, there is

some evidence suggesting that the tolerability of the different antimuscarinics may differ. Wagg et al. [795] analyzed prescription data for patients receiving antimuscarinics for treatment of the OAB syndrome over a 12-month period. At 12 months, they found that the proportions of patients still on their original treatment were: solifenacin 35 %, tolterodine ER 28 %, propiverine 27 %, oxybutynin ER 26 %, trospium 26 %, tolterodine IR 24 %, oxybutynin IR 22 %, darifenacin 17 %, and flavoxate 14 %. The longest mean persistence was reported for solifenacin (187 vs. 77–157 days for the other treatments). Gomes et al. [317] compared the persistence of oxybutynin or tolterodine therapy among older patients who were newly prescribed one of these drugs. This was a retrospective cohort study of Ontarians aged 66 years and older. Persistence with treatment was defined on the basis of refills for the drug within a grace period equal to 50 % of the prescription duration. The authors identified 31,996 patients newly treated with oxybutynin and 24,855 newly treated with tolterodine. After 2 years of follow-up, persistence on oxybutynin (9.4 %) was significantly lower than that on tolterodine (13.6 %, $p<0.0001$). The median time to discontinuation of oxybutynin and tolterodine was 68 and 128 days, respectively. Kessler et al. [443] analyzed 69 trials enrolling 26,229 patients with OABs with the aim to compare adverse events of antimuscarinics using a network meta-analytic approach that overcomes shortcomings of conventional analyses. They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride, but not for oxybutynin orally administered when currently used starting dosages were compared. They concluded that most currently used antimuscarinics seem to be equivalent first choice drugs to start the treatment of OABs, except for oral oxybutynin dosages of ≥10 mg/day, which may have more unfavorable adverse event profiles.

Even if the use of antimuscarinics is associated with many adverse effects, they are generally considered to be "safe" drugs. However, among the more serious concerns related to their use is the risk of cardiac adverse effects, particularly QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes), and increases in heart rate (HR) [37, 47, 649]. QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart. However, the experiences with terodiline, an antimuscarinic drug that caused torsade de pointes in patients [185, 723], have placed the whole drug class under scrutiny.

The parasympathetic actions on the heart oppose the excitatory actions of the sympathetic nervous system and slow the heart rate. An elevated resting HR has been linked to overall increased morbidity and mortality, particularly in patients with cardiovascular diseases. The prevalence of CV comorbidities was found to be significantly higher in patients with than without OABs [50]. Since mean changes in HR reported in population studies might not be applicable to an individual patient, and particularly in patients at risk of cardiac disease, even moderate increases in HR might be harmful. The potential of the different antimuscarinic agents to increase HR and/or prolong the QT time has not been extensively explored for all agents in clinical use. Differences between drugs cannot be excluded, but risk assessments based on available evidence are not possible.

Drugs Acting on Membrane Channels

Calcium Antagonists

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and thereby contribute to the regulation of smooth muscle tone [86]. Two major groups of calcium channels include the voltage-gated [131] and the store-operated channels [488]. While both can contribute to the maintenance of smooth tone in general, store-operated calcium channels apparently contribute only to a limited if any extent to the regulation of bladder smooth muscle tone [675, 676]. On the other hand, various types

of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle including Q-type [286] and L-type channels [819]. The latter appears to be of particular importance as inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in vitro with tissue from multiple mammalian species, including humans [281]. However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species [819]. In confirmation of the role of L-type calcium channels, it has been shown that knock-out mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility [806].

While these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical installation of the calcium channel inhibitor verapamil, the muscarinic receptor antagonists oxybutynin and trospium, and placebo to patients with urgency or urgency incontinence. While the two muscarinic receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function [288]. In a clinical study of limited size the calcium channel inhibitor nimodipine (30 mg/day) did not significantly improve the number of incontinence episodes as compared to placebo [573]. It should be noted that despite a long-standing and widespread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro and the lack of clinical data are not fully clear, but it may relate to pharmacokinetic properties of the currently used drugs which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction (Table 13.1).

Potassium Channel Openers

In a similar fashion to calcium channels, potassium channels also contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. Numerous types of potassium channels exist in the bladder [336, 620]. With regard to bladder function, ATP-dependent (K_{ATP}) and big calcium-activated (BK_{Ca}) channels have been studied most intensively. The BK_{Ca} channels also appear to be important physiologically as their activation can cause hyperpolarization of bladder smooth muscle cells and by this mechanism they can contribute to the relaxation of bladder smooth muscle by, e.g., β-adrenoceptor agonists [281]. Openers of both K_{ATP} [373, 375, 525] and BK_{Ca} channels [375, 691] have been shown to induce bladder smooth muscle relaxation in various mammalian species, but the density of some types of potassium channels may differ markedly between species. Some potassium channel openers have also been shown to suppress non-voiding detrusor contractions in vivo in animal models of DO [373, 525, 752] and this also includes activators of the KCNQ type of potassium channels [729]. Although potassium channel openers are believed to mainly act directly on smooth muscle cells [318, 620], they may also at least in part affect bladder function by modulating the activity of afferent neurons [752].

While the above data demonstrate the potential of potassium channel openers to inhibit non-voiding detrusor contractions, these channels are expressed not only in bladder, but also, e.g., in vascular smooth muscle. Therefore, potassium channel openers may also affect cardiovascular function, and in effective doses may considerably lower blood pressure [373, 693]. While some compounds of this class have a certain degree of selectivity for the bladder as compared to the cardiovascular system, it remains unclear whether the degree of selectivity offers a sufficiently large therapeutic window for clinical use. This consideration has led to a considerable hesitancy to study potassium channel openers in OABs patients. Nevertheless, one randomized, placebo-controlled clinical study on the K_{ATP} opener ZD0947 has been reported [159]. While

ZD0947 at the chosen dose did not lower blood pressure or cause adverse events typical for a vasodilating drug, it also failed to achieve superiority relative to placebo for the treatment of OAB symptoms. Therefore, despite promising preclinical efficacy data, potassium channel openers at present are not a therapeutic option and may never become one due to a lack of selectivity for bladder over cardiovascular tissues (Table 13.1).

Another way to use potassium channels to normalize bladder function was suggested by Christ et al. [169] in a rat model of detrusor hyperactivity. They injected "naked" hSlo/pcDNA3 (maxiK channel) into the bladder and found a significant amelioration of the hyperactivity. As to whether this principle can be therapeutically useful in man is currently under investigation.

α-Adrenoceptor (AR) Antagonists

It is well documented that α_1-AR antagonists can ameliorate lower urinary tract symptoms (LUTS) in men [28, 486, 543, 597]. Currently used α_1-AR antagonists are considered effective for treatment of both storage and voiding symptoms in men with LUTS associated with or suggestive of benign prostatic hyperplasia (BPH) [486]. However, in a study where tamsulosin was given alone, or together with tolterodine, to patients with male LUTS and OAB symptoms, monotherapy with the drug was not effective [424]. Doxazosin monotherapy resulted in only minimal effects in International Prostate Symptom Score (IPSS) storage subscore, urgency episodes, and no improvement in the patient perception of bladder condition [480]. Thus, there is no convincing evidence that α-AR antagonists, given as monotherapy, are effective in patients with storage symptoms only.

A pivotal question is if better efficacy and/or tolerability can be obtained by highly subtype selective drugs than with the commonly used alternatives. α_1-ARs include three receptor subtypes, α_{1A}, α_{1B}, and α_{1D}, which are structurally and pharmacologically distinct and have different tissue distributions [43]. α_{1A}-ARs are the predominant subtype in the human prostate, where they mediate smooth muscle contraction. A fourth subtype, α_{1L}, also present in human prostate, is derived from the same gene as α_{1A}, but α_{1L}- and α_{1A}-receptors have different pharmacologic properties and bind some α-AR antagonists with different affinities. The precise structural relationship between the two subtypes remains to be elucidated. Selectivity for α_{1B}-AR has been considered disadvantageous from a cardiovascular point of view [682, 683]. Kojima et al. [461] studied the expression of α_1-AR in the transitional zone of prostates from 55 patients with BPH, comparing patients treated with tamsulosin presumed to block α_{1A}-ARs and naftopidil presumed to block α_{1D}-ARs. However, the selectivity of naftopidil for α_{1D}- vs. α_{1A}-ARs is modest [744] and its use as a tool to separate between α_1-AR subtypes is questionable. Nevertheless, the tamsulosin and naftopidil groups were classified as α_{1A}-AR dominant (22 and 12 patients) and α_{1D}-AR dominant (11 and 16, respectively). The efficacy of tamsulosin and naftopidil differed depending on the dominant expression of the α_1-AR subtype in the prostate. Tamsulosin was more effective in patients with dominant expression of the α_{1A}-AR subtype, whereas naftopidil was more effective in those with dominant expression of the α_{1D}-AR subtype. In another study, the same group assessed whether there was a direct correlation between the prostatic expression of α_1-AR subtype mRNA and severity of LUTS or bladder outlet obstruction [460]. They found no direct correlation between the expression of α_1-AR subtype mRNA in the prostate and severity of LUTS or BOO, although there was a significant regression of this expression with patient age. Kojima et al. [460] concluded that the expression level of α_1-AR subtype mRNA in the prostate could be a predictor of the efficacy of subtype selective α_1-AR antagonists in patients with BPH and suggested that genetic differences were responsible for the diverse responses to the drugs.

Silodosin (KD-3213), which has a high selectivity for α_{1A}-ARs [485, 753, 754, 837], had clinically good effects on both voiding and storage symptoms in men with BPH [156, 431, 522, 523, 564, 835, 837]. Chapple et al. [156] conducted a multicenter double-blind, placebo-, and active-controlled

parallel group study comparing silodosin, tamsulosin, and placebo. A total of 1,228 men ≥50 year of age with an IPSS ≥13 and a urine maximum flow rate (Q_{max}) >4 and ≤15 mL/s were selected at 72 sites in 11 European countries. The patients were entered into a 2-week wash-out and a 4-week placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg ($n=381$), tamsulosin 0.4 mg ($n=384$), or placebo ($n=190$) once daily for 12 week. Its overall efficacy was not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo. There was no significant difference between the two α_1-AR antagonists and the placebo in terms of Q_{max}. There was also no difference between the two α-AR antagonists for the QoL parameter, whereas both were better than the placebo. Active treatments were well tolerated, and discontinuation rates due to adverse events were low in all groups (2.1 %, 1.0 %, and 1.6 % with silodosin, tamsulosin, and placebo, respectively). The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14 %), a reversible effect as a consequence of the potent and selective α_{1A}-AR antagonism of the drug. The incidence was higher than that observed with tamsulosin (2 %); however, only 1.3 % of silodosin-treated patients discontinued treatment due to this adverse event. Silodosin treatment improved DO and obstruction grade by decreasing detrusor opening pressure, detrusor pressure at Q_{max}, bladder outlet obstruction index, and Schafer's obstruction class significantly [825]. In a different open, non-blinded prospective study silodosin 8 mg led to a significant increase in bladder capacity at first desire to void with no significant change in maximum cystometric capacity. In the voiding phase mean detrusor pressure at maximum flow significantly decreased, mean bladder outlet obstruction index decreased significantly, and obstruction grade as assessed by the Schaefer nomogram improved significantly [531].

It thus seems that selective blockade of α_{1A}-ARs is a clinically effective approach, and silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in male patients with LUTS, even if treatment is associated with a high incidence of ejaculatory dysfunction.

Interest has also been focused on the α_1-ARs (α_{1D}), specifically in the bladder [682, 683], assuming that these receptors were responsible for storage symptoms. However, the interrelationship between the α_{1D}-ARs in the human detrusor smooth muscle and the pathophysiology of LUTS is unclear. Naftopidil was shown to significantly improve the OAB symptom score [666] and urgency episodes [830]. Ikemoto et al. [389] gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the I-PSS for storage symptoms, tamsulosin monotherapy decreased the I-PSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α_1-AR subtypes between the drugs) could not be reproduced in a randomized head to head comparison between the drugs [319]. Based on available evidence, it therefore cannot be concluded that the α_{1D}-ARs on the detrusor smooth muscle are the main therapeutic target. However, α_{1D}-ARs may have effects on different locations in the bladder beside the detrusor smooth muscle: the detrusor vasculature, the urothelium, and the afferent and efferent nerve terminals and intramural ganglia [43]. The importance and functional role of this observation remain to be established.

In females, treatment with OABs, α_1-AR antagonists seems to be ineffective. In an RCT, comprising 364 women with OABs, no effect of tamsulosin vs. placebo could be demonstrated [640]. On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were treated (with modest success) with an α_1-AR antagonist [444, 500]. It should be remembered that in women, these drugs may produce stress incontinence [249].

In patients with neurogenic DO, treatment with a_1-AR antagonists was moderately successful [1].

β-Adrenoceptor Agonists

Background

The three cloned subtypes of β-ARs (β_1, β_2, and β_3) have been identified in the detrusor of most species, including humans [36, 550]. Also the

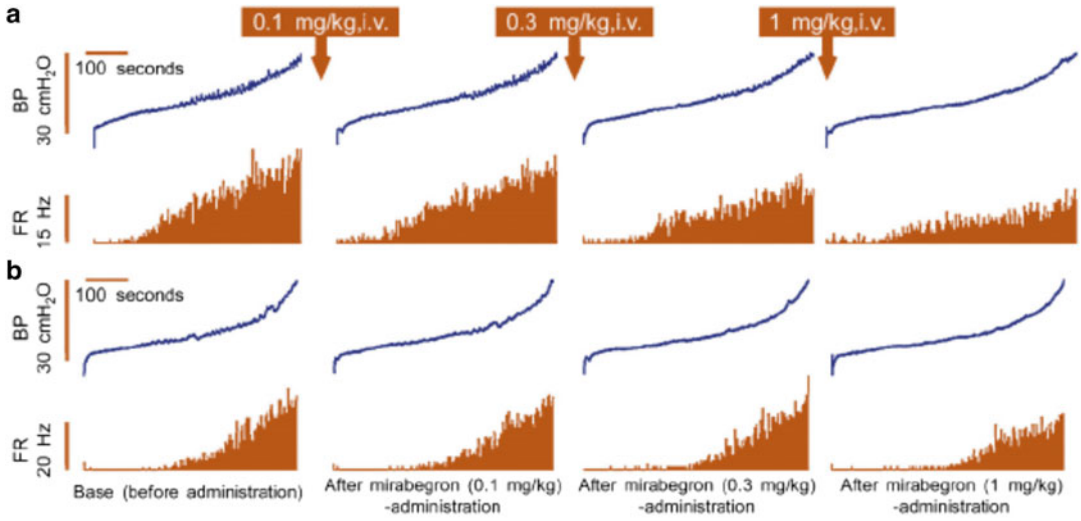

Fig. 13.6 Stimulation by highly selective β_3-adrenoceptor agonists like mirabegron inhibits afferent activity from the bladder

human urothelium contains all three receptor subtypes [605]. Studies, using real-time RT-PCR, have revealed a predominant expression of β_3-AR mRNA in human detrusor muscle [383, 550, 591] and the functional evidence for an important role in both normal and neurogenic bladders is convincing [88, 290, 383, 385, 386, 484, 550, 566, 745]. The human detrusor also contains β_2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in this structure [36, 383, 550].

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder K+ channels, particularly BK_{Ca} channels, may be more important in β-AR-mediated relaxation than cAMP [280, 281, 376, 774]. Aizawa et al. [11] showed that the β_3-AR agonist, mirabegron, could inhibit filling-induced activity in both mechanosensitive Aδ-and C-fiber primary bladder afferents of the rat bladder (Fig. 13.6).

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated [569, 605]. However, to what extent a urothelial signaling pathway contributes in vitro and in vivo to the relaxant effects of β-AR agonists in general, and β_3-AR agonists specifically, remains to be elucidated.

The in vivo effects of β_3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β_3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [290, 383, 412, 743, 746, 818]. For example, Hicks et al. [360] studied the effects of the selective β_3-AR agonist, GW427353, in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid-evoked bladder hyperactivity, without affecting voiding.

Clinical Use

The selective β_3-AR agonist, mirabegron, has been approved for treatment of OABs in Japan (Betanis®), USA (Myrbetriq®), and Europe (Betmiga®), and its properties and clinical effects have been extensively reviewed [45, 658]. There are proof of concept studies for other β_3-AR selective agonists such as solabegron and ritobegron [384, 600]. However, the development of ritobegron has been ceased since it failed to reach the primary efficacy endpoint in phase III studies. Other agents, e.g., TRK-380 [420], are in preclinical development for the treatment of the OAB syndrome.

Mirabegron

Pharmacokinetics. Mirabegron is rapidly absorbed after oral administration. It circulates in the plasma as the unchanged form, its glucuronic acid conjugates and other metabolites, the metabolites being inactive [747]. Of the administered dose, 55 % is excreted in urine, mainly as the unchanged form, and 34 % is recovered in feces, almost entirely as the unchanged form. Mirabegron is highly lipophilic and is metabolized in the liver via multiple pathways, mainly by cytochrome P450 3A4 and 2D6 (CYP3A4; CYP2D6) [748, 749, 779]. It may therefore be subject to clinically relevant drug–drug interactions and should therefore be used with caution in patients who are taking ketoconozole or other potent CYP3A4 inhibitors.

T_{max} in both extensive and poor metabolizers was about 2 h and the terminal elimination half-life ($t_{1/2}$) approximately 23–25 h [256, 464].

Efficacy. Several Phase II randomized controlled clinical trials (RCTs) have shown that in OABs patients mirabegron consistently improved mean number of micturitions in 24 h and number of continence episodes in 24 h [145, 149]. Mirabegron was further evaluated in three pivotal Phase III, 12-week RCTs in patients with OAB symptoms of urgency urinary incontinence, urgency, and urinary frequency [353, 446, 584]. These trials had basically similar design. Entry criteria required that patients had symptoms of overactive bladder for at least 3 months duration, at least 8 micturitions/day, and at least 3 episodes of urgency with or without incontinence over a 3-day period. The majority of patients were Caucasian (94 %) and female (72 %) with a mean age of 59 years (range 18–95 years).

In the study of Nitti et al. [584], 1,329 patients were randomized to receive placebo, or mirabegron 50 or 100 mg once daily for 12 weeks. Co-primary endpoints were change from baseline to final visit (study end) in the mean number of incontinence episodes/24 h and micturitions/24 h. At the final visit, mirabegron 50 and 100 mg showed statistically significant improvements in the co-primary efficacy endpoints and mean volume voided/micturition compared with placebo.

Khullar et al. [446] performed a similarly designed study enrolling 1,978 patients. The study included a fourth arm in which tolterodine SR 4 mg was used as a comparator. Like the study of Nitti et al. [584], it was found that mirabegron caused a statistically significant improvement from baseline compared with placebo in the number of urgency incontinence episodes and number of micturitions per 24 h. Mirabegron 50 and 100 mg was statistically superior to placebo, whereas tolterodine was not, in these two key OAB symptoms, but the study was not powered for head-to-head evaluation.

In a third phase 3 study where Herschorn et al. [353] evaluated the effects of 25 and 50 mg mirabegron, both doses were associated with significant improvements in efficacy measures of incontinence episodes and micturition frequency.

Nitti et al. [587] reported on the effects of mirabegron on maximum urinary flow rate and detrusor pressure at maximum flow rate in a urodynamic safety study on male patients with bladder outlet obstruction (BOO) and LUTS. Two hundred men with OAB symptoms and a BOO index of >20 were randomized to receive placebo, mirabegron 50 mg, or mirabegron 100 once daily for 12 weeks. Mirabegron did not adversely affect flow rate, detrusor pressure at maximum flow rate, or bladder contractile index and was well-tolerated.

Chapple et al. [151] compared the safety and efficacy of long-term administration of mirabegron 50 and 100 mg and tolterodine in a 12-month study 3-armed, parallel group study (no placebo arm). A total of 812 (50 mg) and 820 (100 mg) patients were randomized to receive mirabegron, and 812 patients received tolterodine ER 4 mg. The primary variable was incidence and severity of treatment-emergent adverse, and secondary variables were change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms. Both mirabegron and tolterodine improved key OAB symptoms from the first measured time point of 4 week, and efficacy was maintained throughout the 12-month treatment period.

Tolerability and adverse effects. In a proof of concept study of mirabegron 100 and 150 mg

BID [145], adverse events were experienced by 45.2 % of the patients—the incidence was similar among those treated with placebo (43.2 %) and mirabegron (43.8–47.9 %). The most commonly reported adverse events considered treatment-related was gastrointestinal disorders, including constipation, dry mouth, dyspepsia, and nausea. There was no patient-reported acute retention. No significant difference in ECG parameters between the groups was demonstrated. However, a small but significant increase in mean pulse rate was observed after mirabegron 100 and 150 mg (1.6 and 4.1 beats per minute (bpm), respectively), although this was not associated with an increase in cardiovascular adverse events in this study. The overall discontinuation rate owing to adverse events was 3.2 % (placebo 3.0 % vs. mirabegron 2.4–5.3 %).

In the study of Khullar et al. [446] the incidence of adverse effects was similar across the placebo and mirabegron 50 and 100 mg groups (50.1 %, 51.6 % and 46.9 %, respectively). The most common (≥3 %) adverse effects in any treatment group were hypertension (6.6 %, 6.1 % and 4.9 %, respectively), urinary tract infection (1.8, 2.7 and 3.7 %), headache (2.0, 3.2 and 3.0 %), and nasopharyngitis (2.9, 3.4 and 2.5 %). The incidence of dry mouth was similar in the placebo and mirabegron groups (2.6 % vs. 2.8 %), and lower than observed in patients receiving tolterodine SR (10.1 %). The incidence of constipation was similar in all treatment groups (placebo 1.4 %, mirabegron 1.6 %), including tolterodine (2.0 %).

In the 12-months safety and efficacy study of mirabegron referred to previously [151], the incidence and severity of treatment-emergent and serious adverse effects (primary outcome parameters) were similar across the mirabegron 50 mg (59.7 %), mirabegron 100 mg (61.3 %), and tolterodine SR 4 mg (62.6 %) groups. The most frequent treatment-emergent adverse effects were hypertension, dry mouth, constipation, and headache, which occurred at a similar incidence across all treatment groups, while the incidence of dry mouth was more than threefold lower compared with the tolterodine SR 4 mg group [151].

One concern with the use of β_3-AR agonists has been the possibility of negative cardiovascular effects. In healthy subjects, mirabegron (50–300 mg/day for 10 days) increased *blood pressure* dose-dependently [556]. However, in the studies on OABs patients the mean increase (compared to placebo) in systolic/diastolic blood pressure after therapeutic doses of mirabegron once daily was approximately 0.5–1 mmHg and reversible upon discontinuation of treatment.

In a study on healthy volunteers, mirabegron increased *heart rate* in a dose-dependent manner. Maximum mean increases in heart rate from baseline for the 50, 100, and 200 mg dose groups compared to placebo were 6.7, 11, and 17 bpm, respectively in healthy volunteers [556]. However, in the clinical efficacy and safety studies, the change from baseline in mean pulse rate for mirabegron 50 mg was approximately 1 bpm and reversible upon discontinuation of treatment.

The cardiac safety of mirabegron was evaluated in a thorough QT/QTc (heart rate (HR)-corrected QT interval) study, including supratherapeutic dose. This was a randomized, placebo, and active-controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study [516] and the design followed the recommendations of The International Conference on Harmonisation (ICH). Equal numbers of male and females were enrolled in each treatment group, and the pharmacokinetic and pharmacodynamic analyses comprised 333 and 317 subjects, respectively. The effect of multiple doses of mirabegron 50, 100, and 200 mg once daily on QTc interval was studied, and according to ICH E14 criteria, mirabegron did not cause QTcI prolongation at the 50-mg therapeutic and 100-mg supratherapeutic doses in either sex. Mirabegron prolonged QTcI interval at the 200-mg supratherapeutic dose (upper one-sided 95 % CI > 10 ms) in females, but not in males.

Even if the cardiovascular effects of mirabegron observed in clinical studies have been minimal and clinically not relevant, effects on heart rate and blood pressure need to be monitored when the drug is generally prescribed and patients with cardiovascular morbidities are treated.

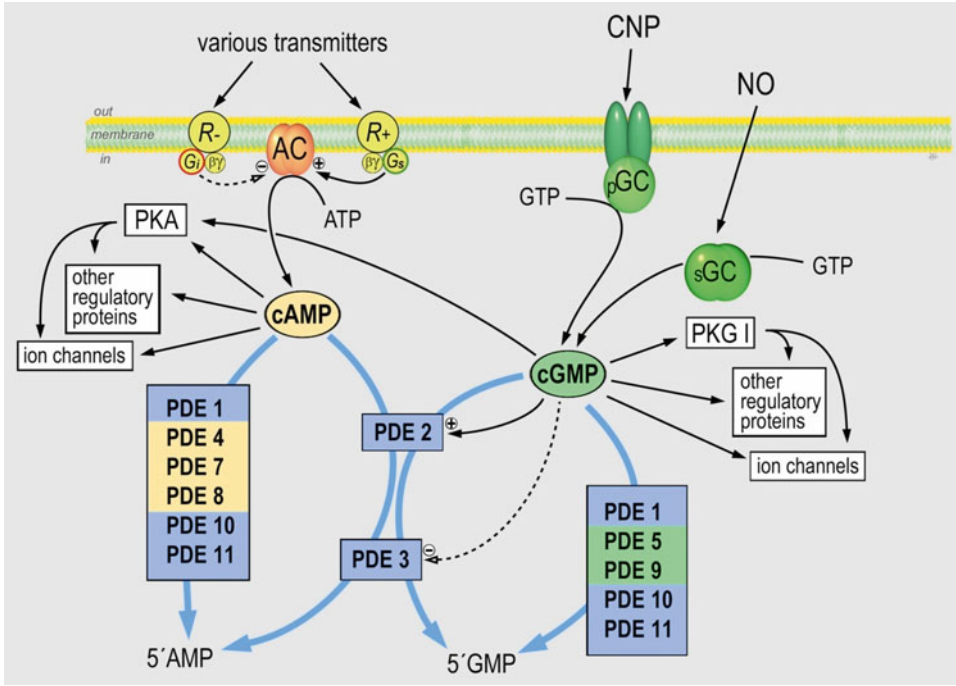

Fig. 13.7 Families of phosphodiesterases (PDE). Inhibitors of both cyclic AMP and cyclic GMP may have inhibitory effects on bladder contraction. However, so far only inhibitors of PDE5 (inhibiting degradation of cyclic GMP) have been clinically useful for treatment of lower urinary symptoms in males

Phosphodiesterase Inhibitors

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [25, 49, 52, 309]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [36]. Use of phosphodiesterase (PDE) inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach [41, 51]. There are presently 11 families of PDEs, some of which preferentially hydrolyze either cAMP or cGMP [775] (Fig. 13.7).

As a basis for PDE inhibitor treatment of LUTS, Uckert et al. [775] investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. In vitro, human detrusor muscle responded poorly to sodium nitroprusside, and to agents acting via the cGMP system [768]. However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone [769]. Significant dose-dependent relaxations were also induced by human cAMP analogs [769]. With these studies as a background, Truss et al. presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders, and not responding to standard antimuscarinic therapy [768]. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OABs. However, the results of a larger RCT in patients with DO showed that vinpocetine only showed statistically significant results for one parameter [769]. Studies with other PDE 1 inhibitors than vinpocetin

(which may not be an optimal drug for elucidation of the principle) do not seem to have been performed.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the in vitro contractile response of guinea pig [495] and rat [413] bladder strips and also suppressed rhythmic bladder contractions of the isolated guinea pig and rat bladder [306, 307, 582]. Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose-limiting effect [304]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

Oger and coworkers showed that PDE5-inhibitor sildenafil-induced relaxation of human detrusor smooth muscle involved cGMP-, cAMP-, and K(+) channel-dependent signaling pathways, with a minor contribution from NO [599]. In combination with the α_1-AR antagonist, doxazosin, sildenafil reduced adrenergic tone of prostatic and cavernosal smooth muscle and their combination provided a significant benefit when targeting relaxation of both tissues [598].

In vivo, several studies have indicated a role for PDE5-inhibitors in the regulation of micturition function. Systemic vardenafil reduced both non-voiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, SCI rats, indicating potential mechanisms by which PDE5-Is improve storage symptoms in SCI patients [83]. The effect of vardenafil on OAB symptoms could be related to a cGMP-dependent RhoA/ROCK signaling inhibition, as shown in spontaneously hypertensive rats (SHR) [559, 560]. Using the same animal model, bladder hypoxia was significantly reduced by acute vardenafil treatment [560]. Thus, besides relaxing muscular wall, PDE5 inhibition may positively affect urinary bladder blood perfusion. In the same respect, tadalafil was shown to increase prostate tissue oxygenation in SHR and human vesicular-deferential artery is characterized by a high expression and activity of PDE5, which was inhibited by tadalafil in vitro; these results suggest another possible mechanism through which PDE5i exert beneficial effects on LUT symptoms [561].

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [36]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita et al. [565] examined the effects of isoproterenol, prostaglandin E_1 and E_2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström et al. [814] characterized the distribution of PDE 5, cGMP, and PKG1 in female pig and human urethra and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil, and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations. Fibbi et al. [269] confirmed that the highest expression and biological activity of PDE5 was found in the bladder. However, a consistent PDE5 expression and activity was also found in prostatic urethra. In contrast, the prostate gland showed the lowest PDE5 abundance and cultures derived from this tissue were less sensitive to vardenafil. Using a different animal model associated with C-fiber afferent activation, it was shown that the NO/cGMP signaling pathway is involved in the regulation of the micturition reflex, with an action that seems more predominant on the sensory rather on the motor component of the micturition reflex [128].

The observation that patients treated for erectile dysfunction with PDE5 inhibitors had an improvement of their LUTS has sparked a new interest in

using these drugs also for treatment of LUTS and OABs. After the report in an open study that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS [664], this observation has been confirmed in several well-designed and conducted RCTs.

To date, several RCTs have been published comparing the effect of PDE5 inhibitors alone to placebo and the combination of α_1-AR antagonists and PDE5 inhibitors vs. α_1-AR antagonists alone [80, 293, 422, 489, 542, 544, 623, 624, 644, 645, 724, 750, 772]. In these studies, different PDE5 inhibitors and different doses were administered.

PDE5-inhibitors significantly improve IPSS and IIEF scores, but not Q_{max} when compared to placebo. According to a recent meta-analysis by Gacci and coworkers, differences in IPSS score were significantly lower in older and obese patients [293]. The combination of PDE5-inhibitors and alpha-blockers led to significant improvements of the IPSS and IIEF score as well as Q_{max} when compared to the use of alpha-blockers alone. Dmochowski showed that tadalafil once daily for LUTS had no significant effect on bladder function as measured by detrusor pressure at maximum urinary flow rate or such as maximum detrusor pressure and bladder outlet obstruction index while improving IPSS [233]. PDE5-inhibitors were generally shown to be safe and well-tolerated.

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OABs and their site(s) of action largely remains to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In none of the trials referred to such an effect was found. However, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstitial cells, and suburothelial afferent nerves). In general, it is believed that major mechanisms contributing to LUTS include reduced NO/cGMP signaling pathway, increased RhoA kinase pathway activity, autonomic overactivity, increased bladder afferent activity, and pelvic ischemia [41].

It has to be mentioned that only tadalafil has been recently approved for the treatment of LUTS due to benign prostatic obstruction (BPO); long-term experience with PDE5 inhibitors in patients with LUTS is still lacking [597]. In addition, insufficient information is available on the combination of PDE5 inhibitors with other LUTS medications such as 5-α-reductase-inhibitors.

Antidepressants

Several antidepressants have been reported to have beneficial effects in patients with DO [496, 526]. The use of antidepressants was shown to be an independent risk factor for LUTS suggestive of BPH in a community-based population of healthy aging men (Krimpen Study: [462]).

Imipramine

Imipramine is the only drug that has been widely used clinically to treat this disorder. Imipramine has complex pharmacological effects, including marked systemic antimuscarinic actions [74] and blockade of the reuptake of serotonin and noradrenaline [509], but its mode of action in DO has not been established [379]. Even if it is generally considered that imipramine is a useful drug in the treatment of DO, no good quality RCTs that can document this have been retrieved. It has been known for a long time that imipramine can have favorable effects in the treatment of nocturnal enuresis in children with a success rate of 10–70 % in controlled trials [311, 379]. It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine [89, 303]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [74]. The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have been performed during the last decade [379, 575]. No good

quality RCTs have documented that the drug is effective in the treatment DO. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

A prospective (no controls) study, the impact of the "three-drug therapy" (antimuscarinic, alpha-blocker and tricyclic antidepressants) on the treatment of refractory detrusor overactivity (DO), showed a significant increase on bladder capacity and decreases on urgency, urge-incontinence, and frequency. Objective urodynamic data as well as symptom score improved significantly with triple therapy [575].

Selective serotonin-reuptake-inhibitors (SSRIs) have been tested with regard to their effects on OAB symptoms. Milnacipran hydrochloride, a serotonin-norepinephrine reuptake inhibitor (SNRI), or paroxetine hydrochloride, a SSRI, were analyzed in a prospective open trial in neurogenic OABs patients. Milnacipran reduced daytime urinary frequency, improved the quality of life index, and increased bladder capacity as shown in urodynamic studies. No such changes were noted in the other categories of the LUTS questionnaire or urodynamic studies, or in the paroxetine group [667].

Duloxetine

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [429, 757]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [279]. In a placebo-controlled study, the drug showed efficacy in patients with OABs [722]. The number of micturition episodes, the primary outcome, was reduced by 2 in the duloxetine arm and by 0.5 in the placebo arm. Episodes of urgency incontinence were also significantly reduced by duloxetine. These data have not been reproduced so far in another trial. However, the high withdrawal rate observed across all studies in which the drug was evaluated for SUI, affecting 20–40 % of the patients at short-term and up to 90 % in long-term studies, do not predict clinical utility of duloxetine in OABs.

Cyclooxygenase Inhibitors

Prostanoids (prostaglandins and thromboxanes) are synthesized by cyclooxygenase (COX) from a common precursor, arachidonic acid. Prostanoids may be involved in the control of bladder function under normal and pathological conditions, including DO and OABs. Human bladder mucosa has the ability to synthesize eicosanoids [400], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [243, 487]. Even if prostaglandins cause contraction of human bladder muscle, it is still unclear whether prostaglandins contribute to the pathogenesis of involuntary detrusor contractions. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Cardozo et al. [127] performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg three times daily. The drug was shown to have favorable effects, although it did not completely abolish DO. There was a high incidence of side effects (43 %) including nausea, vomiting, headache, and gastrointestinal symptoms. Palmer [610] studied the effects of flurbiprofen 50 mg×4 vs. placebo in a double-blind, cross-over trial in 37 patients with idiopathic DO (27 % of the patients did not complete the trial). Active treatment significantly increased maximum contractile pressure, decreased the number of voids, and decreased the number of urgent voids compared to baseline. Indomethacin

50–100 mg daily was reported to give symptomatic relief in patients with DO, compared with bromocriptine in a randomized, single-blind, cross-over study [126]. The incidence of side effects was high, occurring in 19 of 32 patients.

Although these early clinical studies with nonselective COX inhibitors showed some promise in the treatment of these disorders, the drugs were not further developed for this indication mainly due to side effects. The interest in the use of selective COX-2 inhibitors was hampered by concerns about long-term cardiovascular toxicity with these drugs.

Toxins

Intravesical pharmacological therapy for LUTS stems from the fact that circumventing systemic administration of active compounds offers two potential advantages. First, high concentrations of pharmacological agents can be given to the bladder tissue producing enhanced local effects. Second, drugs inappropriate for systemic administration due to off-target effects can be safely used. Attractive as it may be, intravesical pharmacological therapy should still be considered as a second line treatment in patients refractory to oral therapy or who do not tolerate its systemic side effects. However, this statement is based on the assumption that intervention therapy should follow oral medication. Research aiming at defining if patients' subgroups will benefit of intravesical therapy as first line is clearly necessary. Visco et al [792] performed a double-blind, double placebo-controlled, randomized trial comparing oral anticholinergic therapy and onabotulinumtoxinA by injection and found a similar reduction in the frequency of daily episodes of urgency incontinence. Patients treated with the toxin were less likely to have dry mouth, but had a higher rate of urinary retention and urinary tract infection.

Botulinum Toxin

Mechanism of Action

Botulinum toxin (BonT) is a neurotoxin produced by *Clostridium botulinum*. Of the seven subtypes of BoNT, sub-type A (BoNT-A) has the longest duration of action, making it the most relevant clinically. BoNT/A is available in three different commercial forms, with the proprietary names of Botox®, Dysport®, Xeomin®, and Prosigne. Although the toxin is the same, it is wrapped by different proteins which modify the relative potency of each brand. This was the basis for the introduction of the non-proprietary names onabotulinum toxin A (onabotA), abobotulinum toxin A (abobotA), and incobotulinum toxin A (incobotA) for Botox®, Dysport®, and Xeomin®, respectively. Prosigne is the proprietary name of a BoNT/A produced in China, which currently does not have a known non-proprietary name. Although potency of each one is usually expressed in units (U), the doses are not interchangeable. Clinical dose conversion studies for the LUT do not exist. Available information indicates that onabotA is roughly three times more potent than abobotA and equivalent to incobotA. Nevertheless, these equivalences should be approached with caution.

Most of the information available about intravesical application of BoNT/A have been derived from the use of onabotA (Botox®). However, in addition to sub-type A, some studies have investigated the effect of detrusor injection sub-type B, rimabotulinumtoxinB (proprietary names being Miobloc™ or Neurobloc™ according to countries).

BoNT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 [237] by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles (Fig. 13.8). The two chains are then cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble *N*-ethylmaleimide-sensitive fusion attachment protein receptor) includes synaptosome-associated protein 25 kD (SNAP 25), synaptobrevin (vesicle-associated membrane protein—VAMP), and syntaxin. BonT/A cleaves SNAP 25 rendering the SNARE complex inactive [138, 378]. Subtype B acts preferentially through the inactivation of VAMP [378].

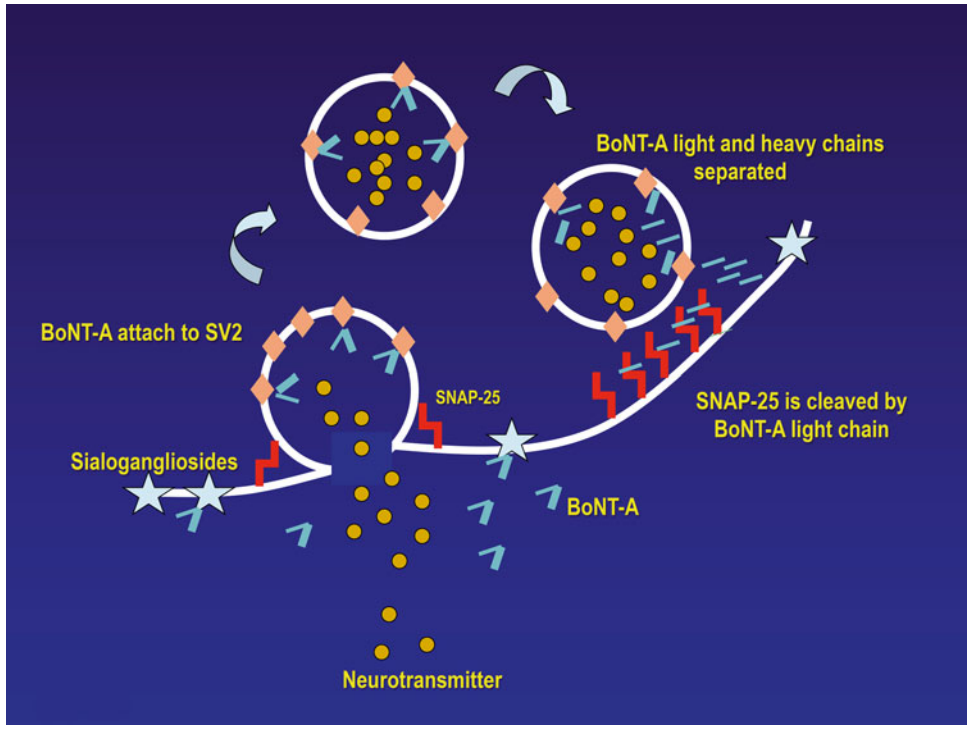

Fig. 13.8 Mechanism of action of botulinum toxin (BoNT). BoNT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles. The two chains are then cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble *N*-ethylmaleimidesensitive fusion attachment protein receptor) include synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle-associated membrane protein—VAMP), and syntaxin

BonT/A application was extensively evaluated in striated muscle. In this tissue paralysis occurs by prevention of ACh release from cholinergic motor nerve endings [378]. Accumulation of neurotransmitter containing synaptic vesicles is followed by terminal axonal degeneration. Striated muscle paralysis recovers within 2–4 months time. During this time axons develop lateral sprouts and eventually regenerate completely [208].

In the human bladder SV2 and SNAP-25 expression has been demonstrated in parasympathetic, sympathetic, and sensory fibers [176–178]. Almost all parasympathetic nerves express the two proteins [177, 178]. As these nerves play a fundamental role for detrusor contraction during voiding, the blockade of ACh release is believed to play an essential role in detrusor hypo- or acontractility that follows BoNT/A injection in the bladder. In accordance with this view, it was shown that in normal or SCI animals BoNTA treatment decreased the bladder contractions evoked by electrical stimulation of spinal nerves without altering intrinsic contractions [388]. However, cholinergic axon sprouting concomitant with clinical remission could not been documented in the detrusor [340].

Bladder sensory impairment is also expected to play an important role in the final effect of BoNT/A bladder injection. BoNT/A inhibits the spinal cord release of glutamate, substance P (SP) and CGRP from sensory nerves [55, 546, 625] as well as the release of neuropeptides at the peripheral extremities [502, 629]. BoNT/A has also been shown to reduce the suburothelium immunoreactivity for TRPV1 or P2X3 [57, 60]. Morenilla-Palao et al. [563] have shown that

BonT/A impedes TRPV1 trafficking from intracellular vesicles to the neuronal membrane, a process that is also dependent on SNARE proteins. All these mechanisms may contribute to the recent observation that BoNT/A reduces afferent firing from bladder afferents and antidromic release of neuropeptides [388]. Although SV2 and SNAP-25 immunoreactivity has not been detected in urothelial cells [178], urothelial function seems also compromised after BoNT/A administration. BonT/A has been shown to inhibit ATP release from urothelium in animal models of SCI [445, 707]. Therefore, it is not surprising that administration of BoNT/A to inflamed rat bladders reduces spinal *c-fos* counts at the L6 and S1 spinal cord segments [788].

Cleaved, inactive SNAP-25 appears rapidly after BoNT/A injection. In the guinea-pig a robust expression of cleaved SNAP 25 could be detected already at 12 h and maximum intensity could be detected at 24 h with little changes afterwards. In guinea-pigs cleaved SNAP-25 expression was restricted to nerve fibers. Almost all parasympathetic fibers, either preganglionic and postganglionic, were affected while less than half of the sensory fibers express the cleaved protein [176, 177]. In the human urinary bladder cleaved SNAP 25 could be detected in NDO patients up to 11 months after BoNT/A injection [681]. The longer duration of cleaved SNAP 25 in the detrusor smooth muscle, longer than in striated muscles, has no firm explanation at the moment. However, the longer persistence of the inactive form of SNAP-25 plus the involvement of pre- and post-ganglionicparasympathetic neurons may contribute to persistence of the BoNT/A effect in the bladder.

Myofibroblasts form a syncytium through extensive coupling via the gap-junction protein connexin 43 and have close contacts with sensory nerves. These facts led to the hypothesis that myofibroblasts act as modulators of bladder behavior [58, 817]. However, the expression of connexin 43 is not altered by BoNT/A [648]. Hence, at the moment a firm evidence for the action of BoNT/A on myofibroblasts is scant.

BonT/A may decrease the levels of neurotrophic agents in the bladder tissue. Levels of nerve growth factor (NGF) [301, 302, 492] and brain-derived neurotrophic factor (BDNF) [621] have been shown to decrease in the bladder and/or urine following BoNT/A injections. As both neurotrophins have paramount roles for growth, maintenance, and plasticity of peptidergic sensory nerves, these findings may point toward another mechanism whereby BonT/A acts upon the bladder.

Clinical Use

Comprehensive reviews of the clinical use of BoNT/A have been produced during the last few years, covering different aspects of this treatment [158, 196, 218, 244, 245, 247, 275, 316, 427, 468–470, 521, 583, 613, 661, 762].

Efficacy. RCTs have documented the clinical effects of onabotulinumtoxinA both in neurogenic and idiopathic DO, where the drug decreases incontinence episodes, frequency, and urgency and improves quality of life [226, 518, 662, 762]. The drug was also shown to be effective in patients with OABs [585]. Successful OABs treatment with BoNT/A does not appear to be related to the existence of DO. No differences in outcomes were found between those with and those without baseline DO [417, 650]. Nitti et al. [585] reported results of the first large ($N=557$) phase 3 placebo-controlled trial of onabotulinumtoxinA in OABs patients. To be included, patients should have ≥3 urgency urinary incontinence (UI) episodes in 3 days and ≥8 micturitions/day. They were randomized 1:1 to receive intradetrusor injection of onabotulinumtoxinA 100 U or placebo (saline). Co-primary endpoints were change from baseline in UI episodes/day and proportion of patients with a positive response on the treatment benefit scale at week 12 post-treatment. Secondary endpoints included other OAB symptoms and health-related quality of life. OnabotulinumtoxinA significantly reduced the daily frequency of UI episodes vs. placebo (−2.65 vs. −0.87; $p<0.001$) and 22.9 % vs. 6.5 % of patients became completely continent. A larger proportion of onabotulinumtoxinA-treated patients than placebo reported a positive response on the TBS (60.8 % vs. 29.2 %;

$p<0.001$). All other OAB symptoms improved vs. placebo ($p \leq 0.05$). OnabotulinumtoxinA improved patients' health-related quality of life across multiple measures ($p<0.001$).

The finding that onabotulinumtoxinA 100 U was consistently effective with a two to fourfold improvement over placebo in all symptoms of OABs is important: an effect of this magnitude vs. placebo does not seem to have been reported previously with antimuscarinics or β_3-AR agonists,

Adverse effects. The most frequent side effects reported after intradetrusor BonT/A injection are bladder pain and urinary infections [214, 427, 471]. Hematuria may also occur, most of the times mild in nature. The most dangerous one, paralysis of the striated musculature due to circulatory leakage of the toxin, has never been reported. Transient muscle weakness was, nevertheless, reported with abobotA application in several studies [12, 214, 822]. Among 199 NDO patients followed during 8 years, 5 developed hypostenia when injected with after abotbotA 1,000 U [214]. In another study with 44 patients, three adults also treated with 1,000 U developed muscular weakness which subsided after 5–7 weeks [12]. No such cases were reported with onabotA [427]. The reason for the lack of transient muscle weakness among BoNT/A-treated patients is unclear, but might be related with the larger size of its molecule which limits diffusion into the blood stream. Caution should be used in selecting high-risk patients for botulism including children, patients with low pulmonary reserve, or patients with myasthenia gravis. Aminoglycosides should be avoided during BoNT-A treatment since they might blockade motor plates and therefore enhance BoNT/A effect.

The most feared complication of BoNT/A application in patients with voluntary voiding is urinary retention and a transient necessity to perform clean intermittent catheterization (CIC). It is, therefore, strongly recommended that in patients with spontaneous voiding BoNT/A administration is preceded by a complete information of this risk. Caregivers should ideally teach CIC to each patient before toxin injection. In the study by Nitti et al. [585], the majority of adverse effects occurred in the first 12 weeks (15.5 % with onabotA vs. 5.9 % with placebo). The most frequently reported adverse effect was uncomplicated urinary tract infection with no upper urinary tract involvement. Other adverse effects were dysuria (12.2 %), bacteriuria (5.0 %), and urinary retention (5.4 %). Post void residual (PVR) urine volume significantly increased with onabotA vs. placebo, with the highest volume at week 2 post-treatment, and 8.7 % of patients had an increase from baseline of ≥200 mL in PVR urine volume at any time following the initial toxin treatment (none with placebo). The proportion of patients who initiated CIC at any time during treatment cycle 1 was 6.1 % vs. none in the placebo group; for over half the patients who initiated CIC (10/17), the duration of CIC was ≤6 weeks. This value is lower than those reported in previous studies on idiopathic DO. In the study of Nitti et al. [585] discontinuation rates due to adverse effects were low in both the onabotulinumtoxinA (1.8 %) and in the placebo (1.4 %) groups.

Capsaicin and Resiniferatoxin

Rationale for Intravesical Vanilloids

The rationale for intravesical vanilloid application in patients with detrusor overactivity (DO) was offered by the demonstration that capsaicin, following bladder C-fiber desensitization, suppresses involuntary detrusor contractions dependent upon a sacral micturition reflex [202]. The C-fiber micturition reflex is usually inactive but it was shown that it is enhanced in patients with chronic spinal-cord lesions above sacral segments [202] in those with chronic bladder outlet obstruction [134] and in those with IDO [696]. In the bladders of NDO patients, the enhancement of the micturition reflex is accompanied by an increase in the number of sub-urothelial C-fibers expressing TRPV1 [101]. Curiously, NDO patients who responded better to intravesical resiniferatoxin (RTX) exhibited a significant decrease in the density of TRPV1 immunoreactive fibers, whereas non-responders experience a non-significant variation [101]. A decrease in TRPV1 expression in urothelial cells

of NDO patients was also demonstrated after intravesical application of RTX [57, 58, 60].

Changes in sub-urothelial C-fiber innervation expressing neuropeptides [705] or TRPV1 [493] were also reported in patients with sensory urgency. In IDO patients, responders to intravesical RTX are closely associated with the overexpression of the receptor in the bladder mucosa [493]. In women with sensory urgency, TRPV1 mRNA expressed in trigonal mucosa was not only increased but also inversely correlated with the bladder volume at first sensation of filling during cystometry, further indicating that TRPV1 play a role in premature bladder sensation [494].

Intravesical Capsaicin

Intravesical capsacin for NDO was studied in six non-controlled [195, 199, 209, 276, 278, 297] and one controlled clinical trial [211]. Capsaicin was dissolved in 30 % alcohol and 100–125 mL (or half of the bladder capacity if lower than that volume) of 1–2 mM solutions were instilled into the bladder and left in contact with the mucosa for 30 min. Best clinical results were found among patients with incomplete spinal cord lesions, in whom clinical improvement could be observed in up to 70–90 % of the patients [195, 209, 276]. In patients with complete spinal cord lesions the success rate was much lower [297].

Only one small randomized controlled study compared capsaicin against 30 % ethanol, the vehicle solution. Ten patients received capsaicin and found a significant regression of the incontinence and urge sensation. In contrast, only 1 among the 10 patients who received ethanol had clinical improvement [211].

The pungency of alcoholic capsaicin solutions has prevented the widespread use of this compound. In particular, the possibility of triggering autonomic dysreflexia with capsaicin, especially in patients with higher spinal cord lesions, has progressively restrained its use. The relevance of capsaicin might, however, be back with a recent observation by de Sèze et al. [210] with a new capsaicin formulation. They conducted a double-blind placebo-controlled study with a glucidic solution of capsaicin in 33 NDO patients. The glucidic-capsaicin-treated group showed improvement both in symptoms and urodynamic parameters above the comparator arm. The global tolerance of this new capsaicin formulation was excellent [210].

RTX in NDO

Resiniferatoxin (RTX) has the advantage over capsaicin in being much less pungent [195]. Intravesical RTX application in NDO patients was evaluated in five small open-label studies [195, 467, 475, 476, 697]. Different RTX concentrations, 10, 50, 100 nM, and 10 μM, were tested. RTX brought a rapid improvement or disappearance of urinary incontinence in up to 80 % of the selected patients and a 30 % decrease in their daily urinary frequency. Furthermore, RTX also increased the volume to first detrusor contraction and maximal cystometric capacity. In general, in patients receiving 50–100 nM RTX the effect was long-lasting, with a duration of more than 6 months being reported. In patients treated with 10 μM doses, transient urinary retention may occur [476].

In a placebo-controlled study, the urodynamic effects of RTX in NDO patients were specifically evaluated. Only in the RTX arm a significant increase in first detrusor contraction and maximal cystometric capacity was found [699]. RTX also caused a significant improvement in urinary frequency and incontinence [699].

RTX, 600 nM was compared against BONT/A (Botox, 300 U) in a study involving 25 patients with NDO due to chronic SCI. Both neurotoxins were capable of significantly reducing the number of daily incontinence episodes and improving maximum bladder capacity, although BONT/A turned out to be more effective.

RTX in IDO

The first study with intravesical RTX in IDO patients was designed as a proof-of-concept study and involved 13 patients. Intravesical RTX 50 nmol/L was associated with an improvement in volume to FDC from 170 ± 109 to 440 ± 153 mL at 30 days, and to 391 ± 165 mL at 90 days. An increase in mean MCC from 291 ± 160 to 472 ± 139 mL at 30 days and to 413 ± 153 mL at

90 days was also observed. These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency [696]. Subsequent small open label studies confirmed these observations using either a single high (50–100 nM) or multiple low (10 nM) dose approaches [221, 467, 469].

The effect of RTX on refractory IDO was evaluated in two randomized clinical trials [472, 635]. Kuo et al. [472] randomized 54 patients to receive 4 weekly instillations of a low concentration RTX solutions (10 nmol/L) or the vehicle solution, 10 % ethanol in saline. Three months after completing the four intravesical treatments, the RTX treated group had 42.3 % and 19.2 % of patients feeling much better or improved, respectively. This was significantly more than in the placebo group, 14.2 % and 7.1 %, respectively. At 6 months treatment remained effective in 50 % patients in the RTX group, but only in 11 % in the placebo group [472]. Such clinical and urodynamic findings could not be reproduced in another study in which patients were randomly assigned to receive a single intravesical dose of 100 mL of either RTX 50 nM or placebo. Patients were followed up only for 4 weeks. During this period a single 50 nM intravesical dose of RTX was not better than placebo for the treatment of women with IDO and urgency incontinence [635].

RTX and Urgency

The involvement of bladder C-fibers in IDO has led some investigators to explore the role of these sensory afferents to the genesis of urgency. In a non-controlled study involving 12 male patients with LUTS associated with BPH, mean IPSS halved following intravesical administration of RTX (50 nmol/L). The decrease in IPSS was largely due to improvements in scores related to urgency, in addition to improvement in nocturia and frequency [222]. In another open-label study 15 patients with intractable urgency and frequency, with or without urgency incontinence or bladder pain/discomfort, and without urodynamic evidence of DO received one single 50 nM RTX solution. A trend towards an improvement of urgency was noticed [58].

In a quasi-randomized study, 23 OABs patients with refractory urgency entered a 30-day run-in period in which medications influencing the bladder function were interrupted. At the end of this period patients filled a 7-day bladder diary. Then, patients were instilled with 100 mL of 10 % ethanol in saline (vehicle solution) and 30 days later a second 7-day diary was collected. Finally, patients were instilled with 100 mL of 50 nM RTX in 10 % ethanol in saline and additional bladder diaries were collected at 1 and 3 months. After vehicle instillation, the mean number of episodes of urgency per week was 56 ± 11. At 1 and 3 months after RTX instillation the number of episodes of urgency decreased to 39 ± 9 ($p = 0.002$) and 37 ± 6 ($p = 0.02$), respectively [698].

Other Drugs

Baclofen

Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex in several points along its central pathway [202, 614]. Experimental data suggest the GABAergic system as an interesting target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin-induced detrusor overactivity, suggesting that the inhibitory actions of GABA (B) receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium [614]. In spinal intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes, whereas intrathecal application of baclofen induced urethral relaxation during isovolumetric bladder contractions [557]. After SCI, Miyazato et al. [557] found signs of hypofunction of the GABAergic system (glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased) and showed that activation of GABA(A) and GABA(B) receptors in the spinal cord inhibited DO as evidenced by a reduction in non-voiding contractions. GABA(B) receptor activation preferentially reduced DO prior to inhibiting

voiding contractions, while GABA(A) receptor activation inhibited DO and voiding contraction at the same concentration.

As a GABA agonist on GABA(B) receptors, *baclofen* was used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood–brain barrier [755]. Baclofen is one of the most effective drugs for the treatment of spasticity following SCI, traumatic or hypoxic brain injury, and cerebral palsy [596], and *intrathecal* baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [110]. Baldo et al. [75] found a rapid (24 h) and persistent increment in the volume to first detrusor contraction and of the maximal cystometric, whereas maximal detrusor pressure decreased. At 10 days the volume to first detrusor contraction had increased from 143 to 486 mL. In selected patients with spasticity and bladder dysfunction, intrathecal baclofen seems to be an effective therapy.

Combinations

α_1-AR Antagonists with Antimuscarinics

Traditionally, male LUTS were thought to result from BPO secondary to benign prostatic enlargement (BPE). However, male LUTS may arise from prostatic pathology, bladder dysfunction, or both. Thus, diagnosis and appropriate treatment of men with OAB symptoms are complex and difficult. α_1-AR antagonists remain the most widely used pharmacologic agents for relief of bladder outflow resistance, as they relax prostatic and urethral smooth muscle tone, the dynamic component of BPO [43, 486]. In contrast, antimuscarinics, which function by competitively blocking the muscarinic receptors, are the first-line pharmacologic treatment for OABs [39]. Given the prevalence of combined voiding and OAB symptoms as well as the finding that the QoL of these patients is affected primarily by the symptoms of OABs, it might be logical for this category of patients to be given antimuscarinic drugs [657].

A variety of such combinations have been evaluated. Several randomized, controlled trials demonstrated that the combination treatment of antimuscarinic drugs and α_1-AR antagonist was more effective at reducing male LUTS than α_1-AR antagonists alone in men with OABs and coexisting BPO [68, 423, 424, 426, 479, 481, 665]. Therapeutic benefit of combining an antimuscarinic agent (propiverine) with α_1-AR antagonists (tamsulosin), as compared to α_1-AR antagonists alone, was reported by Saito and colleagues [665]. The rates of improvement in daytime frequency, incontinence, and urgency were greater in the combination group than the α_1-AR antagonist-alone group. The post-void residual (PVR) was unchanged in both groups, and there was only one case (1.5 %) of acute urinary retention (AUR) with the combined treatment.

Subsequently, Lee et al. [479] compared the efficacy and safety of combination therapy with propiverine and doxazosin in 211 men with urodynamically confirmed bladder outlet obstruction (BOO) and OAB symptoms for 8 weeks. Compared with the doxazosin arm, the patients in the combination therapy group showed greater improvement in urinary frequency, average micturition volume, and storage and urgency scores of IPSS. Patient satisfaction was significantly higher in the combination group. There was also a significant increase in PVR (+20.7 mL) in the combination group, but no case of urinary retention was reported.

A large-scale, multicenter, randomized, double-blind, placebo-controlled trial (the TIMES study) demonstrated the efficacy and safety of tolterodine extended release (ER) alone, tamsulosin alone, and the combination of both in 879 men with OABs and BPO [424]. In the primary efficacy analysis, 172 men (80 %) receiving tolterodine ER plus tamsulosin reported treatment benefits by week 12 ($p<0.001$ vs. placebo; $p=0.001$ vs. tolterodine ER; $p=0.03$ vs. tamsulosin). In the secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin compared with placebo experienced small but significant reductions in urgency incontinence, urgency episodes, daytime frequency, and nocturia. However, there were no significant differences

between tamsulosin monotherapy and placebo for any diary variables at week 12. Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements in total IPSS (−8.02 vs. placebo, −6.19, $p=0.003$) and QoL (−1.61 vs. −1.17, $p=0.003$). Although there were significant improvements in the total IPSS among patients who received tamsulosin alone, the differences in total IPSS among patients who received tolterodine ER vs. placebo were not significant. The combination of antimuscarinics and α_1-AR antagonists may be the most effective therapy in men with OAB symptoms in the presence of BPO.

A subanalysis [651, 652] of data from the TIMES study focused on the urgency perception scale and concluded that the group of 217 men who received tolterodine plus tamsulosin showed significantly improved urgency variables and patient-reported outcomes. Moreover, this group of patients reported increased satisfaction with the treatment as well as willingness to continue the treatment. Another subanalysis [423, 426] of data from the TIMES study examined the effects of the drugs on urinary symptoms as assessed by the IPSS. Based on this subanalysis, the authors concluded that tolterodine ER plus tamsulosin was significantly more effective than placebo in treating storage LUTS, including OAB symptoms. However, these results should be considered with caution, as they were derived from post hoc analysis of the TIMES data.

Maruyama et al. [528] reported different results in their prospective, randomized, controlled study in which naftopidil (25–75 mg/day), an α_{1D}-AR antagonist, alone or in combination with propiverine hydrochloride (10–20 mg/day) or oxybutynin hydrochloride (2–6 mg/day), was administered for 12 weeks to 101 BPH patients. In the study, the IPSS and QoL index improved significantly in both groups, with no marked differences between groups. Maximum flow rate (Q_{max}) and PVR tended to improve in both groups, again with no differences between groups. However, median post-therapeutic PVR was significantly large in the combination group (45.0 mL) than in the monotherapy group (13.5 mL, $p=0.021$). There were significantly more patients with increased residual urine volume relative to unchanged residuals in the combination therapy (22.9 %) group vs. the monotherapy group (5.0 %, $p=0.038$). The authors of this study concluded that combination therapy with a low-dose antimuscarinic agent was not more effective than monotherapy. Moreover, although they did not encounter any cases of urinary retention, the percentage of patients with increased residual urine volume was significantly greater in the combination therapy group than the monotherapy group.

The results of another study using low-dose antimuscarinic therapy was published by Kang et al. [419]. They evaluated the efficacy and safety of combined treatment with tamsulosin 0.2 mg and propiverine hydrochloride 10 mg compared with tamsulosin monotherapy. After 3 months, both groups showed significant improvements in IPSS, QoL, voided volume, Q_{max}, and PVR, but only the QoL index was significantly different between groups in favor of the combination group. No cases of AUR were recorded in this low-dose study.

Medical therapy to reduce detrusor overactivity in a neurogenic bladder has focused on antimuscarinic therapy, which increases bladder capacity, decreases bladder filling pressure, and improves compliance [315, 727]. Although antimuscarinics combined with CIC is the most commonly recommended medical therapy for neurogenic bladder, the results are sometimes unsatisfactory, and many patients continue to have poor bladder compliance and remain incontinent [631]. McGuire and Savastano [539] reported that α-AR antagonists decreased bladder pressure with filling and increased capacity, and that the addition of an antimuscarinic enhanced these effects, indicating that α-AR antagonists and the antimuscarinic had a synergistic effect on detrusor tone in the decentralized bladder. This finding led to the widespread use of α_1-AR antagonists in the treatment of neurogenic bladder [1, 137, 738]. Swierzewski treated 12 patients with SCI who had poor bladder compliance, despite therapy with CIC and an antimuscarinic, with 5 mg terazosin for bladder management [738]. After 4 weeks, compliance increased by 73 %, bladder pressure decreased by 36 cm H_2O,

and capacity increased by 157 mL. These results support the assumption that α_1-AR antagonists and antimuscarinics may have a synergistic effect on the bladder in the neurogenic population.

In a retrospective chart review, combination therapy with an antimuscarinic agent, an α1-AR antagonist, and imipramine produced superior results to those obtained using a single agent in patients with neurogenic bladder dysfunction [113]. These patients showed significant improvement in clinical parameters and compliance and decreased bladder pressures at capacity. It has been shown that in the decentralized human detrusor, there may be an increase in α-AR receptor sites and a switch to α-AR-mediated contractile function from the typical β-AR-mediated relaxation function during bladder filling [735]. The tricyclic antidepressant imipramine is a muscarinic receptor agonist and a direct smooth muscle inhibitor that decreases bladder overactivity by blocking the reuptake of serotonin. Other effects include the peripheral blockade of noradrenaline, stimulating the β-ARs at the dome of the bladder, and decreasing bladder contractility [366]. These results suggest that targeting multiple receptors may maximize the effectiveness of pharmacological treatment of neurogenic bladder and should be considered in patients in whom treatment with antimuscarinics alone fails.

β_3-AR Antagonists with Antimuscarinics

β_3-AR agonists exert their therapeutic effects through stimulation of adenylyl cyclase and activation of potassium K+ channels. The former leads to an increase in cyclic adenosine monophosphate and the latter to hyperpolarization, both of which result in relaxation. The beneficial effects of modulation of these pathways are: inhibition of spontaneous activity, increased bladder compliance (decreased bladder tone during filling), greater distension needed to activate the micturition reflex (increased bladder capacity), and decreased afferent activity, with no effect on voiding contraction (no risk for urinary retention).

These mechanisms are distinct from those of antimuscarinic therapies used to treat OABs. As such, the combination of these two types of medications is being investigated to determine whether concomitant use can result in increased efficacy with an acceptable profile of safety and tolerability. Based on results with an animal model, it was concluded that the "combination of antimuscarinics and β_3-adrenoceptor agonists can result in increased efficacy and potency and supports the hypothesis that combining these compound classes in the clinic could have beneficial effects in treating urinary bladder dysfunction" [632]. Indeed, the results of a phase II clinical study (the Symphony study) evaluating the combination of solifenacin and mirabegron in 1,307 patients with OABs [7]. The subjects were randomized to receive one of six combinations: mirabegron 25 or 50 mg in combination with solifenacin 2.5, 5, or 10 mg; monotherapy with mirabegron or solifenacin (at each of the same doses studied in the combinations); or placebo. The study duration was 12 weeks. The primary efficacy variable was change in mean volume voided (MVV) per micturition; secondary variables included change in micturition frequency (MF) and incontinence episode frequency (IEF) per 24 h. The investigators reported that mirabegron combination therapy with solifenacin (the latter at a dose of >5 mg) demonstrated greater efficacy than solifenacin 5 mg alone on MVV and MF [7]. The enhanced efficacy with the combination was of a magnitude that is probably similar to the enhanced efficacy one might expect from uptitrating the dose of the antimuscarinic. However, the combination was not associated with the adverse effects one would expect to encounter with higher doses of antimuscarinics. In this study, all six combinations appeared to be well tolerated and there appeared to be no safety concern or significant increase in adverse effects with the combination treatment compared with either monotherapy [7].

Combined Antimuscarinics

Although antimuscarinic agents are the first choice of treatment for patients with OAB symptoms, these drugs do not always lead to the desired effect of detrusor stability and continence, especially for patients with SCI or neurologic diseases such as multiple sclerosis or meningomyelocele. In these patients, the goal of urological therapy is

to maintain continence and to reduce intravesical pressure. When antimuscarinic treatment fails, however, invasive procedures such as the injection of BoNT/A, intravesical application of drugs, or surgery are necessary.

A combined antimuscarinic regimen was evaluated as a non-invasive alternative by Amend et al. [21] for patients who had neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure. They added secondary antimuscarinics to the existing double-dosed antimuscarinics for patients who previously demonstrated unsatisfactory outcomes with double-dosed antimuscarinic monotherapy. The study drugs were tolterodine, oxybutynin, and trospium. After a 4-week combined regimen, incontinence episodes decreased and reflex volume, maximal bladder capacity, and detrusor compliance increased. Side effects were comparable to those seen with normal-dosed antimuscarinics. Those positive findings were speculated to be due to: (1) synergistic activation of different muscarinic receptors or interactions of receptors on different parts of the bladder wall, (2) undiscovered faster metabolism of antimuscarinics requiring an increased dosage of different antimuscarinic drugs, and/or (3) down-regulation of subdivisions of antimuscarinic receptors under monotherapy that may lead to better susceptibility of other subdivisions when treated by the second drug. The combined regimen needs further investigation to verify its efficacy as a non-invasive alternative for patients in whom antimuscarinic monotherapy fails.

Antimuscarinics and 5a-Reductase Inhibitors

The standard first-line medical therapy for men with moderate-to-severe LUTS is an α_1-AR antagonist, a 5α-reductase inhibitor, or combination therapy with both. Both α_1-AR antagonist and 5α-reductase inhibitors alleviate LUTS in men by reducing bladder outlet resistance. α_1-AR antagonists decrease smooth muscle tone in the prostate and bladder neck, while 5α-reductase inhibitors reduce prostate volume. As mentioned, several trials have demonstrated the efficacy and safety of the combination therapy of antimuscarinics and α_1-AR antagonist for patients with OABs and coexisting BPO. However, post-hoc analyses of the TIMES study [424] suggested that men with smaller prostates benefit more from antimuscarinic therapy than those with larger prostates [643–645]. Chung et al. [172] conducted an open-label, fixed-dose study to assess the efficacy and safety of tolterodine ER in combination with dutasteride in men with a large prostate (≥30 g) and persistent OAB symptoms after α_1-AR antagonist therapy who had been unsuccessfully treated with dutasteride alone. At the start of the study, all patients had been on dutasteride 0.5 mg daily for at least 6 months and α_1-AR antagonist therapy had failed. All patients were given 4 mg tolterodine ER daily for 12 weeks and had discontinued α_1-AR antagonist before the start of the study. At 12 weeks, the frequency (−3.2/24 h, $p<0.02$), urgency (19.2 %, $p<0.03$), number of severe OABs episodes (71.4 %, $p<0.05$), and incidence of nighttime voiding (−0.9, $p<0.003$) were found to have decreased significantly from baseline. The IPSS decreased with dutasteride treatment (from 19.3 to 14.3) and further decreased with the addition of tolterodine to 7.1 ($p<0.001$). Storage symptoms decreased from 9.8 to 4.5 ($p<0.001$). Dry mouth occurred in four (7.5 %) subjects, constipation in one (2 %), and decreased sexual function in two (3.9 %). Post-void residual increased by 4.2 mL, Q_{max} decreased by 0.2 mL/s, and no patients went into retention. The authors concluded that the combination of tolterodine and dutasteride was effective, safe, and well-tolerated in men with large prostates with persistent OAB symptoms and LUTS secondary to BPO.

The results of this study indicate that antimuscarinics are safe and effective in selected patients with OABs and BPO when used in combination with 5α-reductase inhibitors. Further studies are required to verify the efficacy of antimuscarinics combined with 5α-reductase inhibitors in these patients.

5α_1-AR Antagonists with 5a-Reductase Inhibitors

It has been well established that the combinations of α_1-AR antagonists with 5-α reductase inhibitors (doxazosin finasteride: MTOPS; dutasteride + tamsulosin: CombAT) can improve

clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention, or progression to surgery [537, 646].

Future Possibilities

Peripherally Acting Drugs

Vitamin D_3 Receptor Analogues

It is well known that vitamin D affects skeletal muscle strength and functional efficiency, and vitamin D insufficiency has been associated with notable muscle weakness. The levator ani and coccygeus skeletal muscles are critical components of the pelvic floor and may be affected by vitamin D nutritional status. Weakened pelvic floor musculature is thought to be associated with the development of urinary incontinence and fecal incontinence symptoms. Aging women are at increased risk for both pelvic floor dysfunction and vitamin D insufficiency; to date, only small case reports and observational studies have shown an association between insufficient vitamin D and pelvic floor dysfunction symptom severity [612]. Rat and human bladders were shown to express receptors for vitamin D [193], which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D_3 have also been shown to inhibit BPH cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [191, 192, 194]. Experiments in rats with bladder outflow obstruction [677] showed that one of the analogues, BXL-628, at non-hypercalcemic doses, did not prevent bladder hypertrophy, but reduced the decrease in contractility of the bladder smooth muscle which occurred with increasing bladder weight [677]. The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [562]. Upregulation of his pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO [168, 618]. In rats with outflow obstruction, previous elocalcitol-treatment improved the effects of tolterodine on bladder compliance [728]. It was suggested that in rats elocalcitol exerted additional beneficial actions on outflow obstruction-induced functional changes during the filling phase of micturition. If valid in humans, combined therapy with the drug would be of value.

The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that elocalcitol was able to arrest prostate growth within 12 weeks in men aged ≥50 years with prostatic volume ≥40 mL [182]. In an RCT enrolling 120 female patients with OABs, where the primary endpoint was an increase in the MVV, a significant increase vs. placebo (22 % vs. 11 %) was demonstrated [181]. Whether or not vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OABs requires further RCTs. However, currently, the development of the drug seems to be stopped [763].

TRP Channel Antagonists

The transient receptor potential (TRP) channel superfamily has been shown to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder and may act as sensors of stretch and/or chemical irritation [44, 63, 64, 262]. TRPV1 and TRPV4 channels have been found to be expressed in the urinary bladder [92, 299, 767]. TRPV1 is present and active both in the urothelium and in the nerve fibers of several species including humans [166, 401]. TRPV4 was initially described in the urothelium of rodents and humans [399]. Co-expression of the two receptors was observed in 20 % of rat urothelial cells [466]. Recent observations indicate, however, that TRPV4 may also be expressed in bladder afferents. In fact, about 30 % of L6 dorsal root ganglia neurons that project to the urinary bladder co-express TRPV1 and TRPV4 [116]. The physiological meaning of this observation is unclear.

TRPV1 KO mice have a normal or quasi-normal phenotype. In awake animals, the only change detected in TRPV1 KO mice was a smaller volume per void when compared with

wild-type (WT) controls [92]. In cystometries performed under anesthesia, the TRPV1 KO mice phenotype seems also very benign. Some studies reported that these animals have totally normal cystometric traces [164]. However, other studies showed that TRPV1 KO mice develop a few non-voiding contractions preceding the voiding contraction [92, 287]. Accordingly, TRPV1 antagonists (GRC 6211) did not show any relevant effect on bladder activity of intact rodents [165]. In contrast with TRPV1 KO mice, the micturition phenotype of TRPV4 KO animals is clearly abnormal. TRPV4 KO mice are incontinent, most probably due to incomplete bladder emptying [299]. Cystometric studies carried out under physiological conditions revealed that TRPV4 KO mice have a marked increase in the inter-contraction interval when compared to wild-type (WT) littermates [93, 299]. Likewise, TRPV4 antagonists (HC-067047) decreased the frequency of bladder contractions and increased the inter-contraction interval [263]. These observations indicated that TRPV4 has a role in the control of normal micturition reflex.

Indisputably, TRPV1 or TRPV4 have a role in the increase of micturition frequency associated with cystitis [164, 263]. While inflamed WT mice exhibit bladder hyperactivity and intense spinal Fos expression after different forms of bladder inflammation, including acetic acid or bacterial extracts, TRPV1 KO mice have normal cystometries and normal spinal c-fos expression [164]. The same holds true for TRPV4. In fact, TRPV4 KO mice exhibit significantly lower voiding frequencies and larger voided volumes than WT after inflammation with cyclophosphamide [263].

The blockade of TRPV1 and TRPV4 with specific antagonist confirm the observations carried out in knock-out animals. As a matter of fact, the TRPV1 antagonist GRC 6211 or the TRPV4 antagonist HC-067047 both abolish the increase of micturition frequency associated with chemical cystitis [165, 263]. Systemic co-administration of TRPV1 and TRPV4 antagonist was more effective in treating the cystitis-induced increase of micturition frequency than the individual application of each antagonist [70]. In particular, the effect could be observed at very low doses of the TRPV1 and TRPV4 antagonists, which had no effect when given isolated. This observed effect might be the answer to overcome the eventual adverse events related with the application of some of these antagonists [622]. Just to mention a few, TRPV1 antagonists are associated with hyperthermia and increased risk of cardiac ischemia [70], while TRPV4 antagonists may eventually precipitate urinary retention and overflow incontinence [299].

It is known for long that TRPV1 is involved in the emergence of neurogenic detrusor overactivity following spinal cord transaction [71]. A TRPV1 antagonist, GRC 6211, has been shown to decrease reflex detrusor overactivity in rats after chronic spinal cord transaction. With increasing doses it was possible to obtain a total suppression of bladder activity [673].

There seem to be several links between activation of different members of the TRP superfamily and LUTS/DO/OABs, and further exploration of the involvement of these channels in LUT function, normally and in dysfunction, may be rewarding. However, proof of concept studies in humans is still lacking.

Prostanoid Receptor Agonists/Antagonists

Developments in the field of prostanoid receptors may open new possibilities to use selective prostanoid receptor antagonists for OABs/DO treatment [56, 403]. There is evidence suggesting that PGE2 contributes to the pathophysiology of OABs/DO: PGE2 infused into the bladder induces DO in humans and animals, increases PGE2 production in DO models, and there are high concentrations of PGE2 in the urine of patients with OABs [536]. PGE2 is an agonist at EP receptors 1–4, all G-protein coupled, which mediate its physiological effects. Based on studies using knockout (KO) mice and EP1 receptor antagonists, it was suggested that the effects of PGE2 on bladder function were mediated through EP1 receptors [678]. EP receptors can be found on urothelium/urothelium, in detrusor smooth muscle, and in intramural ganglia [627, 628, 804]. Functionally, it has been proposed that modulation of bladder activity exerted via EP1

receptors occurs via an afferent mechanism. Schroder et al. [678] found no difference in urodynamic parameters between unobstructed EP1 receptor KO and WT mice. However, EP1 receptor KO mice did not respond to intravesical PGE2 instillation, while WT mice developed DO. The lack of EP1 receptor did not prevent bladder hypertrophy due to partial bladder outflow obstruction but after obstruction WT mice had pronounced DO, while this was negligible in EP1 receptor KO mice.

Lee et al. [478] found that in normal rats a selective EP receptor antagonist significantly increased bladder capacity, micturition volume, and micturition intervals. The antagonist significantly decreased the stimulatory effects of PGE2 and decreased the frequency and amplitude of non-voiding contractions in animals with BOO. It has been shown that also EP3 receptor KO mice have a diminished response to bladder infusion of PGE2 and demonstrate an enhanced bladder capacity under basal conditions [403]. This findings suggest an important contribution for EP3 receptors in the modulation of bladder function under physiological conditions as well as under conditions of enhanced PGE2 production evoking DO. Thus, EP1 and EP3 receptors may have a role in PGE2-mediated DO.

Interestingly, activation of EP3 receptors evoked diuresis and EP3 receptor antagonism was found to induce an antidiuretic effect [406]. Thus, to modulate bladder activity, it appears that the EP3 receptor has a role in regulating urine production. Both effects may be useful for treatment of OABs/DO. It cannot be denied that EP1/EP3 receptors constitute interesting and promising targets for drugs aimed at OABs/DO treatment. However, a randomized, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of the EP-1 receptor antagonist, ONO-8539, in patients with the OAB suggests that the role of EP1 receptor antagonism in the management of the OAB syndrome is minimal [144].

Intraprostatically Injected Drugs

(a) *NX-1207*. NX-1207 is a new drug under investigation for the treatment of LUTS associated with BPH. It is a new therapeutic protein of proprietary composition with selective pro-apoptotic properties [694]. The drug is injected directly into the transitional zone of the prostate as a single administration to induce focal cell loss in prostate tissue through apoptosis, leading to non-regressive prostate shrinkage and both short- and long-term symptomatic improvement. Information about the drugs is scarce and mostly published in abstract form and not yet in the peer-reviewed literature. Two US Phase II trials have been performed [694]. One of them was a multicenter, randomized, non-inferiority study involving 32 clinical sites with 85 subjects and two dose ranges (2.5 and 0.125 mg) and an active open-label comparator (finasteride). Subjects and investigators on NX-1207 were double-blind as to dosage. The primary endpoint was change in AUASI at 90 and 180 days for a single injection of NX-1207 as compared to finasteride on a non-inferiority basis. Inclusion criteria included an AUA Symptom Score ‡ 15, diminished peak urine flow (<15 mL/s), and a prostate size of >30 and <70 mg. The mean AUA Symptom Score improvement after 90 days in the intent-to-treat group was 9.71 points for 2.5 mg NX-1207 ($n=48$) vs. 4.13 points for finasteride ($n=24$) ($p=0.001$) and 4.29 for 0.125 mg NX-1207 ($n=7$) ($p=0.034$). The 180-day results also were positive (NX-1207 2.5 mg non-inferior to open-label finasteride).

No significant changes were found in serum testosterone or serum prostate-specific antigen (PSA) levels in the NX-1207 cohorts. There were no reported adverse effects on sexual function. Two US multicenter, double-blind, placebo-controlled Phase III studies are currently under way. The results of such studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

(b) *PRX302*. PRX302 is a modified form of proaerolysin, a highly toxic bacterial pore-forming protoxin that requires proteolytic processing by PSA [702]. The safety and efficacy of PRX302 was evaluated in men with moderate-to-severe BPH [217]. The patients were refractory, intolerant, or unwilling to undergo medical therapies for BPH and had

an IPSS >12, a quality of life (QoL) score >3, and prostate volumes between 30 and 80 g. Fifteen patients were enrolled in phase 1 studies, and 18 patients entered phase 2 studies. Subjects received intraprostatic injection of PRX302 into the right and left transition zone via a transperineal approach in an office-based setting. Phase 1 subjects received increasing concentrations of PRX302 at a fixed volume; phase 2 subjects received increasing volumes per deposit at a fixed concentration. Out to day 360, sixty percent of men in the phase 1 study and 64 % of men in the phase 2 study treated with PRX302 had >30 % improvement in IPSS compared to baseline. Patients also experienced improvement in QoL and reduction in prostate volume out to day 360. Patients receiving >1 mL of PRX302 per deposit had the best response overall. There was no deleterious effect on erectile function. Adverse events were mild to moderate and transient in nature. The major study limitation was the small sample size.

Elhilali et al. [254] conducted a phase IIb double-blind safety and efficacy evaluation of intraprostatic injection of PRX302 in 92 patients with I-PSS 15 or greater, peak urine flow 12 mL or less per second, and prostate volume 30–100 mL. The patients were randomized 2:1 to a single ultrasound-guided intraprostatic injection of PRX302 vs. vehicle (placebo). It was concluded that PRX302 produced clinically meaningful and statistically significant improvement in patient subjective (I-PSS) and quantitative objective (peak urine flow) measures sustained for 12 months.

Cannabinoids

There is increasing evidence that cannabinoids can influence micturition in animals as well as in humans, both normally and in bladder dysfunction [656]. The effects of the cannabinoids are exerted via two types of well-defined receptors, CB1 and CB2, distributed widely in the body. However, additional receptor subtypes cannot be excluded [617, 656]. Both in the CNS and in peripheral tissues, CB1 and CB2 receptors have been identified; centrally CB1 and peripherally CB2 receptors seem to be predominant [617, 656]. CBI as well as CB2 receptors have been identified in all layers of the human bladder [321, 547, 773, 798]; their expression in the urothelium was found to be significantly higher than in the detrusor, and the expression of CB1 was higher than that of CB2 [773]. Gratzke et al. [321] found higher expression of CB2 receptors, but not CB1 receptors, in the mucosa than in the detrusor. Compared to the detrusor, larger amounts of CB2 receptor containing nerves that also expressed TRPV1 or CGRP were observed in the suburothelium. Nerve fibers containing CB2 receptors and VAChT (cholinergic neurons) were located in the detrusor. In general, activation of CB1 peripherally has been associated with vasodilation and motility changes via suppression of release of neurotransmitters, whereas activation of CB2 appears to induce anti-inflammatory, antinociceptive, and immunosuppressive actions [617, 656]. Several animal studies have suggested a modulatory role of CB2 receptors in both afferent signaling and cholinergic nerve activity [321–323]. Thus, in vivo the selective CB2 receptor agonist, cannabinor, increased micturition intervals and volumes and increased threshold and flow pressures, suggesting that peripheral CB2 receptors may be involved in sensory functions. In rats with partial urethral obstruction treated daily for 14 days with cannabinor, bladder weight was lower, the ability to empty the bladder was preserved, and non-voiding contraction frequency was low compared to those in controls.

The key enzyme for the degradation of anandamide and other endogenous cannabinoids is fatty acid amide hydrolase (FAAH) (Fig. 13.9). FAAH was found to be expressed in rat and human urothelium and was coexpressed with CB2 receptors. In rats, a FAAH inhibitor altered urodynamic parameters that reflect sensory functions, suggesting a role for the endocannabinoid system in bladder mechanoafferent functions [731].

It has not been established whether the effects of the cannabinoids are exerted in the CNS (brain, spinal cord) or peripherally. A preliminary report

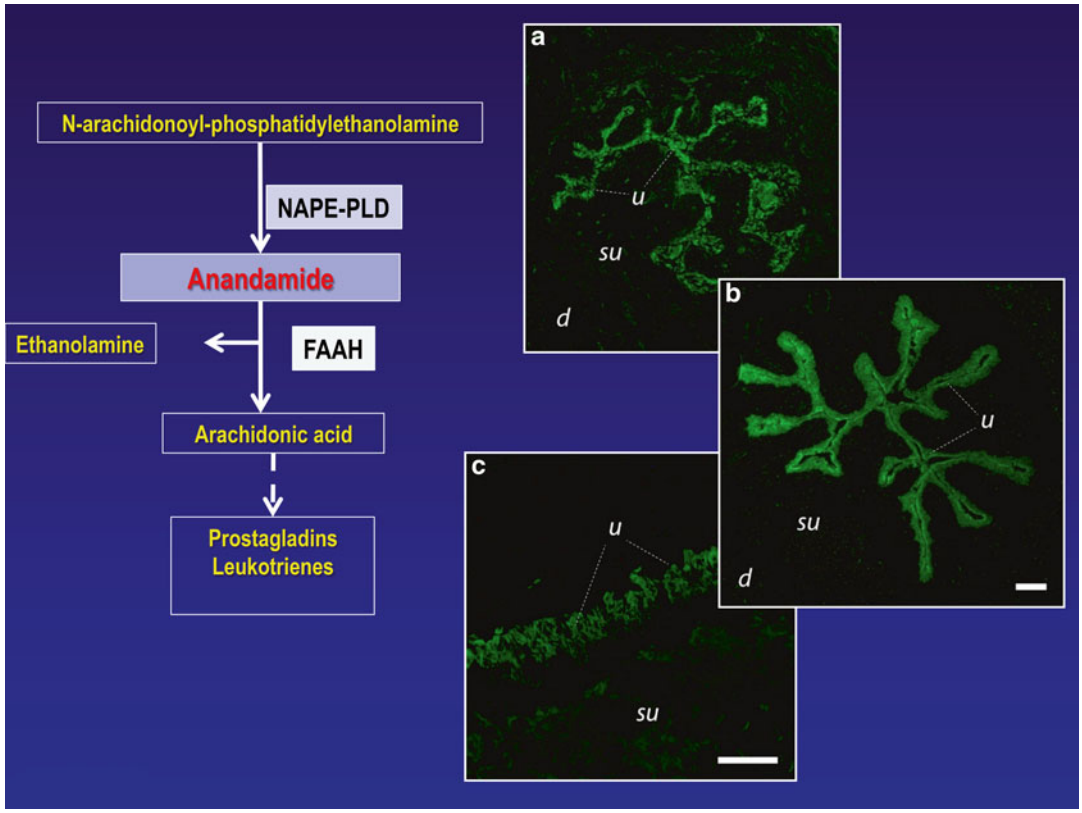

Fig. 13.9 Metabolism of and distribution of fatty acid amide hydrolase (FAAH; cannabinoid degrading enzyme) immunoreactivity in the rat urothelium

[96] demonstrated an effect of combined CB1/CB2 receptor activation on detrusor overactivity in rats with spinal cord transection, which seemed to exclude the brain as a main site of action.

The clinical experiences of the cannabinoid treatment of micturition disturbances including LUTS are limited [656], but both open-label and placebo-controlled studies have demonstrated that orally administered cannabinoid modulators may alleviate neurogenic OAB symptoms refractory to first-line treatment [102, 283, 430]. Brady et al. [102] evaluated the efficacy of two whole plant extracts (δ9-tetrahydrocannabinol and cannabidiol) of Cannabis sativa in patients with advanced MS and refractory LUTS. Urinary urgency, the number and volume of incontinence episodes, frequency, and nocturia decreased significantly following treatment. Freeman et al. [283] tested in a subanalysis of a multicenter trial (the CAMS study) whether cannabinoids could decrease urge incontinence episodes without affecting voiding in patients with MS. The CAMS study randomized 630 patients to receive oral administration of the cannabis extract δ9-tetrahydrocannabinol or matched placebo. Based on incontinence diaries a significant decrease in incontinence episodes was demonstrated.

Kavia et al. [430] assessed the efficacy, tolerability, and safety of Sativex(®) (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS. They performed a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial on 135 randomized subjects with MS and OABs. The primary endpoint, reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks), showed little difference between Sativex and placebo. However, four out

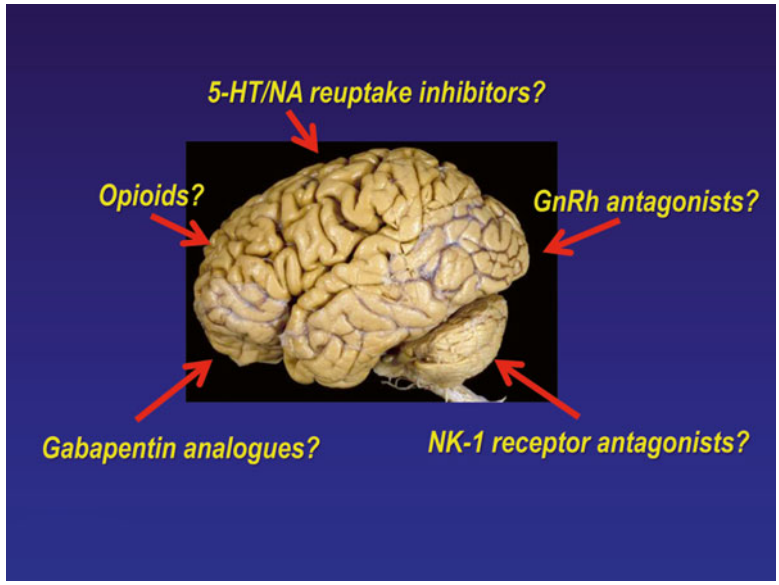

Fig. 13.10 OABs drugs with a central mode of action. Several principles seem to work, but currently used drugs have low efficacy and/or unacceptable side effects. However, there is great potential for further developments

of seven secondary endpoints were significantly in favor of Sativex, including number of episodes of nocturia, number of voids/day, and number of daytime voids. The improvement in I-QOL was in favor of Sativex, but did not reach statistical significance.

Systemic cannabinoids have effects on the LUT that may have a therapeutic potential; local delivery (intravesical, spinal) may be possible, but more information is needed. The mechanisms of cannabinoid receptors in control of the human LUT is incompletely known, and further research is necessary for the development of novel cannabinoid drugs for treatment of LUT disorders.

Centrally Acting Drugs

Many parts of the brain seem to be activated during storage and voiding (see, [277, 325–327]), and there is increasing interest in drugs modulating the micturition reflex by a central action [48] (Fig. 13.10). Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples. However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OABs, since selective actions may be difficult to obtain. Holstege [369], reviewing some of the central mechanisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that "the problem in OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level."

Gonadotropin-releasing hormone antagonists. The beneficial effects of the 5α-reductase inhibitors, finasteride and dutasteride, in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example, antiandrogens or gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone: LHRH) agonists, is either poor or at the expense of unacceptable side effects such as medical castration associated with hot flushes, decrease of potency and libido, and negative effects on bone density following long-term androgen ablation [99, 261, 619, 679]. With GnRH antagonists submaximal, non-castrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus avoiding medical castration. Several GnRH antagonists—such as cetrorelix, ozarelix, and teverelix—have been tested in

Phase IIA/IIB clinical trials for their ability to improve LUTS in patients with BPH [183].

Debruyne et al. [213] demonstrated in a phase 2 RCT that the LHRH antagonist cetrorelix, given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS ≥ 13, peak urinary flow rates 5–13 mL/s), rapidly caused a significant improvement in the mean IPSS: the peak decrease was −5.4 to −5.9 vs. −2.8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug offered a safe and effective treatment of male LUTS.

Due to these results, two phase III studies were conducted in the United States and Europe (AEterna Zentaris); in the US study, 637 men were randomized to receive either two doses of placebo or cetrorelix on weeks 2 and 26. The drug showed no statistically significant benefit in improving IPSS. In addition, cetrorelix did not have a significant effect on peak flow rate or prostate volume vs. placebo. It is difficult to reconcile this lack of efficacy given favorable prior results. A subsequent multicenter European trial also failed to show any treatment-related efficacy of cetrorelix. The experience with cetrorelix highlights the importance of randomized, placebo-controlled trials that are appropriately powered to show clinical benefit and safety.

Gabapentin. Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [730]. It was originally designed as an anticonvulsant GABA mimetic capable of crossing the blood–brain barrier [517]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [517]. It has been suggested that it acts by binding to a subunit of the $\alpha_2\delta$ unit of voltage-dependent calcium channels [296, 730]. Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone et al. [118] reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim et al. [450] studied the effects of gabapentin in patients with OABs and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other $\alpha_2\delta$ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives, but convincing RTC are still lacking.

Tramadol. Tramadol is a well-known analgesic drug [330]. By itself, it is a weak μ-receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ-receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and noradrenaline reuptake [330]. This profile is of particular interest, since both μ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS/OABs/DO, as shown in a placebo-controlled study with duloxetine [722].

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction [633]. Tramadol also inhibited DO induced by apomorphine in rats [615]—a crude model of bladder dysfunction in Parkinson's disease. Singh et al. [701] gave tramadol epidurally and found the drug to increase bladder capacity and compliance, and to delay filling sensations without adverse effects on voiding. Safarinejad and Hosseini [659] evaluated in a double-blind, placebo-controlled, randomized study the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100 mg tramadol sustained release every 12 h for 12 weeks. Clinical evaluation was performed at baseline and every 2 weeks during treatment. Tramadol significantly ($p<001$) reduced the number of incontinence periods per 24 h from 3.2 ± 3.3 to 1.6 ± 2.8 and induced improvements in urodynamic parameters. The

main adverse event was nausea. It was concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the best suitable drug for treatment of LUTS/OABs, the study suggests efficacy for modulation of micturition via the μ-receptor.

NK1-receptor antagonists. The main endogenous tachykinins, substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control [189, 477, 660, 685]. NK1 receptor expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via NK1 receptors in the micturition reflex induced by bladder filling has been demonstrated [395] in normal, and more clearly, rats with bladder hypertrophy secondary to BOO. Capsaicin-induced detrusor overactivity was reduced by blocking NK1 receptor-expressing neurons in the spinal cord, using intrathecally administered substance P-saponin conjugate [395]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [397].

In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses, and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction [332]. Intracerebroventricular administration of NK1 and NK2 receptor antagonists to awake rats suppressed detrusor activity induced by dopamine receptor (L-DOPA) stimulation [396]. Taken together, available information suggests that spinal and supraspinal NK1 and NK2 receptors may be involved in micturition control.

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting [529], significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), as shown in a well-designed pilot RCT [324]. The primary end-point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary endpoints included average daily total urinary incontinence and urgency incontinence episodes, and urgency episodes. Aprepitant significantly ($p<0.003$) decreased the average daily number of micturitions (-1.3 ± 1.9) compared with placebo (-0.4 ± 1.7) at 8 weeks. The average daily number of urgency episodes was also significantly ($p<0.047$) reduced (-23.2 ± 32 %) compared to placebo (-9.3 ± 40 %), and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. Since this initial proof of concept study suggested that NK-1 receptor antagonism hold promise as a potential treatment approach for OAB symptoms, a randomized, double-blind, multicenter trial enrolled 557 adults with overactive bladder (8 or more average daily micturitions and 1 or more daily urge incontinence episodes) [285]. After a 1-week placebo run-in the patients were randomized to treatment with 8 weeks of daily 0.25, 1, or 4 mg serlopitant, 4 mg tolterodine extended release, or placebo. Patients kept 7-day voiding diaries. The primary endpoint was change from baseline in micturitions per day. Secondary endpoints included urgency, total incontinence, urge incontinence episodes, and incidence of dry mouth. Of the 557 patients randomized, 476 completed the trial and had valid efficacy data for analysis. Mean change from baseline in daily micturitions was significantly greater for 0.25 (-1.1) and 4 mg (-1.1) serlopitant, and for tolterodine (-1.5) than for placebo (-0.5), but not for 1 mg serlopitant (-0.8). No serlopitant dose response was demonstrated. Tolterodine was numerically superior to all doses of serlopitant in mean micturitions per day and secondary endpoints. The incidence of dry mouth on serlopitant (3.3 %) was comparable to placebo (4.6 %) and lower than tolterodine (8.8 %). Serlopitant was generally well tolerated.

NK-1 receptor antagonists may have a role in the treatment of overactive bladder but at least

the compounds tested so far does not offer advantages in efficacy compared to tolterodine.

A different approach, modulation of neuropeptide release rather than NK receptor blockade, was tested in a pilot study with cizolirtine, which is a substance-P and CGRP release modulator at the spinal cord level. The modulation of substance-P and CGRP is probably related to the increase of extracellular levels of noradrenaline and serotonin. Cizolirtine 200 and 400 mg were compared to placebo in 79 OABs patients. Although the decrease in key OAB symptoms was significantly higher in the active arms, adverse events were reported in 68 and 81 % of the patients on cizorlitine 200 and 400 mg. More commonly reported side effects were gastrointestinal in nature, including dry mouth and vomiting [527].

Drugs Used for Treatment of Stress Incontinence in Women

Many factors seem to be involved in the pathogenesis of stress urinary incontinence (SUI) in women: urethral support and function, bladder neck support and function of the nerves and musculature of the bladder, urethra, and pelvic floor [155, 215, 459, 567]. Pure structural factors cannot be treated pharmacologically. However, SUI in women is generally thought to be characterized by decreases in urethral transmission pressure and, in most cases, resting urethral closure pressure [351, 363, 459]. It, therefore, seems logical that increasing urethral pressure should improve the condition.

Factors which may contribute to urethral closure include the tone of the urethral smooth and striated muscle (the rhabdosphincter) and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacological evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by released noradrenaline [24, 52, 53]. A contributing factor to SUI, mainly in elderly women with lack of estrogen, may be lack of mucosal function. The pharmacological treatment of SUI (Table 13.2) aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated musculature, either directly or through increased motorneuron activity. Several drugs may contribute to such an increase [53], but relative lack of efficacy or/and side effects have limited their clinical use.

α-Adrenoceptor Agonists

Several drugs with agonistic effects on peripheral α-ARs have been used in the treatment of SUI. Relatively recently, a central role of noradrenaline (NA) in increasing the excitability of urethral rhabdosphincter motorneurons in the rat analogue of Onuf's nucleus has been observed, an effect

Table 13.2 Drugs used in the treatment of stress incontinence

Drug	Level of evidence	Grade of recommendation
Clenbuterol	3	C
Duloxetine	1	B
Ephedrine	3	D
Estrogen	2	D
Imipramine	3	D
Methoxamine	2	D
Midodrine	2	C
Norephedrine (phenylpropanolamine)	3	D

Assessments according to the Oxford system (modified)

due at least in part to α_1-AR receptor-dependent depolarization. This could contribute to the mechanism by which NA reuptake inhibitors improve SUI [828]. Ephedrine and norephedrine (phenylpropanolamine; PPA) seem to have been the most widely used [53]. The original United States Agency for Healthcare Policy and Research Guidelines [9] reported eight randomized controlled trials with PPA, 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) were listed as 0–14 %, percent reduction in continence as 19–60 %, and percent side effects and percent dropouts as 5–33 % and 0–4.3 %, respectively. The most recent Cochrane review on the subject [14], reprinted virtually unchanged in 2008) assessed randomized or quasi-randomized controlled trials in adults with stress urinary incontinence which included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1,099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in 2, norepinephrine in 3, clenbuterol in 3, terbutaline in 1, eskornade in 1, and RO 115-1240 in 1). The authors concluded, "there was weak evidence to suggest that use of an adrenergic agonist was better than placebo in reducing the number of pad changes and incontinence episodes, as well as, improving subjective symptoms." There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination. Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25 % of subjects reported such effects, but when these consisted of effects due to adrenergic stimulation, they caused discontinuation in only 4 % of the total.

Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [53]. Kernan et al. [442] reported the risk of hemorrhagic stroke to be 16 times higher in women less than 50 years of age who had been taking PPA as an appetite suppressant (statistically significant) and three times higher in women who had been taking the drug for less than 24 h as a cold remedy (not statistically significant). There was no increased risk in men. PPA has been removed from the market in the United States. It is still allowed as a treatment for SUI in a few countries. Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some [85] had suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003, the Food and Drug Administration (FDA) of the US decreed such a ban, a move which has survived legal appeal.

Midodrine and methoxamine stimulate α_1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate at best, and the clinical usefulness seems to be limited by adverse effects [15, 626, 809].

Attempts continue to develop agonists with relative selectivity for the human urethra. Musselman et al. [572] reported on a phase 2 randomized crossover study with RO 115-1240, a peripheral active selective $\alpha_{1A/1L}$-AR partial agonist [95] in 37 women with mild-to-moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug. PF-3774076, a CNS penetrating partial α_{1A}-AR agonist, increased peak urethral pressure in dogs and was selective with respect to α_{1B} and α_{1D} receptors, but heart rate and blood pressure changes caused significant concern [184]. Furuta et al. [291] reported that the α_2-AR can inhibit the release of glutamate presynaptically in the spinal cord and proposed that α_2-AR antagonists would be useful as a treatment for SUI. This hypothesis awaits testing.

β-Adrenoceptor Agonists

Clenbuterol. β-AR stimulation is generally conceded to decrease urethral pressure [24], but β_2-AR agonists have been reported to increase the contractility of some fast contracting striated muscle fibers and suppress that of slow contracting fibers of others [268]. Some β-AR agonists also stimulate skeletal muscle hypertrophy—in

fast twitch more so than slow twitch fibers [451]. Clenbuterol has been reported to potentiate the field stimulation-induced contraction in rabbit isolated periurethral muscle preparations, an action which is suppressed by propanolol and greater than that produced by isoprotererol [454]. These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yaminishi et al. [826] reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs, abolished by β-AR blockade.

Yasuda et al. [829] described the results of a double-blind placebo-controlled trial with this agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad usage per day, and overall global assessment. Pad weight decreased from 11.7 ± 17.9 to 6.0 ± 12.3 g for drug and from 18.3 ± 29.0 to 12.6 ± 24.7 g for placebo, raising questions about the comparability of the two groups. The "significant" increase in maximal urethral closure pressure (MUCP) was from 46.0 ± 18.2 to 49.3 ± 19.1 cm H_2O, vs. a change of −1.5 cm H_2O in the placebo group. 56/77 patients in the Clenbuterol group reported some degree of improvement vs. 48/88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko et al. [394] investigated the effects of clenbuterol on 61 female patients with stress incontinence in a 12-week randomized study, comparing drug therapy to pelvic floor exercises (PFEs). The frequency and volume of stress incontinence and the patient's own impression were used as the basis for the assessment of efficacy. The improvement of incontinence was 76.9 %, 52.6 %, and 89.5 % in the respective groups. In an open study, Noguchi et al. [590] reported positive results with clenbuterol (20 mg BID for 1 month) in 9 of 14 patients with mild-to-moderate stress incontinence after radical prostatectomy. Further well-designed RTCs investigating effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence.

β-Adrenoceptor Antagonists

The theoretical basis for the use of β-AR antagonists in the treatment of stress incontinence is that blockade of urethral β-As may enhance the effects of noradenaline on urethral α-ARs. Propranolol has been reported to have beneficial effects in the treatment of stress incontinence [312, 414], but there are no RCTs supporting such an action. In the Gleason et al. [312] study, the beneficial effects become manifest only after 4–10 weeks of treatment, a difficult to explain phenomenon. Donker and Van der Sluis [238] reported that β-blockade did not change UPP in normal women. Although suggested as an alternative to α-AR agonists in patients with SUI and hypertension, these agents may have major potential cardiac and pulmonary side effects of their own, related to their therapeutic β-AR blockade.

Serotonin-Noradrenaline Uptake Inhibitors

Imipramine

Imipramine, among several other pharmacological effects, has classically been reported to inhibit the re-uptake of noradrenaline and serotonin in adrenergic nerve endings. In the urethra this could be expected to enhance the contractile effects of noradrenaline on urethral smooth muscle. Gilja et al. [305] reported in an open study on 30 women with stress incontinence that imipramine, 75 mg daily, produced subjective continence in 21 patients and increased mean MUCP from 34 to 48 mmHg. A 35 % cure rate was reported by pad test and, in an additional 25 %, a 50 % or more improvement. Lin et al. [490] assessed the efficacy of imipramine (25 mg imipramine three times a day for 3 months) as a treatment of genuine stress incontinence in 40 women with genuine stress incontinence. A 20-min pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of "successful treatment" was 60 % (95 % CI 11.8–75.2). There are

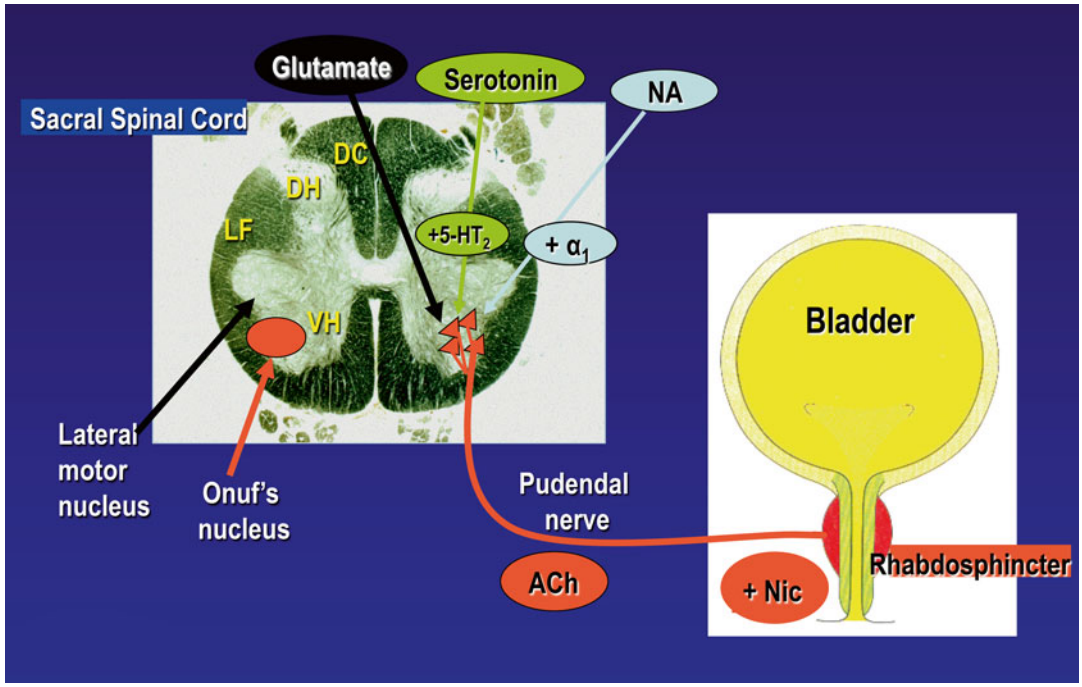

Fig. 13.11 The striated urethral sphincter is innervated by the pudendal nerve, which contains the axons of motor neurons whose cell bodies are located in Onuf's nucleus. Glutamate exerts a tonic excitatory effects on these motor neurons, and this effect is enhanced by noradrenaline (NA) and serotonin (5-HT), acting on α1-adrenoceptors and 5-HT2-receptors, respectively. By inhibition of the reuptake of noradrenaline and serotonin, duloxetine increases the contractile activity in the striated sphincter (nicotinic receptors: + Nic). *DC* dorsal commissure, *DH* dorsal horn, *VH* ventral horn, *LF* lateral funiculus, *ACh* acetylcholine

no RCTs on the effects of imipramine on SUI. No subsequent published reports have appeared.

Interestingly, Gillman [308] reported that clomipramine had far greater 5HT reuptake inhibition than imipramine and roughly similar NA reuptake inhibition. Desipramine and reboxetine had greater NA reuptake inhibition (desipramine superior), with less effects than imipramine on 5HT uptake (desipramine superior).

Duloxetine

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition (Fig. 13.11) in the cat acetic acid model of irritated bladder function [429, 757]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [279]. The sphincteric effects were reversed by α_1 adrenergic (praxosin) and 5HT2 serotonergic (LY 53857) antagonism, while the bladder effects were mediated by temporal prolongation of the actions of serotonin and norephinephrine in the synaptic cleft [279]. Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 h [690].

Thor et al. [758] described the mechanisms of action and the physiologic effects of duloxetine. 5HT (serotonin) and NA terminals are dense in spinal areas associated with LUT functioning especially around the pudendal nerve neurons in Onuf's nucleus. These are projections from separate areas in the brain stem.

Glutamate is the primary excitatory neurotransmitter in the spinal cord, activating the pudendal neurons in Onuf's nucleus causing contraction of the urethral rhabdosphincter. The rhabdosphincter innervation is proposed as distinct from that of the levator ani [756]. The responsiveness of the rhabdosphincter motor neurons to glutamate is modulated (facilitated) by 5HT (through $5HT_2$ receptors) and NA (through α_1-ARs). 5HT and NA, however, only modulate, and when micturition occurs, glutamate excitation and the rhabdosphincter contraction cease. Excitatory effects on urethral sphincter activity are shared to a lesser extent by receptors for $5HT_{1A}$ (indirect through a supraspinal stimulation), TRH, Vasopressin, NMDA, and AMPA; inhibitory effects are similarly mediated by κ_2 opioid, α_1 ARs, GABA-A, GABA-B, and glycine receptors [756]. Some CNS penetrant selective $5HT_{2C}$ agonists have been found to increase urethral muscle tone and inhibit micturition reflexes in animal models, and these are additional candidates for clinical development for the treatment of SUI [756].

Several RTCs have documented the effect of duloxetine SUI [229, 554, 593, 780]. A Cochrane review of the effects of duloxetine for stress urinary incontinence in women is available; the last substantive amendment listed as 25 May, 2005 [521]. Fifteen reports were deemed eligible for analysis, nine primary studies and six additional reports related to one or two of the primary references. An additional analysis "performed under the auspices of the Cochrane Incontinence Group" was performed on just the nine primary trials comparing duloxetine and placebo and published separately [521]. The results can be summarized as follows. Subjective "cure" in the duloxetine 80 mg daily (40 mg BID) was higher than in the placebo group (10.8 % vs. 7.7 %, overall RR = 1.42; 95 % CI, 1.02–1.98; $p = 0.04$). The estimated absolute size of effect was about 3 more patients cured of every 100 treated. Objective cure data, available from only one trial, showed no clear drug/placebo difference. Duloxetine showed greater improvement in I-QOL (WMD for 80 mg: 4.5; 95 % CI 2.83–6.18, $p < 0.00001$). Adverse effects in six trials were analyzed. These were reported by 71 % of drug subjects and 59 % of those allocated to placebo. Nausea was the most common adverse event and the incidence ranged from 23 to 25 % and was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness, and insomnia, overall RR 1.30 (95 % CI, 1.23–1.37). Across these six trials 17 % in the drug group withdrew, 4 % in the placebo arm. In the 2007 article, the authors conclude by saying that further research is needed as to whether management policies incorporating duloxetine are clinically effective and cost-effective compared to other current minimally invasive and more invasive approaches in patients with varying severity of SUI, and that "longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications."

Hurley et al. [380] characterized the safety of duloxetine for treatment of SUI in women, using an integrated database generated from four published placebo-controlled clinical trials. The database included 1,913 women randomized to duloxetine ($N = 958$) or placebo ($N = 955$), examining adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiograms (ECGs), and laboratory analytes. AEs occurring initially or worsening during the double-blind treatment period were considered treatment-emergent (TEAE). Differences between duloxetine-treated and placebo-treated groups were compared statistically. Common TEAEs included: nausea (23.2 %), dry mouth (13.4 %), fatigue (12.7 %), insomnia (12.6 %), constipation (11.0 %), headache (9.7 %), dizziness (9.5 %), somnolence (6.8 %), and diarrhea (5.1 %). Most TEAEs that emerged early were mild to moderate, rarely worsened, and resolved quickly. Overall AE discontinuation rates were 20.5 % for duloxetine and 3.9 % for placebo ($P < 0.001$). Most discontinuations (83 %) occurred within the first month of treatment. SAEs were uncommon and did not differ between treatments. Statistically significant, but clinically unimportant mean increases in heart rate (2.4 bpm) and systolic and diastolic blood pressure ($\leq$2 mmHg) occurred. No arrhythmogenic potential was observed and

any rare, transient, asymptomatic increases in hepatocellular enzymes normalized. The authors concluded that duloxetine was safe and tolerable, although transient AEs were not uncommon. Hashim and Abrams [345] suggested, to reduce the risk of nausea, to begin with a dose of 20 mg twice daily for 2 weeks, then to increase to the recommended 40 mg BID dosage.

Ghoneim et al. [300] randomized women with SUI to one of four treatment combinations: duloxetine alone (40 mg BID), pelvic floor muscle training, combination, and placebo. Overall, drug with or without PFMT was superior to PFMT alone or placebo, while pad results and QOL data favored combination therapy to single treatment. Cardozo et al. [123] reported that 20 % of women awaiting continence surgery changed their minds while taking duloxetine. Duckett et al. [246] offered a 4-week course to women awaiting a TVT operation. Thirty-seven percent (of 73) declined. Excluding women for whom concomitant prolapse surgery was planned, 8/33 (24 %) scheduled for incontinence surgery alone came off the list. Sixteen (48 %) discontinued duloxetine because of AEs, 9 (27 %) found the drug ineffective.

Bent et al. [84] reported on the effects of 12 weeks of duloxetine (40 mg BID) vs. placebo in a large group of women with MUI. For SUI episodes, the mean IEF per week decreased 58.9 % with drug (7.69 to 3.93) vs. 43.3 % for placebo (8.93 to 6.05). Interestingly, corresponding decreased for UUI episodes were 57.7 % vs. 39.6 %. Both sets of values are statistically significant, but the baselines are different and the absolute change for SUI amounted to −3.76 episodes per week for drug, −2.87 for placebo. Nausea was reported by 18 % of patients on drug, 4.5 % on placebo. Corresponding percents for other AEs include dry mouth (12 vs. 2.8), dizziness (9.7 vs. 2.4), constipation (8.3 vs. 4.2), and fatigue (6.7 vs. 2.8). Nausea and dizziness were less common in a subgroup taking concurrent antidepressants. Women 65 years and older with SUI or stress predominant MUI (S-MUI) were given duloxetine (40 mg BID after a 2-week start on 20 mg BID) or placebo for 12 weeks by Schagen van Leeuwen et al. [674]. They conclude, "this study supports the use of duloxetine in elderly women with SUI or S-MUI." The data show an absolute change in SUI + S-MUI episodes of −11.7 and −6.9 IEF/week (drug and placebo) and median percent changes of −52.5 % vs. −36.7 % from 24 h diaries, both significant at $p < 0.001$. However, the changes for SUI alone were −53 % vs. −42 % (NS), while for S-MUI alone they were −51.6 % vs. −32.7 % ($p < 0.001$). Nausea was less than in other trials (7.5 % vs. 3.1 %), perhaps due to the lower starting dose. Other AEs included fatigue (14.2 % vs. 5.4 %), constipation (10.4 vs. 0.8), dizziness (9.0 vs. 4.6), and excess sweating (5.2 vs. 0).

Persistence on duloxetine was studied by Vella et al. [787] who found that only 31 % of an original cohort of 228 were still taking drug beyond 4 weeks, 12 % at 4 months, 10 % at 6 months, and 9 % at 1 year. Fifty-six percent of the discontinuations were attributed to side effects, 33 % to lack of efficacy; Bump et al. [109], however, reported that the positive effects of duloxetine were maintained in patients who continued treatment up to 30 months, but admitted that this subgroup was likely to include predominantly patients who had favorable responses. The number decreased from 1,424 in this cohort at 3 months to 368 at 30 months.

Shaban et al. [689] concluded that duloxetine is "optional second line for women not willing or unfit for surgery after warning against side effects as recommended by NICE guidelines in the UK." Similar sentiments are expressed by Robinson and Cardozo [638].

Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in the European Union (European Medicines Agency, Scientific Discussion, 2005) in women with moderate-to-severe incontinence (defined as 15 or more episodes per week). It was withdrawn from the FDA consideration process in the United States for the treatment of SUI, but is approved for the treatment of major depressive disorder (20–30 mg BID initially, 60 mg once daily maintenance), diabetic peripheral neuropathic pain (60 mg once daily), generalized anxiety disorder (60 mg once daily), fibromyalgia (c0 mg once daily initially, 60b mg once daily maintenance), and chronic musculoskeletal pain (30 mg once daily initially,

60 mg once daily as maintenance). The product information contains a "black box" warning of "increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders," noting also that "depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide" (Prescribing Information, revised September 2011, Eli Lilly and Company, Indianapolis, Indiana 46285). Other warnings and precautions in the U.S. in the United States Product Information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease), orthostatic hypotension, serotonin syndrome (general statement regarding SSRIs and SNRIs), abrupt discontinuation (may result in dizziness, paresthesias, irritability, and headache), inhibitors of CYP1A2 (such as ciprofloxacin), thioridaxine (do not administer concomitantly), potent inhibitors of CYP2D6 (may increase concentration), and others. Adverse events for 6,801 drug and 4,487 placebo-treated patients reported in the US Product Information (treatment for the indications mentioned) are nausea (24 % vs. 8 %), dry mouth (13 vs. 5), fatigue (10 vs. 5), somnolence (10 vs. 3), insomnia (10 vs. 6), constipation (10 vs. 4), and dizziness (10 vs. 5).

Stress Urinary Incontinence in Men

Although a problem of significant magnitude, especially after radical prostatectomy (RP) for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention.

Intrinsic sphincter function is the most important outlet factor maintaining continence in men. Urethral support is less important, and there is no entity similar to the hypermobility phenomenon in women. The proximal urethral sphincter extends from the bladder neck through the prostatic urethra. Its function is removed by radical prostatectomy. The distal urethral sphincter includes the rhabdosphincter, urethral smooth muscle, and extrinsic paraurethral skeletal muscle, extending from the prostatic urethra below the verumontanum through the membranous urethra [459]. Tsakiris et al. [770] searched for articles on drug treatment of male SUI published between 1966 and June 2007 and did a generalized database search in addition. Nine trials were identified using alpha adrenergic agonists, beta-2 antagonists, or SNRSs. Only one of these included a comparison arm [270], 40 mg BID duloxetine plus PFE vs. PFE with placebo. The results suggested a positive effect of drug, but were a bit confusing. Of those patients completing the 4-month trial (92/112), 78 % of the drug-treated patients vs. 52 % of those in the placebo group were "dry." However, 1 month after the end of the study, the corresponding figures were 46 % vs. 73 %, a shift still observed 2 months later. The authors of the review article suggested further larger and well-designed studies on duloxetine for this potential usage.

Cornu et al. [188] reported a series of post-RP men with SUI or MUI (stress predominant) randomized to duloxetine (I5) and placebo (16) after a 2-week placebo run in. Dosage was 20 mg BID for 7 days, 40 mg BID for 67 days, 20 mg for 14 days. Subjects were at least 1 year post-surgery. Outcome measures included percent decrease in IEF, 1 h pad test and various QOL measures. Statistical significance for IEF percent decrease occurred only at week 8 and 12 [(−) 52.2 ± 38.6 % vs. (+)19 ± 43.5 %], but there was clearly a trend at 4 weeks. There was no statistical difference in 1 h pad test weights, but there was in various QOL scores. A 50–100 % decrease in IEF was seen at 12 weeks in over half of the patients. Adverse events for drug and placebo included fatigue (50 % vs. 13 %), insomnia (25 vs. 7), libido loss (19 vs. 7), constipation (13 vs. 7), nausea (13 vs. 7), diarrhea (13 vs. 7), dry mouth (6 vs. 0), anorexia (6 vs. 0), and sweating (25 vs. 20). Drawbacks and concerns are the small number (the original proposed sample size was 90) and the lack of any placebo effect on IEF and QOL. There were four men with MUI in the drug group, five in the placebo group. Results for SUI and UUI were not separated. One would logically not expect improvement to continue after drug withdrawal unless a permanent change occurred in behavior, anatomy, or neuromuscular

function. In an uncontrolled usage study on men with post-RP SUI, Collado Serra et al. [179] reported that the benefit remained in 85 % after the drug was stopped. In that series, 25 % of patients withdrew because of AEs and 33 % because of lack of effect.

Usage of duloxetine for SUI in the male is universally off-label. A drug for this indication would be welcome. Larger controlled and better designed studies are necessary to provide conclusive positive or negative data on this subject.

Drugs to Treat Overflow Incontinence/Acute Urinary Retention

Urinary incontinence most often results from involuntary bladder contractions and/or too little resistance generated by the bladder outflow tract during the storage phase of the micturition cycle (urgency incontinence and stress incontinence, respectively). More rarely, incontinence can also occur because of too little pressure generation and/or too much outflow resistance, which can lead to a markedly distended bladder and urinary retention and, secondarily, overflow incontinence [4].

Based upon theoretical reasoning, animal studies [331, 416], and reports of drugs that can cause overflow incontinence [22], a variety of medical approaches to the treatment of overflow incontinence have been proposed [173, 223, 342]. Treatment may aim to increase bladder contractility, decrease bladder outlet resistance, or both. Theoretically, all drugs that improve decreased sensation (and increase afferent activity) or drugs that increase detrusor contractile force could be useful. Alternatively, agents that decrease outflow resistance, thereby restoring an appropriate balance between detrusor strength and urethral resistance, could be used.

These drugs include direct or indirect muscarinic receptor agonists, α_1-adrenoceptor antagonists, choline esterase inhibitors, prostaglandins (PG), and skeletal muscle relaxants [223]. The use of muscarinic receptor agonists, such as bethanechol, to stimulate detrusor muscarinic receptors, or choline esterase inhibitors, such as distigmine, to reduce the degradation of acetylcholine, is based upon the idea that stimulation of muscarinic receptors may overcome a hypocontractile detrusor [77]. However, a recent systematic review of controlled clinical studies that used direct and indirect parasympathetic agonists in patients with an underactive detrusor reported that these drugs do not provide consistent benefits and may even be harmful. The available information indicates that muscarinic receptor agonists and choline esterase inhibitors have little, if any, beneficial effects on preventing and treating detrusor underactivity. While there is a theoretical basis for the use of β-agonists to relax the sphincter, no definite improvements in symptoms have yet been demonstrated [10, 77, 200, 634]. As bethanechol exerts its effect on intact smooth muscle cells only, it is of limited use for the treatment of bladder atony. Idiopathic detrusor atony is poorly responsive to medical treatment [589].

The use of α_1-AR antagonists has repeatedly been shown to be beneficial in patients with AUR due to BPE [272, 540, 541]. These drugs are believed to facilitate bladder emptying by relaxing tone at the bladder neck. Administration of alfuzosin 10 mg daily almost doubles the likelihood of a successful trial without a catheter, even in patients who are elderly with a PVR > 100 mL. Continued use of alfuzosin significantly reduced the risk of BPH surgery in the first 3 months; however, this effect was not significant after 6 months [258, 273, 415]. Thus, α_1-AR antagonists provide rapid symptom relief from outlet obstruction caused by BPE and delay the time to AUR; however, they do not decrease the overall risk of AUR or surgery [252, 257, 272].

AUR may occur after surgery. Buckley and Lapitan [108] reviewed drugs used for treatment of post-operative urinary retention either alone or in combination, assessing cholinergic agents, α_1-AR blockers, sedatives, and prostaglandins. A statistically significant association between intravesically administered prostaglandins and successful voiding was detected, but no such association was found for the other drugs investigated. When cholinergic agents were combined with

sedative there was an improved likelihood of spontaneous voiding compared with placebo.

There are some potential new agents for the treatment of an underactive bladder. Misoprostol, a cholinesterase inhibitor, and cholinergic agents are potential candidates for the treatment of the underactive bladder, but their safety and lack of benefit is of concern. The prokinetics used in gastroenterology and the smooth muscle ionotropics used in cardiology warrant consideration. The use of trophic factors such as insulin-like growth factor and NGF may improve muscle and nerve function in the LUT. Furthermore, the use of stem cells, regenerative medicine, and gene therapy might facilitate improved contractility in a weak detrusor [139].

However, these agents have never been tested systematically in patients with overflow incontinence; there have been no randomized controlled trials to demonstrate the effectiveness and safety of these agents. Therefore, there is no empirical basis to select medical treatments for overflow incontinence and all previously recommended treatments must be rated as "expert opinion" at best. Better systemic studies are required to determine the best medical treatment for overflow incontinence. Any medical treatment for overflow incontinence should be compared to catheterization or surgery.

Hormonal Treatment of Urinary Incontinence

Estrogens

Estrogens and the Continence Mechanism

The estrogen-sensitive tissues of the bladder, urethra and pelvic floor all play an important role in the continence mechanism. For women to remain continent the urethral pressure must exceed the intra-vesical pressure at all times except during micturition. The urethra has four estrogen-sensitive functional layers all of which have a role in the maintenance of a positive urethral pressure (1) epithelium, (2) vasculature, (3) connective tissue, (4) muscle.

Two types of estrogen receptor (α and β) have been identified in the trigone of the bladder, urethra, and vagina as well as in the levator ani muscles and fascia and ligaments within the pelvic floor [186, 295, 709]. After the menopause estrogen receptor α has been shown to vary depending upon exogenous estrogen therapy [289]. In addition exogenous estrogens affect the remodeling of collagen in the urogenital tissues resulting in a reduction of the total collagen concentration with a decrease in the cross-linking of collagen in both continent and incontinent women [265, 435]. Studies in both animals and humans have shown that estrogens also increase vascularity in the peri-urethral plexus which can be measured as vascular pulsations on urethral pressure profilometry [259, 641, 790].

Estrogens for Stress Urinary Incontinence

The role of estrogen in the treatment of stress urinary incontinence has been controversial despite a number of reported clinical trials [358]. Some have given promising results but this may have been because they were small observational and not randomized, blinded or controlled. The situation is further complicated by the fact that a number of different types of estrogen have been used with varying doses, routes of administration, and duration of treatment.

Fantl et al. [266] treated 83 hypo-estrogenic women with urodynamic stress incontinence and/or detrusor overactivity with conjugated equine estrogens (CEEs) 0.625 mg and medroxyprogesterone 10 mg cyclically for 3 months. Controls received placebo tablets. At the end of the study period the clinical and quality of life variables had not changed significantly in either group. Jackson et al. [398] treated 57 post-menopausal women with urodynamic stress or mixed incontinence with estradiol 2 mg or placebo daily for 6 months. There was no significant change in objective outcome measures, although both the active and placebo groups reported subjective benefit.

Two meta-analyses of early data have been performed. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee, the use of estrogens to treat all causes of incontinence

in post-menopausal women was examined [267]. Of 166 articles identified, which were published in English between 1969 and 1992, only six were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with urodynamic stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost. Maximum urethral closure pressure increased significantly but this result was influenced by only one study showing a large effect.

In the second meta-analysis Sultana and Walters [734] reviewed eight controlled and 14 uncontrolled prospective trials and included all types of estrogen treatment. They also found that estrogen therapy was not an efficacious treatment for stress urinary incontinence, but may be useful for the often associated symptoms of urgency and frequency. Estrogen when given alone therefore does not appear to be an effective treatment for stress urinary incontinence.

Several studies have shown that estrogen may have a role in combination with other therapies, e.g., α-adrenoceptor agonists. However, phenylpropamalamine (the most widely used α-adrenoceptor agonist in clinical practice) has now been restricted or banned by the FDA.

In a randomized trial Ishiko et al. [393] compared the effects of the combination of PFE and estriol (1 mg/day) in 66 patients with post-menopausal stress urinary incontinence. Efficacy was evaluated every 3 months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate stress incontinent patients in both groups 3 months after the start of therapy and concluded that combination therapy with estriol plus PFE was effective and could be used as first line treatment for mild stress urinary incontinence. Unfortunately this has not been reproduced in other clinical trials.

Thus even prior to the more recently reported secondary analyses of the heart and estrogens/progestogen replacement study (HERS) [320] and Women's Health Initiative (WHI) [349] it was already recognized that estrogen therapy had little effect in the management of urodynamic stress incontinence [13, 637].

Estrogens for Urgency Urinary Incontinence and Overactive Bladder Symptoms

Estrogen has been used to treat post-menopausal urgency and urge incontinence for many years but there have been few controlled trials to confirm that it is of benefit [358]. A double-blind multicenter study of 64 post-menopausal women with "urge syndrome" failed to show efficacy [119]. All women underwent pre-treatment urodynamic investigation to ensure that they had either sensory urgency or detrusor overactivity. They were randomized to treatment with oral estriol 3 mg daily or placebo for 3 months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Estriol produced subjective and objective improvements in urinary symptoms but was not significantly better than placebo.

Another randomized controlled trial from the same group using 25 mg estradiol implants confirmed the previous findings [655], and furthermore found a high complication rate in the estradiol treated patients (vaginal bleeding).

Symptoms of an overactive bladder increase in prevalence with increasing age and LUTS and recurrent urinary tract infections are commonly associated with urogenital atrophy. Whilst the evidence supporting the use of estrogens in LUT dysfunction remains controversial there are considerable data to support their use in urogenital atrophy and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritis and dyspareunia, greater improvement in cytological findings and higher serum estradiol levels [119]. Overall vaginal estradiol has been found to be the most effective in reducing patient symptoms although conjugated estrogens produced the most cytological change and the greatest increase in serum estradiol and estrone. The most recent meta-analysis of intravaginal estrogen treatment in the management of urogenital atrophy was reported by the Cochrane group in 2003 [732]. Overall 16 trials including 2,129 women were included and intravaginal estrogen was found to be superior to placebo in terms of efficacy although there were

no differences between types of formulation. Fourteen trials compared safety between the different vaginal preparations and found a higher risk of endometrial stimulation with CEEs as compared to estradiol.

Thus, theoretically there could be a role for combination treatment with an anti muscarinic agent and vaginal estrogen in post-menopausal women. However, the two clinical trials which have been reported to date differ in their outcome. Tseng et al. [771] showed superior efficacy in terms of symptom improvement for the overactive bladder when tolterodine was used with vaginal estrogen cream as opposed to tolterodine alone. However, Serati et al. [686] found no difference between tolterodine with or without topical estrogen in women with symptomatic detrusor overactivity.

Evidence Regarding Estrogens and Incontinence from Large Clinical Trials

The HERS study included 763 post-menopausal women under the age of 80 years with coronary heart disease (CHD) and intact uteri [320]. It was designed to evaluate the use of estrogen in secondary prevention of cardiac events. In a secondary analysis 1,525 participants who reported at least one episode of incontinence per week at baseline were included. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate (MPA) in one tablet ($N=768$) or placebo ($N=757$) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged or worsened. The results showed that incontinence improved in 26 % of the women assigned to placebo compared to 21 % assigned to hormones whilst 27 % of the placebo group worsened compared with 39 % of the hormone group ($P=0.001$). This difference was evident by 4 months of treatment, for both urgency and stress urinary incontinence. The number of incontinence episodes per week increased an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group ($p<0.001$). The authors concluded that daily oral estrogen plus progestogen therapy was associated with worsening urinary incontinence in older post-menopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.

The WHI was a multicenter double-blind placebo controlled randomized clinical trial of menopausal hormone therapy in 27,347 post-menopausal women age 50–79 years enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23,296 participants at baseline and 1 year [349]. The women were randomized based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg/day of CEE plus 2.5 mg/day of medroxyprogesterone acetate (CEE + MPA), whereas those who had undergone hysterectomy received estrogen alone (CEE). At 1-year hormone therapy was shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline. The risk was highest for stress urinary incontinence CEE + MPA: RR, (1.7 95 % continence interval) CI (1.61–2.18); CEE alone RR 2.15 mg, 95 % CI, 1.77–2.62, followed by mixed urinary incontinence CEE + MPA: RR 1.49 95 % CI 1.10–2.01. On CEE alone RR was 1.79 95 % CI, 1.26–2.53. The combination of CEE and MPA had no significant effect on developing urge urinary incontinence RR, 1.15; 95 % CI, 0.99–1.34 but CEE alone increased the risk RR 1.32; 95 % CI, 1.10–1.58. For those women experiencing urinary incontinence at baseline frequency worsened in both active groups CEE + MPA; RR, 1.38 95 % CI 1.28–1.49; CEE alone: RR, 1.47 95 % CI, 1.35–1.61. Quantity of urinary incontinence worsened at 1 year in both active groups, CEE + MPA: RR, 1.20 95 % CI, 1.06–1.76; CEE alone: RR, 1.59 95 % CI, 1.39–1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities CEE + MPA: RR 1.18 95 % CI, 1.06–1.32. CEE alone: RR 1.29 95 % CI, 1.15–1.45 at 1 year. Thus based on this secondary analysis of data from a huge study CEE alone or in combination with MPA was shown to increase the risk of urinary incontinence amongst continent women and worsen urinary incontinence amongst asymptomatic women after 1 year of therapy.

The Nurses Health Study [329] was a biennial postal questionnaire starting in 1976. In 1996, 39,436 post-menopausal women aged 50–75 years was reported no urinary leakage at the start of the study were followed up for 4 years to identify incident cases of urinary incontinence. Five thousand and sixty cases of occasional and 2,495 cases of frequent incontinence were identified. The risk of developing urinary incontinence was increased among post-menopausal women taking hormones compared to women who had never taken hormones (oral estrogen: RR1.54 95 % CI 1.44, 1.65; transdermal estrogen: RR1.68, 95 % CI 1.41, 2.00; oral estrogen with progestin: RR1.34, 95 % CI 1.24, 1.44; transdermal estrogen with progestin: RR1.46, 95 % CI 1.16, 1.84). After cessation of hormone therapy there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

The most recent meta analysis of the effect of estrogen therapy on the LUT has been performed by the Cochrane Group [175] and is notable as the conclusions are starkly different from those drawn from the previous review [558]. Overall 33 trials were identified including 19,313 incontinent women (1,262 involved in trials of local administration) of which 9,417 received estrogen therapy.

Systemic administration (of unopposed oral estrogens—synthetic and CEEs) resulted in worse incontinence than placebo (RR1.32; 95 % CI: 1.17–1.48). Although this is heavily influenced by the size of the WHI study [349]. When considering combination therapy there was a similar worsening effect on incontinence when compared to placebo (RR1.11; 95 % CO: 1.04–1.08). There was some evidence suggesting that the use of local estrogen therapy may improve incontinence (RR0.74; 95 % CI: 0.64–0.86) and overall there were 1–2 fewer voids in 24 h and less frequency and urgency.

The authors conclude that local estrogen therapy for incontinence may be beneficial although there was little evidence of long-term effect. The evidence would suggest that systemic hormone replacement using CEEs may make incontinence worse. In addition they report that there are too few data to comment reliably on the dose type of estrogen and route of administration.

Other Hormones

Progesterone and progestogens are thought to increase the risk of urinary incontinence. LUTS especially stress urinary incontinence have been reported to increase in the progestogenic phase of the menstrual cycle [359]. In similar studies progesterone has been shown to increase beta adrenergic activity leading to a decrease in the urethral closure pressure in female dogs [630]. However, in the WHI there appeared to be no difference whether or not progestin was given in addition to estrogen [349].

Selective estrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both estrogenic and anti estrogenic effects. In the clinical trials of levormeloxifene there was a fourfold increase in the incidence of incontinence leading to cessation of the clinical trial [350]. However raloxifene has not been shown to have any effect at all on urinary incontinence [794]. There are no reported clinical trials evaluating the effect of androgens, and in particular Testosterone, on urinary incontinence in women.

Conclusions. Estrogen has an important physiological effect on the female LUT and its deficiency is an etiological factor in the pathogenesis of a number of conditions. However the use of estrogen either alone or in combination with progestogen has yielded poor results. The current level 1 evidence against the use of estrogen for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events and therefore the secondary analyses have only been based on self reported symptoms of urinary leakage without any objective data (Table 13.3). Despite this all of these large randomized controlled trials show a worsening of pre-existing urinary incontinence both stress and urgency and an increased new incidence of urinary incontinence with both estrogen and estrogen plus progestogen.

Table 13.3 ICI assessments 2008: Oxford guidelines (modified)

Levels of evidence
Level 1: Systematic reviews, meta-analyses, good quality randomized
controlled clinical trials (RCTs)
Level 2: RCTs, good quality prospective cohort studies
Level 3: Case–control studies, case series
Level 4: Expert opinion
Grades of recommendation
Grade A: Based on level 1 evidence (highly recommended)
Grade B: Consistent level 2 or 3 evidence (recommended)
Grade C: Level 4 studies or "majority evidence" (optional)
Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

However, the majority of subjects in all of these studies were taking combined equine estrogen and this may not be representative of all estrogens taken by all routes of administration.

In a systematic review of the effects of estrogens for symptoms suggestive of an overactive bladder the conclusion was that estrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration [124, 125]. It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency and urge incontinence may be a manifestation of urogenital atrophy in older post-menopausal women rather than a direct effect on the LUT [637]. Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal estrogen therapy there is currently no evidence that estrogens with or without progestogens should be used in the treatment of urinary incontinence.

Desmopressin

The endogenous hormone vasopressin (also known as anti-diuretic hormone) has two main functions: it causes contraction of vascular smooth muscle and stimulates water reabsorption in the renal medulla. These functions are mediated by two specific vasopressin receptors of which there are two major subtypes, namely the V_1 and V_2 receptors. The V_2 subtype is particularly important for the anti-diuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to central diabetes insipidus, and genetic defects in the gene encoding the V_2 receptor can cause nephrogenic diabetes insipidus [390]. Accordingly, decreased vasopressin levels are believed to be important in the pathophysiology of polyuria, specifically nocturnal polyuria, which can lead to symptoms such as nocturia [532, 813]. Nocturia is currently defined by the ICS as the complaint that an individual has to wake at night one or more times to void. It is, however, "an underreported, understudied, and infrequently recognized problem in adults" [812]. Nocturia leads to decreased quality of life [473], and has been associated with both increased morbidity and mortality [474, 574]. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioral factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist. While it remains largely unknown in what fraction of patients nocturia is explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioral factors that can explain it (e.g., excessive fluid intake) is usually considered to indicate decreased vasopressin levels [100, 812]. Based upon these considerations, vasopressin receptor agonists have been used to treat nocturia, both in children and in adults. Desmopressin is the most common vasopressin analogue used to treat nocturia. Desmopressin shows selectivity for anti-diuretic over vasopressor effects. It has a more powerful and longer-lasting antidiuretic action than vasopressin. It is available in formulations for oral, parenteral, and nasal administration. It has a fast onset of action, with urine production decreasing within 30 min of oral administration [636]. Because of symptomatic hyponatremia with water intoxication which is the only SAE reported in children,

occurred after intranasal or intravenous administration of desmopressin [642, 759, 778], the FDA and the European Medicines Agency (EMA) removed the indication for the treatment of primary nocturnal enuresis from all intranasal preparations of desmopressin. An oral lyophilisate (MELT) formulation requiring no concomitant fluid intake is currently available. In a recent open-label, randomized, cross-over study, desmopressin MELT was shown to have similar levels of efficacy and safety at lower doses than the tablet formulation of desmopressin in children. A recent study confirmed the superior pharmacodynamic characteristics of desmopressin MELT to desmopressin tablets [204].

The use of desmopressin in children with nocturnal enuresis was comprehensively reviewed by the Cochrane Collaboration in 2002 [310]. These authors evaluated 47 randomized controlled trials involving 3,448 children, of whom 2,210 received desmopressin. According to their analysis, desmopressin was effective relative to placebo in reducing bed-wetting e.g., a dose of 20 μg resulted in a reduction of 1.34 wets/night (95 % CI 1.11; 1.57), and children were more likely to become dry with desmopressin (98 %) than with placebo (81 %). However, there was no difference between desmopressin and placebo after discontinuation of treatment, indicating that desmopressin suppresses symptom enuresis but does not cure the underlying cause. Additionally, not all children responded sufficiently to desmopressin monotherapy. The combination of desmopressin and an enuresis alarm resulted in a greatly improved short-term success rate and decreased relapse rates [18]. The combination of desmopressin and antimuscarinics resulted in better short- and long-term success rates as well as a lower relapse rate than desmopressin alone [17, 69]. For non-responders to desmopressin, replacement of desmopressin with other medications such as tricyclic antidepressants or loop diuretics could be of benefit, whereas muscarinic receptor antagonists may be ineffective in such children [205, 576].

Other studies have explored a possible treatment role for desmopressin in the treatment of nocturia in adults. A search for these studies in Medline using the terms “desmopressin” and “nocturia” was performed and limited to clinical studies of de novo nocturia, i.e., those that excluded subjects in whom childhood enuresis persisted into adulthood. Several previous studies investigated the use of desmopressin for the treatment of nocturia in the context of multiple sclerosis [250, 251]. One study with single dose administration reported a reduction in nocturnal polyuria, but by design did not assess nocturia [250]. Three placebo-controlled double-blind studies with a small patient number (16–33 patients total per study) reported a significant reduction in nocturia [251, 363, 777]. Other controlled studies of similar size, most with a cross-over design, used micturition frequency within the first 6 h after desmopressin administration rather than nocturia as their primary endpoint. These studies consistently reported that desmopressin treatment for up to 2 weeks was efficacious [282, 372, 453]. While desmopressin treatment was generally well tolerated, 4 of 17 patients in one study discontinued treatment due to asymptomatic or minimally symptomatic hyponatremia [777]. Accordingly, desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients [197]. In a small open-label study, desmopressin was also reported to reduce nocturnal polyuria in SCI patients [841].

Further studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurological damage. The recruited patient populations were based upon different criteria, including having at least two nocturia episodes per night or having nocturnal polyuria. Earlier studies mostly used a desmopressin dose of 20 μg given either orally [66] or intranasally [115, 364] and tended to be very small (≤25 patients). Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1,003 screened patients, and higher oral doses (0.1–0.4 mg) were administered for a period of 3 weeks of double-blind treatment in adults [497, 498, 533, 782]. A total of 632 patients entered the dose-titration phase and 422 patients the double-blind phase of the three NOCTUPUS trials. To counter the argument that the study was performed in desmopressin responders after the

dose titration phase, all patients in the NOCTUPUS trials were washed out following the dose-titration phase, and in order to be randomized, it was a requirement that the patients returned to baseline nocturnal diuresis before inclusion in the double-blind phase. The trials showed that oral desmopressin (0.1, 0.2 or 0.4 mg) is effective in both men and women aged ≥18 years with nocturia. The number of nocturnal voids decreased from 3 to 1.7 in the desmopressin group compared to 3.2 to 2.7 in the placebo group. In women, the number of nocturnal voids in the desmopressin group decreased from 2.92 to 1.61, whereas that in the placebo group decreased from 2.91 to 2.36. When clinical response was defined as ≥50 % reduction in nocturnal voids from baseline, 34 % of men experienced clinical response with desmopressin, compared with 3 % of men who received placebo. In women, 46 % of desmopressin-treated patients experienced a clinical response, compared with 7 % of patients on placebo.

The efficacy of desmopressin for the treatment of nocturia was confirmed in a long-term (10–12 months) open-label study involving 249 patients, which was an extension of the randomized studies in known desmopressin responders. However, a rebound effect was seen when treatment was withdrawn, confirming the association between continued treatment and response [498]. An open-label pilot study in a nursing home setting also reported that desmopressin had beneficial effects [402].

Around 75 % of community-dwelling men and women with nocturia (≥2 voids/night) have nocturnal polyuria (NP) [633, 739]. The key urological factors most relevant to nocturia are NP and OABs in women [391], and NP and BPH in men. About 74 % of women with OABs have nocturia and 62 % of patients with OABs and nocturia have NP. Among men with nocturia, 83 % have NP, 20 % have NP alone, and 63 % have NP in combination with another factor such as a small nocturnal bladder capacity or bladder outlet obstruction [143]. Therefore, desmopressin combination therapy with α_1-AR antagonists and/or antimuscarinics should be considered for patients with treatment-resistant nocturia. Seventy-three percent of α_1-AR antagonist-resistant BPH patients experienced a ≥50 % reduction in nocturnal voids with oral desmopressin [633, 833]. A randomized, double-blind, placebo-controlled study evaluating the long-term (1, 3, 6, and 12 months) efficacy and safety of low-dose (0.1 mg) oral desmopressin in elderly (≥65 years) patients reported that low-dose oral desmopressin led to a significant reduction in the number of nocturnal voids and nocturnal urine volume in patients with BPH [803].

Because nocturia can be caused by different factors, several studies have investigated whether desmopressin may be beneficial in patients with other symptoms in addition to nocturia. In a small, non-randomized pilot study of men believed to have BPH, desmopressin was reported to improve not only nocturia, but also to reduce the overall IPSS [136]. An exploratory, placebo-controlled double-blind study in women with daytime urinary incontinence reported that intranasal administration of 40 μg desmopressin increased the number of leakage-free episodes 4 h after drug administration [639]. One double-blind, placebo-controlled pilot study in patients with OABs treated with 0.2 mg oral desmopressin reported a reduction in voids along with an improvement in quality of life (QoL) [346]. While these data indicate that desmopressin may be effective in treating voiding dysfunction not limited to nocturia, they are too sparse to allow treatment recommendations.

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL. However, one of the main clinically important side effects of demopressin usage is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death. Hyponatremia usually occurs soon after treatment is initiated. The risk of hyponatremia appears to increase with age, cardiac disease, and increasing 24-h urine volume [633]. Based on a meta-analysis, the incidence is around

7.6 % [805]. Increased age and female gender are well-known risk factors for the development of desmopressin-induced hyponatremia. Bae et al. [72] assessed the effects of long-term oral desmopressin on serum sodium and baseline antidiuretic hormone secretion in 15 elderly male patients with severe nocturia (greater than 3 voids nightly), who did not show hyponatremia within 7 days of administration of 0.2 mg desmopressin. Desmopressin (0.2 mg) was administered orally nightly for 1 year. Before and 1 month after the 1-year medication 24-h circadian studies were performed to monitor changes in antidiuretic hormone. Every 3 months during the 1-year medication, serum changes and timed urine chemistry were monitored. The results showed that long-term desmopressin administration gradually decreased serum sodium and induced statistically, but not clinically significant, hyponatremia after 6 months of treatment. Administration of desmopressin for 1 year did not affect baseline antidiuretic hormone secretion. The authors recommended that for long-term desmopressin administration serum sodium should be assessed regularly, at least every 6 months.

Little focus has been on exploring gender differences in the antidiuretic response to desmopressin. Juul et al. [410] found an increasing incidence of hyponatremia with increasing dose, and at the highest dose level of 100 μg, decreases in serum sodium were approximately twofold greater in women over 50 year of age than in men. A new dose recommendation stratified by gender was suggested in the treatment of nocturia: for men, 50- to 100 μg melt was suggested to be an efficacious and safe dose, while for women a dose of 25 μg melt was recommended as efficacious with no observed incidences of hyponatremia. Initiation of desmopressin is currently not indicated for patients aged ≥65 years. The mechanisms behind desmopressin-induced hyponatraemia are well understood, and serum sodium monitoring at baseline and early during treatment of older patients for whom treatment with desmopressin is indicated can greatly reduce their risk of developing the condition. Other advice regarding treatment administration, such as restriction of evening fluid intake and adherence to recommended dosing, should be followed to minimize the risk of hyponatremia [784].

Desmopressin is useful for patients with nocturia as well as for children with nocturnal enuresis. The drug has been proven to be well-tolerated and effective by several randomized, placebo-controlled trials and is recommended as a first-line treatment (either as monotherapy or in combination with other agents) for patients who have been appropriately evaluated and whose nocturia is related to NP, whether or not this is accompanied by BPH or OABs. For assessment, see Table 13.1.

Appendix

Antimuscarinics with "Specific" Action

Below data on the different antimuscarinics are presented. These drugs are assumed to block only muscarinic receptors (motivating the term "specific"). The amount of information for the individual drugs varies, and so does the degree of details from the different studies presented. However, the information has been chosen to give a reasonable efficacy and adverse effect profile of each individual drug.

Atropine Sulfate

Atropine (DL-hyoscyamine) is rarely used for treatment of OABs/DO because of its systemic side effects, which preclude its use as an oral treatment. However, in patients with neurogenic DO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [212, 253, 260, 264, 314]. It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with neurogenic DO [264].

The pharmacologically active antimuscarinic component of atropine is L-hyoscyamine. Although still used, few clinical studies are available to evaluate the antimuscarinic activity of L-hyoscyamine sulfate [571]. For assessment, see Table 13.1.

Darifenacin Hydrobromide

Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolized in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6, the latter saturating within the therapeutic range [704]. UK-148,993, UK-73,689, and UK-88862 are the three main circulating darifenacin metabolites of which only UK-148,993 is said to have significant antimuscarinic activity. However, available information suggests that various metabolites of darifenacin contribute little to its clinical effects [549]. The metabolism of darifenacin by CYP3A4 suggests that co-administration of a potent inhibitor of this enzyme (e.g., ketoconazole) may lead to an increase in the circulating concentration of darifenacin [441].

Darifenacin is a relatively selective muscarinic M_3 receptor antagonist. In vitro, it is selective for human cloned muscarinic M_3 receptors relative to M_1, M_2, M_4, or M_5 receptors. Theoretically, drugs with selectivity for the M_3 receptor can be expected to have clinical efficacy in OABs/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes [27]. However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg/day. The clinical effectiveness of the drug has been documented in several RCTs [6, 122, 138, 140, 148, 150, 152, 154, 161, 163, 248, 274, 338, 339, 361, 721, 848; for reviews, see 153, 162, 334, 594, 844]. Haab et al. [339] reported a multicenter, double-blind, placebo-controlled, parallel-group study which enrolled 561 patients (19–88 years; 85 % female) with OAB symptoms for more than 6 months and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were randomized (1:4:2:3) to once-daily oral darifenacin controlled-release tablets: 3.75 mg ($n=53$), 7.5 mg ($n=229$), or 15 mg ($n=115$) or matching placebo ($n=164$) for 12 weeks. Patients recorded daily incontinence episodes, micturition frequency, bladder capacity (MVV), frequency of urgency, severity of urgency, incontinence episodes resulting in change of clothing or pads and nocturnal awakenings due to OABs using an electronic diary during weeks 2, 6, and 12 (directly preceding clinic visits). Tolerability data were evaluated from adverse event reports. Darifenacin 7.5 and 15 mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). Darifenacin 7.5 mg and 15 mg, respectively, were significantly superior to placebo for (median) improvements in micturition frequency (7.5 mg: −1.6; 15 mg: −1.7; placebo −0.8), frequency of urgency per day (−2.0; −2.0; −0.9) and number of incontinence episodes leading to a change in clothing or pads (−4.0; −4.7; −2.0). There was no significant reduction in nocturnal awakenings due to OABs. The most common adverse events were mild-to-moderate dry mouth and constipation with a CNS and cardiac safety profile comparable to placebo. No patients withdrew from the study as a result of dry mouth and discontinuation related to constipation was rare (0.6 % placebo vs. 0.9 % darifenacin).

In a dose titration study on 395 OABs patients, darifenacin, allowing individualized dosing (7.5 or 15 mg), was found to be effective and well-tolerated [721]. A 2-year open label extension study of these investigations (i.e., [339, 721]) confirmed a favorable efficacy, tolerability, and safety profile [338].

A review of the pooled darifenacin data from the three phase III, multicenter, double-blind clinical trials in patients with OABs was reported by Chapple et al. [152, 154, 161]. After a 4-week washout/run-in period, 1,059 adults (85 % female) with symptoms of OAB (urgency incontinence, urgency, and frequency) for at least 6 months were randomized to once-daily oral treatment with darifenacin: 7.5 mg ($n=337$) or 15 mg ($n=334$) or matching placebo ($n=388$) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence

episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates, and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, −8.8 [−68.4 %; placebo −54 %, $P<004$]; 15 mg, −10.6 [−76.8 %; placebo 58 %, $p<0.001$]). Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg 0.6 % of patients; darifenacin 15 mg 2.1 %; placebo 0.3 %). The incidences of CNS and cardiovascular adverse events were comparable to placebo. The results were confirmed in other RCTs, including also a pooled analysis of three phase III studies in older patients (≥65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability, and safety profile [274, 361, 849].

The time-to-effect with darifenacin was analyzed in a pooled analysis of efficacy and safety data from 1,059 patients participating in three double-blind 12-week studies [447]. Darifenacin significantly improved all OAB symptoms as early as 6–8 days.

One of the most noticeable clinical effects of antimuscarinics is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin, on the "warning time" associated with urinary urgency. Warning time was defined as the time from the first sensation of urgency to the time of voluntary micturition or incontinence. This was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks' washout, 2 weeks' medication-free run-in, and a 2-week treatment phase [122]. Warning time was defined as the time from the first sensation of urgency to voluntary micturition or incontinence and was recorded via an electronic event recorder at baseline (visit 3) and study end (visit 4) during a 6-h clinic-based monitoring period, with the subject instructed to delay micturition for as long as possible. During each monitoring period, up to three urgency-void cycles were recorded. Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant ($p<0.004$) increase in mean warning time with a median increase of 4.3 min compared with placebo (darifenacin group from 4.4 to 1.8 min; placebo from 7.0 to −1.0 min). Overall, 47 % of darifenacin-treated subjects compared with 20 % receiving placebo achieved a 30 % increase in mean warning time. There were methodological problems associated with this study; it utilized a dose of 30 mg (higher than the dose recommended for clinical use), the treatment period was short, it was conducted in a clinical-centered environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. In another warning time study [848] on 445 OABs patients, darifenacin treatment (15 mg) resulted in numerical increases in warning time; however, these were not significant compared to placebo.

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements on health-related quality of life (HRQoL) in patients with OABs [6], and such improvements were sustained as shown in a 2-year extension study [248]. It was shown that neither the positive effects on micturition variables, nor on HRQoL produced by darifenacin (7.5 and 15 mg) were further enhanced by a behavioral modification program including timed voiding, dietary modifications, and Kegel exercises [138, 140].

Since darifenacin is a substrate for the P-glycoprotein drug efflux transporter [142, 555], which is present both in the blood–brain and blood-ocular barriers, several clinical studies have been devoted to investigate possible effect

of darifenacin on cognition. Neither in healthy volunteers (19–44 years) and healthy subjects (≥60 years), nor in volunteers 65 years or older could any effect of darifenacin (3.75–15 mg daily) be demonstrated, compared to placebo [142, 432–434, 491].

To study whether darifenacin had any effect on QT/QTc intervals, Serra et al. [688] performed a 7-day, randomized, parallel-group study ($n=188$) in healthy volunteers receiving once-daily darifenacin at steady-state therapeutic (15 mg) and supratherapeutic (75 mg) doses, alongside controls receiving placebo or moxifloxacin (positive control, 400 mg) once daily. No significant increase in QTcF interval could be demonstrated compared with placebo. Mean changes from baseline at pharmacokinetic T_{max} vs. placebo were −0.4 and −2.2 ms in the darifenacin 15 mg and 75 mg groups, respectively, compared with +11.6 ms in the moxifloxacin group ($P<0.01$). The conclusion was that darifenacin does not prolong the QT/QTc interval.

Darifenacin 15 mg/day given to healthy volunteers did not change heart rate significantly compared to placebo [604].

Assessment. Darifenacin has a well-documented beneficial effect in OABs/DO (Table 13.1), and tolerability and safety seem acceptable.

Fesoterodine Fumarate

Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases [511, 548]. This compound, which is chemically identical to the 5-hydroxy metabolite of tolterodine, is a non-subtype selective muscarinic receptor antagonist [577]. All of the effects of fesoterodine in man are thought to be mediated via 5-HMT, since the parent compound remains undetectable upon oral dosing. 5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism. Since the renal clearance of 5-HMT is about 250 mL/min, with >15 % of the administered fesoterodine dose excreted as unchanged 5-HM, this raises the possibility that 5-HMT also could work from the luminal side of the bladder [548]. The bioavailability of fesoterodine, averaging 52 %, was independent of food intake and the drug may be taken with or without a meal [514]. Peak plasma concentration of 5-HMT is reached at 5 h following oral administration and has a half-life of 7–9 h [513]. The suggested starting dose, 4 mg/day, can be used in patients with moderately impaired renal or hepatic function due to the combination of renal excretion and hepatic metabolism of 5-HMT [207, 510].

The clinical efficacy and tolerability of fesoterodine have been documented in several RCTs [148, 150, 163, 226, 232, 233, 357, 421, 425, 586, 588; see 216]. In a multicenter, double-blind, double-dummy RCT with tolterodine ER, 1,132 patients were enrolled and received treatment [148, 150, 163]. The trial showed that both the 4 and 8 mg doses of fesoterodine were effective in improving symptoms of OAB, with the 8 mg dose having a greater effect at the expense of a higher rate of dry mouth. There appeared to be little difference between fesoterodine 4 mg and tolterodine ER. Only one subject from the fesoterodine 8 mg group and one subject from the tolterodine ER group withdrew from the study due to dry mouth. The dose–response relationship was confirmed in another study that pooled data from two phase III RCTs [448]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and urge UI as recorded by 3-day bladder diary, offering the possibility of dose titration.

A head-to-head placebo controlled trial has been completed comparing fesoterodine 8 mg to tolterodine-extended release 4 mg and placebo [357]. The study randomized 1,590 patients to assess the primary outcome of reduced urgency incontinence episodes at 12 weeks. Fesoterodine produced statistically significant improvements in urgency incontinence episodes, complete dry rates (64.0 % vs. 57.2 %, $p=0.015$), mean voided volume per void (+32.9 mL vs. +23.5 mL, $p=0.005$), and in patients' assessments of bladder-related problems as measured by OABs questionnaire (except sleep domain), Patient Perception of Bladder Condition (40 % vs. 33 % with >2 point improvement, $p<0.001$), and

Urgency Perception Scale (46 % vs. 40 % with improvement, $p=0.014$) compared with tolterodine. The clinical significance of these statistically significant findings is questionable as there was no difference between agents with respect to number of micturitions, urgency episodes, and frequency-urgency sum per 24 h. The improved efficacy of fesoterodine came at the cost of greater dry mouth (27.8 % vs. 16.4 %), headache (5.6 % vs. 3.4 %), constipation (5.4 % vs. 4.1 %), and withdrawal rates (6 % vs. 4 %). Nonetheless, this first head-to-head trial comparing two drugs in class supports the use of fesoterodine 8 mg for additional benefit over tolterodine ER 4 mg.

Wyndaele et al. [821] reported the first flexible-dose open-label fesoterodine trial, which was conducted at 80 different centers worldwide and comprised 516 participants (men and women) >18 years who self-reported OAB symptoms for at least 3 months before screening and had been treated with either tolterodine or tolterodine ER within 2 years without symptom improvement. Approximately 50 % opted for dose escalation to 8 mg at week 4. Significant improvements from baseline to week 12 were observed in micturitions, urgency urinary incontinence episodes, micturition-related urgency episodes, and severe micturition-related urgency episodes per 24 h. Significant improvements from baseline were observed in QoL parameters. Dry mouth (23 %) and constipation (5 %) were the most common adverse events; no safety issues were identified.

The largest double-blind, double-dummy, flexible-dose fesoterodine RCT, which was conducted at 210 different centers with a total of 2,417 patients enrolled, was performed by Kaplan et al. [421]. All patients were healthy, >18 years of age, and self-reported OAB symptoms for at least 3 months. The 960 patients who received fesoterodine 8 mg showed significantly greater mean improvements at week 12 in most efficacy parameters (diary variables) than those receiving either tolterodine ER or placebo; UUI and urgency episodes, micturition frequency, and MVV. No statistically significant changes were shown in reduction of nocturnal micturitions compared with the tolterodine group, whereas when comparing the mean changes in nighttime micturition with the placebo group a significant difference was found. This phase III study confirmed the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for improving UUI and urgency episodes and 24-h micturitions but not for MVV and nocturia. In another RCT of flexible-dose fesoterodine, Dmchowski et al. reported statistically significant improvements at week 12 in the mean number of micturition per 24 h and in both UUI and urgency episodes. Between groups, difference in nocturnal micturition was not statistically significant.

Nitti et al. [588] determined whether the presence of DO in patients with OABs and urgency urinary incontinence was a predictor of the response to treatment with fesoterodine in a phase 2 randomized, multicenter, placebo-controlled trial. They concluded that regardless of the presence of DO, the response to fesoterodine treatment was dose-proportional and associated with significant improvements in OAB symptoms, indicating that *the response to OABs pharmacotherapy in patients with UUI was independent of the urodynamic diagnosis of DO*.

Kelleher et al. [439] evaluated the effect of fesoterodine on HRQoL in patients with OAB syndrome. Pooled data from two randomized placebo-controlled phase III studies [148, 150, 163, 586] were analyzed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolterodine-extended release (tolterodine-ER) 4 mg. By the end of treatment, all active-treatment groups had significantly improved HRQoL compared with those on placebo. In a post hoc analysis of data pooled from these studies, significant improvements in all KHQ domains, ICIQ-SF scores, and bladder-related problems were observed at months 12 and 24 compared to open label baseline [438]. The authors concluded that treatment satisfaction was high throughout the open-label treatment regardless of gender and age.

Malhotra et al. [515] performed a thorough QT study to investigate the effects of fesoterodine on cardiac repolarization in a parallel-group study. Subjects were randomly assigned to receive double-blind fesoterodine 4 mg, fesoterodine 28 mg, or placebo or open-label moxifloxacin 400 mg

(positive control) for 3 days. ECGs were obtained on Days −1 (baseline), 1, and 3. The primary analysis was the time-averaged changes from baseline for Fridericia's-corrected QT interval (QTcF) on Day 3. Among 261 subjects randomized to fesoterodine 4 mg ($n=64$), fesoterodine 28 mg ($n=68$), placebo ($n=65$), or moxifloxacin 400 mg ($n=64$), 256 completed the trial. The results indicated that fesoterodine is not associated with QTc prolongation or other ECG abnormalities at either therapeutic or supratherapeutic doses.

Assessment. Fesoterodine has a well-documented beneficial effect in OABs (Table 13.1), and the adverse event profile seems acceptable.

Imidafenacin

Imidafenacin(KRP-197/ONO-8025,4-(2-methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide) is an antagonist for the muscarinic ACh receptor with higher affinities for M_3 and M_1 receptors than for the M_2 receptor. Metabolites of imidafenacin (M-2, M-4, and M-9) had low affinities for muscarinic ACh receptor subtypes [458]. The drug blocks pre- as well as postjunctional muscarinic receptors and was shown to block both detrusor contractions and acetylcholine release [570]. The receptor-binding affinity of imidafenacin in vitro was found to be significantly lower in the bladder than submaxillary gland or colon [823], and in rats orally administered imidafenacin distributes predominantly to the bladder and exerts more selective and longer-lasting effect here than on other tissues. Whether this can be translated to the human situation has to be established before claims of clinical bladder selectivity can be made.

Imidafenacin is well absorbed from the gastrointestinal tract and its absolute bioavailability in human is 57.8 % [601, 602]. It is rapidly absorbed with maximum plasma concentration occurring 1–3 h after oral administration [602]. Metabolites in the plasma are produced mainly by first-pass effects. The major enzymes responsible for the metabolism of the drug are CYP3A4 and UGT1A4. The oxidative metabolism is reduced by concomitant administration of CYP3A4 inhibitors. In contrast, imidafenacin and its metabolites have no inhibitory effect on the CYP-mediated metabolism of concomitant drugs [418].

Kitagawa et al. [455] reported that the subjective efficacy of imidafenacin was observed from 3 days after the commencement of administration and that mean total overactive bladder symptom score (OABSS) decreased gradually during 2 weeks after administration.

A randomized, double-blind, placebo-controlled phase II dose-finding study in Japanese OABs patients was performed to evaluate the efficacy, safety/tolerability, and dose–response relationship of imidafenacin [371]. Overall, 401 patients were enrolled and randomized for treatment with 0.1 mg of imidafenacin/day (99 patients), 0.2 mg of imidafenacin/day (100), 0.5 mg of imidafenacin/day (101), or a placebo (101). After 12 weeks of treatment, the number of incontinence episodes was reduced in a dose-dependent manner, and a significant difference between the imidafenacin treatment and the placebo was observed ($P<0.0001$). Compared with the placebo, imidafenacin caused significant reductions in urgency incontinence, voiding frequency, and urinary urgency, and a significant increase in the urine volume voided per micturition. Imidafenacin was also well tolerated. The incidence of dry mouth in the imidafenacin groups increased dose-dependently. Even though the percentage of patients receiving 0.5 mg/day who discontinued treatment due to dry mouth was high (8.9 %), the percentages in the 0.1 and 0.2 mg/day groups (1.0 % and 0.0 %, respectively) were comparable with that in the placebo group (0.0 %).

A randomized, double-blind, placebo- and propiverine-controlled trial of 781 Japanese patients with OAB symptoms was conducted by Homma et al. [370]. They were randomized to imidafenacin (324), propiverine (310), or a placebo (147). After 12 weeks of treatment, a significantly larger reduction in the mean number of incontinence episodes was observed in the imidafenacin group than in the placebo group ($P<0.0001$). The non-inferiority of imidafenacin compared with propiverine was confirmed for the reduction in using incontinence episodes ($P=0.0014$, non-inferiority margin: 14.5 %).

Imidafenacin was well tolerated. The incidence of adverse events with imidafenacin was significantly lower than with propiverine ($P=0.0101$). Dry mouth, the most common adverse event, was significantly more common in the propiverine group than in the imidafenacin group. There were no significant increases in either the imidafenacin or placebo group in the mean QTc interval, whereas there was a significant increase in the mean QTc interval in the propiverine group ($P<0.0001$). However, there were no clinical arrhythmia and clinical arrhythmic events in any of the treatment groups.

The long-term safety, tolerability, and efficacy of imidafenacin were studied in Japanese OABs patients [370], of whom 478 received treatment and 376 completed a 52-week program. Imidafenacin was well tolerated, the most common adverse event being a dry mouth (40.2 % of the patients). Long-term treatment did not produce an increase in the frequency of adverse events compared with short-term treatment. A significant efficacy of the drug was observed from week 4 through week 52. After 52 weeks, imidafenacin produced mean changes from baseline in the number of incontinence episodes (−83.51 %), urgency incontinence episodes (−84.21 %), voiding frequency (−2.35 micturitions/day), urgency episodes (−70.53 %), and volume voided per micturition (28.99 mL). There were also significant reductions from baseline in all domains of the King's Health Questionnaire. Imidafenacin had no significant effects on the corrected QT interval, vital signs, results from laboratory tests, or post-void residual volume.

A 52-week prospective, open randomized comparative study to evaluate the efficacy and tolerability of imidafenacin (0.2 mg/day) and solifenacin (5 mg/day) was conducted in a total of 41 Japanese patients with untreated OABs [842]. They were randomly assigned to imidafenacin and solifenacin groups. There was no difference in OABSS and KHQ scores between the two groups, but the severity and incidence of adverse events caused by the drugs showed increased differences between the groups with time. The severity of dry mouth and the incidence of constipation were significantly lower in the imidafenacin group ($P=0.0092$ and $P=0.0013$, respectively). An important limitation of this study is the low number of patients. Only 25 patients (17 males, 8 females) were available for long-term analysis.

Assessment. Imidafenacin seems to be effective and to have an acceptable tolerability. However, the documentation is relatively scarce and the drug is not yet available in the Western countries.

Propantheline Bromide

Propantheline is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes, which has a low (5–10 %) and individually varying biological availability. It is metabolized (metabolites inactive) and has a short half-life (less than 2 h) [82]. It is usually given in a dose of 15–30 mg four times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher dosages are required. Using this approach in 26 patients with detrusor overactivity contractions [94] in an open study obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline 15 mg four times daily. The range of dosages varied from 7.5 to 60 mg four times daily. In contrast, Thüroff et al. [760] comparing the effects of oxybutynin 5 mg three times daily, propantheline 15 mg three times daily, and placebo in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency, and incontinence related to DO (154 patients) found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic DO), and with dose titration, Holmes et al. [368] found no differences in efficacy between oxybutynin and propantheline. Controlled randomized trials ($n=6$) reviewed by Thüroff et al. [761] confirmed a positive, but varying, response to the drug.

Assessment. Although the effect of propantheline on OABs/DO has not been well documented in controlled trials satisfying standards of today, it can be considered effective, and may, in individually titrated doses, be clinically useful (Table 13.1). No new studies on the use of this drug for treatment

of OABs/DO seem to have been performed during the last decade.

Solifenacin Succinate

Solifenacin succinate (YM905) is a tertiary amine and well absorbed from the gastrointestinal tract (absolute bioavailability 90 %). The mean terminal half-life is 45–68 h [465, 710, 711]. It undergoes significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg), C_{max} and $AUC_{0\text{-inf}}$ were increased by only approximately 40 % and 56 %, respectively [737]. Solifenacin has a modest selectivity for M3 over M2 (and M1) receptors [2]. Supporting an effect on sensory function by solifenacin, 15 women with DO receiving 10 mg/day of the drug showed an increase in the area under the bladder-volume sensation curve [501]. Solifenacin also increased maximum bladder capacity, a finding in agreement with other studies [374, 751].

Two large-scale phase 2 trials with parallel designs, comprising men and women, were performed [146, 708]. The first dose-ranging study evaluated solifenacin 2.5, 5, 10, and 20 mg and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO [146]. Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Inclusion criteria for this and subsequent phase 3 studies of patients with OABs included at least 8 micturitions/24 h and either one episode of incontinence or one episode of urgency daily as recorded in 3-day micturition diaries. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg (−2.21), 10 mg (−2.47), and 20 mg (−2.75), but not in patients receiving placebo (−1.03) or tolterodine (−1.79). This effect was rapid with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, there were numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations due to adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. As the 5 and 10 mg doses caused lower rates of dry mouth than tolterodine, and superior efficacy outcomes relative to placebo, these dosing strengths were selected for further evaluation in large-scale phase 3 studies.

The second dose-ranging study of solifenacin 2.5–20 mg was carried out in the United States (USA) [708]. This trial included 261 evaluable men and women receiving solifenacin or placebo for 4 weeks followed by a 2-week follow-up period. Micturition frequency was statistically significantly reduced relative to placebo in patients receiving 10 and 20 mg solifenacin. The number of micturitions per 24 h showed reductions by day 7 and continued to decrease through day 28; day 7 was the earliest time point tested in solifenacin trials and these findings demonstrate efficacy as early as 1 week. The 5, 10, and 20 mg dosing groups experienced statistically significant increases in volume voided; the 10 mg solifenacin dose was associated with statistically significant reductions in episodes of incontinence.

In one of the early RCTs, a total of 1,077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg twice daily), or placebo [160]. It should be noted that this study was powered only to compare active treatments to placebo. Compared with placebo (−8 %), mean micturitions/24 h were significantly reduced with solifenacin 10 mg (−20 %), solifenacin 5 mg (−17 %), and tolterodine (−15 %). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9 % with placebo, 14.0 % with solifenacin 5 mg, 21.3 % with solifenacin 10 mg, and 18.6 % with tolterodine 2 mg twice daily.

Cardozo et al. [124, 125] randomized 911 patients to 12-week once daily treatment with solifenacin 5 mg, solifenacin 10 mg or placebo. The primary efficacy variable was change from baseline to study endpoint in mean number of micturitions per 24 h. Secondary efficacy variables included changes from baseline in mean number of urgency, nocturia, and incontinence episodes per 24 h, and MVV per micturition. Compared with changes obtained with placebo (−1.6), the number of micturitions per 24 h was

statistically significantly decreased with solifenacin 5 mg (−2.37) and 10 mg (−2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg: −1.63, 61 %; 10 mg: −1.57, 52 %), but not with placebo (−1.25, 28 %). Of patients reporting incontinence at baseline, 50 % achieved continence after treatment with solifenacin (based on a 3-day micturition diary, placebo responses not given). Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg vs. placebo. Episodes of urgency and MVV per micturition were statistically significantly reduced with solifenacin 5 and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7 % of patients receiving solifenacin 5 mg and 23 % receiving solifenacin 10 mg (vs. 2.3 % with placebo). A 40-week follow-up of these studies (i.e., [124, 125, 160]) demonstrated that the favorable profile, both in terms of efficacy and tolerability, was maintained over the study period [337].

The STAR trial [148, 150, 152, 154, 161, 163] was a prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study which was conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and TOLT-ER 4 mg once daily in OABs patients. The primary effect variable was micturition frequency. After 4 weeks of treatment patients had the option to request a dose increase, but were dummied throughout as approved product labeling only allowed an increase for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was "non-inferior" to tolterodine concerning the primary effect variable, micturition frequency. However, solifenacin showed significant greater efficacy to tolterodine in decreasing urgency episodes (−2.85 vs. −2.42), incontinence (−1.60 vs. −0.83), urgency incontinence (−1.42 vs. −0.83), and pad usage (−1.72 vs. −1.19). More solifenacin-treated patients became continent by study endpoint (59 vs. 49 %) and reported improvements in perception of bladder condition (−1.51 vs. −1.33) assessments. However, this was accompanied by an adverse event incidence which was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild + moderate + severe) were the most common (solifenacin 30 and 6.4 %, tolterodine 23 and 2.5 %). The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low (5.9 and 7.3 %) in both groups.

Luo et al. (2012) performed a systematic review and meta-analysis of solifenacin RCTs and provided a comprehensive assessment regarding the efficacy and safety of the drug. Their results which largely confirmed what could be deduced from previously published information indicated that solifenacin could significantly decrease the number of urgency episodes per 24 h, micturitions per 24 h, incontinence episodes per 24 h, nighttime micturitions per 24 h, and UUI episodes per 24 h and improve volume voided per micturitions compared with the placebo or tolterodine treatment.

A number of studies and reviews have further documented the effects of solifenacin [120, 147, 148, 150, 159, 163, 519, see also 153, 162, 503, 594, 687, 765, 785], including men with OABs without bladder outlet obstruction [421]. In a pooled analysis of four RCTs, Abrams and Swift [8] demonstrated positive effects on urgency, frequency, and nocturia symptoms in OABs dry patients. In an analysis of four phase III clinical trials, Brubaker and FitzGerald [105] confirmed a significant effect of solifenacin 5 and 10 mg on nocturia in patients with OABs (reductions of nocturia episodes with 5 mg: −0.6, $p < 0.025$; with 10 mg: −0.6, $p < 0.001$ vs. placebo: −0,4) but without nocturnal polyuria. A positive impact on nocturia and sleep quality in patients with OABs treated with solifenacin has also been reported in other studies [742, 831]. Kelleher et al. [437] and Staskin and Te [720] presented data showing efficacy in patients with mixed incontinence.

A pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly (≥65 years) patients and also showed a high level of persistence in a 40-week extension trial [797]. Post hoc analysis of two 12-week, open label, flexible-dosing studies on 2,645 patients over 65 years of age with OABs

revealed that solifenacin was associated with improvements in measures assessing patients' perception of their bladder problems, symptom bother, and aspects of health-related quality of life [117]. Solifenacin was equally well tolerated in younger (<65 years) and older (>65 years) patients [356]. An exploratory pilot study with single doses of solifenacin 10 mg to 12 elderly volunteers suggested no clear propensity to impair cognitive functions [815].

Improvement of QoL by solifenacin treatment has been documented in several studies [294, 436]. In 30 patients with multiple sclerosis, van Rey and Heesakkers [783] improved OAB symptoms as well as neurogenic disease-specific QoL measures.

Information on solifenacin treatment in children is scarce. In a prospective open label study in 72 children (27 with neurogenic bladders) Bolduc et al. [98] improved urodynamic capacity and improved continence. Chart review of 138 children with therapy-resistant OABs treated with solifenacin increased mean voided volume and improved continence [365].

In female volunteers, aged 19–79 years, the effect of 10 and 30 mg solifenacin on the QT interval was evaluated at the time of peak solifenacin plasma concentration in a multi-dose, randomized, double-blind, placebo, and positive-controlled (moxifloxacin 400 mg) trial. The QT interval prolonging effect appeared greater for the 30 mg (8 ms, 4, 13: 90%CI) compared to the 10 mg (2 ms, −3, 6) dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

Michel et al. [551] studied cardiovascular safety and overall tolerability of solifenacin in routine clinical use in a 12-week, open-label, post-marketing surveillance study. They concluded that "in real-life conditions, i.e., with inclusion of large numbers of patients with cardiovascular co-morbidities and taking comedications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure."

Assessment. Solifenacin has a well-documented beneficial effect in OABs/DO (Table 13.1), and the adverse event profile seems acceptable.

Tolterodine Tartrate

Tolterodine is a tertiary amine, rapidly absorbed, and extensively metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacological profile as the mother compound [579] and significantly contributes to the therapeutic effect of tolterodine [106, 107]. Both tolterodine and 5-HMT have plasma half-lifes of 2–3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for <1–2.4 % of the dose; 5–14 % of 5-HMT is eliminated in the urine [107]. Whether or not the total antimuscarinic activity of unchanged tolterodine and 5-HMT excreted in urine is sufficient to exert any effect on the mucosal signaling mechanisms has not been established. However, the preliminary studies by Kim et al. [450] and Chuang et al. [171] do not support such an effect.

The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [174, 362, 668]. However, tolterodine may disturb sleep in subjects unable to form the even less lipophilic 5-HMT due to a low activity of CYP 2D6 [219].

Tolterodine has no selectivity for muscarinic receptor subtypes, but is claimed to have functional selectivity for the bladder over the salivary glands [578, 713]. In healthy volunteers, orally given tolterodine in a high dose (6.4 mg) had a powerful inhibitory effect on micturition and also reduced stimulated salivation 1 h after administration of the drug [713]. However, 5 h after administration, the effects on the urinary bladder were maintained, whereas no significant effects on salivation could be demonstrated.

Animal experiments have suggested that antimuscarinics may affect signaling from the bladder [33]. Cirfirming data in humans were found by Vijaya et al. [791]. In a randomized, placebo-controlled study, they evaluated the effect of tolterodine on urethral and bladder afferent nerves in women with DO in comparison to placebo, by studying the changes in the current perception threshold (CPT). They found a significantly increased CPT value at 5 (described as urgency) and 250 Hz upon both urethral and bladder stimulation after 1 week of treatment. When compared with placebo, women taking tolterodine had significantly increased bladder CPT values at 5 Hz (P-value <0.05).

Tolterodine is available as immediate-release (TOLT-IR; 1 or 2 mg; twice daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability [781].

Several randomized, double-blind, placebo-controlled studies on patients with OABs/DO (both idiopathic and neurogenic DO) have documented a significant reduction in micturition frequency and number of incontinence episodes [174, 362, 668]. Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment) and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness.

The OBJECT trial compared oxybutynin ER (OXY-ER) 10 mg once daily with TOLT-IR 2 mg twice daily [62] in a 12-week randomized, double-blind, parallel-group study including 378 patients with OABs. Participants had between 7 and 50 episodes of urgency incontinence per week and 10 or more voids in 24 h. The outcome measures were the number of episodes of urgency incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, OXY-ER was found to be significantly more effective than TOLT-IR in each of the main outcome measures adjusted for baseline (see also below: oxybutynin chloride). Dry mouth, the most common adverse event, was reported by 33 % and 28 % of participants taking OXY-ER and TOLT-IR, respectively. Rates of CNS and other adverse events were low and similar in both groups. The authors concluded that OXY-ER was more effective than TOLT-IR and that the rates of dry mouth and other adverse events were similar in both treatment groups.

In the OPERA study [224], OXY-ER at 10 mg/day or TOLT-ER at 4 mg/day were given for 12 weeks to women with 21–60 urgency incontinence episodes per week and an average of 10 or more voids per 24 h. Episodes of incontinence episodes (primary endpoint), total (urgency and non-urgency) incontinence, and micturition were recorded in seven 24-h urinary diaries at baseline and at weeks 2, 4, 8, and 12 and compared. Adverse events were also evaluated. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER ($n=391$) or TOLT-ER ($n=399$). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0 % of women taking OXY-ER reported no episodes of urinary incontinence compared with 16.8 % of women taking TOLT-ER. Dry mouth, usually mild, was more common with OXY-ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable, including adverse events involving the CNS.

In the ACET (Antimuscarinic Clinical Effectiveness Trial) [736] study, which consisted of two trials, patients with OABs were randomized to 8 weeks of open-label treatment with either 2 or 4 mg of once-daily TOLT-ER (study one) and to 5 or 10 mg of OXY-ER (study two). A total of 1,289 patients were included. Fewer patients prematurely withdrew from the trial in the TOLT-ER 4 mg group (12 %) than either the OXY-ER 5 mg (19 %) or OXY-ER 10 mg groups (21 %). More patients in the OXY-ER 10 mg group than the TOLT-ER 4 mg group withdrew because of poor tolerability (13 % vs. 6 %). After 8 weeks, 70 % of patients in the TOLT-ER 4 mg

group perceived an improved bladder condition, compared with 60 % in the TOLT-ER 2 mg group, 59 % in the OXY-ER 5 mg group, and 60 % in the OXY-ER 10 mg group. Dry mouth was dose-dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; $p=0.05$). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) than of OXY-ER (10 mg) is weakened by the open label design of the study.

Zinner et al. [847] evaluated the efficacy, safety, and tolerability of TOLT-ER in older (≥65) and younger (<65) OABs patients, in a 12-week RCT including 1,015 patients with urgency incontinence and urinary frequency. Patients were randomized to treatment with TOLT-ER 4 mg once daily ($n=507$) or placebo ($n=508$) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments, safety, and tolerability endpoints, was evaluated, relative to placebo. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment arms, irrespective of age (<65: ER 22.7 %, placebo 8.1 %; ≥65: ER 24.3 %, placebo 7.2 %). A few patients (<2 %) experienced severe dry mouth. No CNS (cognitive functions were not specifically studied), visual, cardiac (per ECG), or laboratory safety concerns were noted in this study. Withdrawal rates due to adverse events on TOLT-ER 4 mg QD were comparable in the two age cohorts (<65: 5.5 %; ≥65: 5.1 %).

The central symptom in the OAB syndrome is urgency. Freeman et al. [284] presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OABs. Patients with urinary frequency (8 or more micturitions per 24 h) and urgency incontinence (5 or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily ($n=398$) or placebo ($n=374$) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44 % reported improved urgency symptoms (compared with 32 % for placebo), and 62 % reported improved bladder symptoms (placebo, 48 %). The proportion of patients unable to hold urine upon experiencing urgency was decreased by 58 % with TOLT-ER, compared with 32 % with placebo ($P<0.001$).

In the Improvement in Patients: Assessing symptomatic Control with Tolterodine ER (IMPACT) study [255], the efficacy of TOLT-ER for patients' most bothersome OAB symptom was investigated in an open label, primary care setting. Patients with OAB symptoms for ≥3 months received TOLT-ER (4 mg once daily) for 12 weeks. By week 12, there were significant reductions in patients' most bothersome symptom: incontinence, urgency episodes, nocturnal and daytime frequency. The most common adverse events were dry mouth (10 %) and constipation (4 %), and it was concluded that in primary care practice, bothersome OAB symptoms can be effectively and safely treated with TOLT-ER, even in patients with comorbid conditions.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs [87, 167, 190, 225, 228, 647, 651; see further: 153, 162, 594]. Importantly, the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500 ms absolute QTc or 60 ms change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval [512].

Olshansky et al. [604] compared the effects on heart rate of TOLT-ER 4 mg/day with those of darifenacin 15 mg/day in healthy volunteers. They found that tolterodine, but not darifenacin, significantly increased mean heart rate per 24 h. The proportion of subjects with an increase >5 beats/min was significantly greater in those receiving TOLT-ER (25 % than with darifenacin (8.9 %)).

Hsiao et al. [374] compared the urodynamic effects, therapeutic efficacy, and safety of solifenacin (5 mg) vs. tolterodine ER (4 mg) treatment in women with the OAB syndrome. Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy and adverse events; however, tolterodine had a greater effect in increasing heart rate than solifenacin.

In a prospective, open study, Song et al. [712] compared the effects of bladder training and/or tolterodine as first-line treatment in female patients with OABs. One hundred and thirty-nine female patients with OABs were randomized to treatment with bladder training (BT), tolterodine (2 mg twice daily) or both for 12 weeks. All treatments were efficacious; however, combination therapy was the most effective. Mattiasson et al. [534] compared the efficacy of tolterodine 2 mg twice daily plus simplified bladder training (BT) with tolterodine alone in patients with OABs in a multicenter single-blind study. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine + BT than with tolterodine alone (33 % vs. 25 %; $p < 0.001$), while the median percentage increase in volume voided per void was 31 % with tolterodine + BT and 20 % with tolterodine alone ($p < 0.001$). There was a median of 81 % fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine + BT (−87 %). It was concluded that the effectiveness of tolterodine 2 mg twice daily can be augmented by a simplified BT regimen. However, Millard et al. [553] investigated whether the combination of tolterodine plus a simple pelvic floor muscle exercise program would provide improved treatment benefits compared with tolterodine alone in 480 patients with OABs. Tolterodine therapy for 24 weeks resulted in significant improvement in urgency, frequency, and incontinence; however, no additional benefit was demonstrated for a simple pelvic floor muscle exercise program. In a 16-week, multicenter, open label study tolterodine-extended release plus behavioral intervention resulted in high treatment satisfaction and improved bladder diary variables in patients who had previously been treated and were dissatisfied with tolterodine or other antimuscarinics [457].

Abrams et al. [5] studied the safety and tolerability of tolterodine for the treatment of OAB symptoms in men with BOO. They found that tolterodine did not adversely affect urinary function in these men. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. It was suggested that antimuscarinics can be safely administered in men with BOO. Lee et al. [483] reviewed the safety and efficacy of antimuscarinic agents in treating men with BOO and OABs and emphasized their safety and efficacy. They also concluded that combination therapy of antimuscarinic and α_1-AR antagonists improves the symptoms effectively without increasing the incidence of AUR.

The beneficial effect of TOLT-ER in men with BPE and LUTS, including OABs, has been well documented. Both as monotherapy, but in particularly in combination with α_1-adenoceptor (AR) antagonist, TOLT-ER was found effective [367, 423, 424, 426, 644, 645, 651, 652]. This effect was obtained irrespective of prostate size and was not associated with increased incidence of AUR [644, 645]. A large, 26-week, multicenter, randomized, double-blind, placebo-controlled, three-period crossover study enrolled women aged ≥18 years who were diagnosed with OABs and reported ≥8 micturitions/24 h and ≥4 urgency episodes/week on 5-day bladder diary at baseline [520]. Subjects were randomized to 1 of 10 treatment sequences and received three of five treatments, each for 4 weeks with 4-week washout periods: standard-dose pregabalin/tolterodine ER (150 mg twice daily [BID]/4 mg once daily [QD], $n = 102$), pregabalin alone (150 mg BID, $n = 105$), tolterodine ER alone (4 mg QD, $n = 104$), low-dose pregabalin/tolterodine ER (75 mg BID/2 mg QD, $n = 105$), and placebo ($n = 103$). Subjects completed 5-day diaries at the end of treatment and washout periods. The primary endpoint was change from baseline to week 4 in mean voided volume (MVV) per micturition. Baseline-adjusted changes in MVV were significantly greater after treatment with standard-dose pregabalin/tolterodine ER (39.5 mL) vs. tolterodine ER alone (15.5 mL; $P < 0.0001$), and with pregabalin alone (27.4 mL) vs. tolterodine ER

alone ($P=0.005$) and placebo (11.9 mL; $P=0.0006$). Treatments were generally well tolerated; discontinuation rates due to adverse events were 4 %, 2 %, 5 %, 0 %, and 1 % with standard- and low-dose pregabalin/tolterodine ER, pregabalin, tolterodine ER, and placebo, respectively. (See further section on "Combinations"]).

Assessment. Both the IR and ER forms of tolterodine have a well-documented effect in OABs/DO (Table 13.1) and are well tolerated.

Trospium Chloride

Trospium is a quaternary ammonium compound with a biological availability less than 10 % [240, 292]. The drug has a plasma half-life of approximately 20 h and is mainly (60 % of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model [452]. Whether or not it contributes to the clinical efficacy of the drug remains to be established.

Trospium is not metabolized by the cytochrome P450 enzyme system [81, 240]. It is expected to cross the blood–brain to a limited extent since it is a substrate for the drug-efflux transporter P-glycoprotein, which restricts its entry into the brain [716]. This was demonstrated by Staskin et al. [716], showing that trospium chloride levels in CSF samples were undetectable on Day 10 at steady-state peak plasma concentration concurrent with measureable peak plasma values. Clinically, trospium seems to have no negative cognitive effects [142, 292, 716, 764, 816].

Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions [776].

Several RCTs have documented positive effects of trospium both in neurogenic [507, 545, 725] and non-neurogenic DO [16, 121, 235, 341, 407, 653, 719, 846]. In a placebo-controlled, double-blind study on patients with neurogenic DO [725], the drug was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure, and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects [507].

The effect of trospium in urgency incontinence has been documented in several RCTs. Allousi et al. [16] compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3-week duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum bladder capacity. Cardozo et al. [121] investigated 208 patients with DO, who were treated with trospium 20 mg twice daily for 2 weeks. Also in this study, significant increases were found in mean volume at first unstable contraction (from 233 to 299 mL; placebo 254–255 mL) and in maximum bladder capacity (from 329 to 356 mL; placebo 345–335 mL) in the trospium-treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Jünemann and Al-Shukri [407] compared trospium 20 mg twice daily with tolterodine 2 mg twice daily in a placebo-controlled double-blind study on 232 patients with urodynamically proven DO, urgency incontinence without demonstrable DO, or mixed incontinence. Trospium reduced the frequency of micturition, which was the primary endpoint, more than tolterodine and placebo, and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7 and 9 %, respectively).

Halaska et al. [341] studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urgency syndrome. The trial comprised a total of 358 patients with urgency syndrome or urgency incontinence. After randomization in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily).

Urodynamic measurements were performed at the beginning, and at 26 and 52 weeks to determine the maximal cystometric bladder capacity. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgency episodes in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 mL after 26 weeks and 115 mL after 52 weeks ($P=0.001$). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 65 % of the patients treated with trospium and 77 % of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the mouth. An overall assessment for each of the drugs revealed a comparable efficacy level and a better benefit-risk ratio for trospium than for oxybutynin due to better tolerability.

Zinner et al. [846] treated 523 patients with symptoms associated with OABs and urgency incontinence with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo-controlled trial. Dual primary endpoints were change in average number of toilet voids and change in urgency incontinent episodes per 24 h. Secondary efficacy variables were change in average of volume per void, voiding urgency severity, urinations during day and night, time to onset of action, and change in Incontinence Impact Questionnaire. By week 12, trospium significantly decreased average frequency of toilet voids per 24 h (–2.37) and urgency incontinent episodes 59 % compared to placebo (–1.29; 44 %). It significantly increased average volume per void (32 mL; placebo: 7.7) mL and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (–0.43; placebo: 0.17) and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8 %; placebo 6.5 %), constipation (9.5 %; placebo 3.8 %), and headache (6.5 %; placebo 4.6 %). In a large US multicenter trial with the same design, and including 658 patients with OABs, Rudy et al. [653] confirmed the data by Zinner et al. [846], both with respect to efficacy and adverse effects.

Dose escalation seems to improve therapeutic efficacy. In a 12-week, randomized, double-blind, phase IIIb study including 1,658 patients with urinary frequency plus urgency incontinence received trospium chloride 15 mg TID ($n=828$) or 2.5 mg oxybutynin hydrochloride TID ($n=830$). After 4 weeks, daily doses were doubled and not readjusted in 29.2 % (242/828) of patients in the trospium group, and in 23.3 % (193/830) in the oxybuytnin group, until the end of treatment. At study end, there were no relevant differences between the "dose adjustment" subgroups and the respective "no dose adjustment" subgroups (trospium: $P=0.249$; oxybutynin: $P=0.349$). After dose escalation, worsening of dry mouth was higher in both dose-adjusted subgroups compared to the respective "no dose adjustment" subgroups ($P<0.001$). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups [97].

An extended release formulation of trospium allowing once daily dosing has been introduced [700] and its effects tested in controlled trials [141, 235, 504, 671, 672, 719, 845]. These studies demonstrated similar efficacy as found with previous formulations, but include experiences in, e.g., elderly patients (>75 years), obese patients, and in patients who use multiple concomitant medications. The most frequent side effects were dry mouth (12.9 %; placebo 4.6) and constipation (7.5 %; placebo 1.8) [235].

Intravesical application of trospium may be an interesting alternative. Fröhlich et al. [288] performed a randomized, single-blind, placebo-controlled, mono-centre clinical trial in 84 patients with urgency or urgency incontinence. Compared to placebo, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium

does not seem to be absorbed [800], thus offering an opportunity for treatment with minimal systemic antimuscuscarinic effects.

Assessment. Trospium has a well-documented effect in OABs/DO, and tolerability and safety seem acceptable (Table 13.1).

Antimuscarinics with "Mixed" Action

Some drugs used for treatment of the OABs/DO have been shown to have more than one mechanism of action. They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined "direct" action on bladder muscle. For several of these drugs, the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage-operated Ca^{2+} channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action. Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsade de pointes) in some patients [185, 723].

Oxybutynin Chloride

Oxybutynin is a tertiary amine that is well absorbed and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite, *N*-desethyloxybutynin (DEO), has pharmacological properties similar to the parent compound [799], but occurs in much higher concentrations after oral administration [377]. It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander et al. [607]. The plasma half-life of the oxybutynin is approximately 2 h, but with wide interindividual variation [242, 377].

Oxybutynin has several pharmacological effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent [411]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions [581, 799]. The drug was shown to have slightly higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors [580, 592], but the clinical significance of this is unclear.

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other antimuscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR, and the advantage of the newer formulations lies in improved dosing schedules and side effect profile [62, 224, 227]. An extended release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability. Some of the available formulations of oybutynin were overviewed by McCrery and Appell [538].

Immediate-release oxybutynin (*OXY-IR*). Several controlled studies have shown that OXY-IR is effective in controlling DO, including neurogenic DO [38, 827]. The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff et al. [761] summarized 15 randomized controlled

studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52 % and the mean reduction in frequency per 24 h was 33 % (data on placebo not presented). The overall "subjective improvement" rate was reported as 74 % (range 61–100 %). The mean percent of patients reporting an adverse effect was 70 (range 17–93 %). Oxybutynin, 7.5–15 mg/day, significantly improved quality of life of patients suffering from overactive bladder in a large open multicenter trial. In this study, patients' compliance was 97 % and side effects, mainly dry mouth, were reported by only 8 % of the patients [20]. In nursing home residents ($n=75$), Ouslander et al. [608] found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double-blind, cross-over trial. On the other hand, in another controlled trial in elderly subjects ($n=57$), oxybutynin with bladder training was found to be superior to bladder training alone [741].

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit [449, 740].

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80 % with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting [73, 239, 404, 405]. The effects on the ECG of oxybutynin were studied in elderly patients with urinary incontinence (Hussain et al., 1998); no changes were found. It cannot be excluded that the commonly recommended dose 5 mg×3 is unnecessarily high in some patients, and that a starting dose of 2.5 mg×2 with following dose-titration would reduce the number of adverse effects [20].

Extended release oxybutynin (*OXY-ER*). This formulation was developed to decrease liver metabolite formation of DEO with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy (see [65]). The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 h distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [61]. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [135].

The effects of OXY-ER have been well documented [695]. In the OBJECT study [62], the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6 to 6.1 %; TOLT-IR 24.1 to 7.8), total incontinence (OXY-ER from 28.6 to 7.1 %; TOLT-IR 27.0 to 9.3), and frequency (OXY-ER from 91.8 to 67.1 %; TOLT-IR 91.6 to 71.5) and both medications were equally well tolerated. The basic study was repeated as the OPERA study [224] with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg), and the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urgency incontinence; however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should no longer be compared with ER entities of the other.

Greater reductions in urgency and total incontinence have been reported in patients treated in dose-escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with OXY-IR. In the 1999 study [23], 105 patients with urgency or mixed incontinence were randomized to receive 5–30 mg OXY-ER once daily or 5 mg of OXY-IR 1–4 times/day. Dose titrations began at 5 mg and

the dose was increased every 4–7 days until one of three endpoints was achieved. These were (1) the patient reported no urgency incontinence during the final 2 days of the dosing period; (2) the maximum tolerable dose was reached; the maximum allowable dose (30 mg for OXY-ER or 20 mg for OXY-IR) was reached. The mean percentage reduction in weekly urgency and total incontinence episodes was statistically similar between OXY-ER and OXY-IR, but dry mouth was reported statistically more often with OXY-IR. In the 2000 study [789], 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg daily up to 20 mg daily. As in the 1999 study, OXY-ER again achieved a >80 % reduction in urgency and total incontinence episodes and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naïve patients included, as all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naïve population [313].

In an RCT comparing different daily doses of oxybutynin (5, 10 and 15 mg), Corcos et al. [187] found a significant dose–response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg oxybutynin/day.

In a multicenter, prospective, observational, flexible-dosing Korean study, Yoo et al. [832] investigate the prescription pattern and dose distribution of OXY-ER in patients with the OAB syndrome in actual clinical practice. The dosage for each patient was adjusted after discussions of efficacy and tolerability between doctor and patient, over a 12-week treatment period. Efficacy was measured by administering the Primary OAB Symptom Questionnaire (POSQ) before and after treatment. Patients were also administered; the patient perception of treatment benefit (PPTB) questionnaire is at the end of the study. Of the 809 patients enrolled, 590 (73.2 %) continued to take study medication for 12 weeks. Most patients were prescribed 5–10 mg/day oxybutynin ER as both starting and maintenance doses, with a dose escalation rate of only 14.9 %. All OAB symptoms evaluated by the POSQ were improved; 94.1 % of patients reported benefits from treatment and 89.3 % were satisfied.

Transdermal oxybutynin (OXY-TDS). Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study [201] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66 % for OXY-TDS, and 7.4 to 2.6: 72 % for OXY-IR), but much less dry mouth (38 % for OXY-TDS and 94 % for OXY-IR). In another study [227] the 3.9-mg daily dose patch significantly (vs. placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from 5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 mL; placebo from 175 to 182 mL). Furthermore, dry mouth rate was similar to placebo (7 % vs. 8.3 %). In a third study [229, 234] OXY-TDS was compared not only to placebo but to TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14 % and erythema in 8.3 % with nearly 9 % feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a randomized, 2-way crossover study [61]. Multiple blood and saliva samples were collected and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared to OXY-ER which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER.

Dmochowski et al. [231] analyzing the combined results of two RCTs concluded that transdermal oxybutynin was shown to be efficacious and well tolerated. The most common systemic

side effect was dry mouth (7.0 % vs. placebo 5.3 %). Application site erythema occurred in 7 % and pruritus in 16.1 %. Also Cartwright and Cardozo [129], reviewing published and presented data, concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower that with oral antimuscarinics—however, this benefit was offset by the rate of local skin reaction. The reviews of Sahai et al. [663] and Staskin and Salvatore [718] largely confirmed these conclusions, which also have been supported by further studies [130].

Oxybutynin topical gel. Given the efficacy and tolerability of the transdermal application, limited only by skin site reactions, a gel formulation was developed. Oxybutynin topical gel (OTG) was approved by the US FDA in January 2009. OTG is applied once daily to the abdomen, thigh, shoulder, or upper arm area [715]. The 1 g application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations and a "favorable" DEO metabolite: oxybutynin ratio believed to minimizing antimuscarinic side effects [717]. In a multicenter RCT, 789 patients (89 % women) with urgency-predominant incontinence were assigned to OTG or placebo once daily for 12 weeks [715]. The mean number of urgency episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes/day vs. 2.5 in the placebo arm ($P<0.0001$). Urinary frequency decreased by 2.7 episodes/day and voided volume increased by 21 mL (vs. 2.0 episodes ($P=0.0017$) and 3.8 mL ($P=0.0018$), respectively, in the placebo group). Dry mouth was reported in 6.9 % of the treatment group vs. 2.8 % of the placebo group. Skin reaction at the application site was reported in 5.4 % of the treatment group vs. 1.0 % in the placebo arm. It was felt that improved skin tolerability of the gel over the OXY transdermal patch delivery system was secondary to lack of adhesive and skin occlusion. The gel dries rapidly upon application and leaves no residue; person-to-person transference via skin contact is largely eliminated if clothing is worn over the application site [230]. The evolution of the transdermal gel allows greater patient tolerability and improved compliance. This was confirmed by Sand et al. [669, 670] showing that in 704 women with OABs, OTG significantly reduced the number (mean ± standard deviation) of daily incontinence episodes (OTG, −3.0 ± 2.8 episodes; placebo, −2.5 ± 3.0 episodes), reduced urinary frequency, increased voided volume, and improved select health-related quality-of-life domains vs. placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4 %) than with placebo (2.8 %).

Other administration forms. Rectal administration [180] was reported to have fewer adverse effects than the conventional tablets.

Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults [264, 298, 335, 499], although adverse effects may occur [428, 611].

Effects on cognition. Several studies have documented the possibility that oxybutynin may have negative effects on cognitive functions, particularly in the elderly population but also in children (see, e.g., [432, 433, 456]). This factor should be taken into consideration when prescribing the drug.

Assessment. Oxybutynin has a well-documented efficacy in the treatment of OABsDO (Table 13.1). Despite the adverse effect profile, it is still an established therapeutic option.

Propiverine Hydrochloride

Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Mürz [506]. The drug is rapidly absorbed (t_{max} 2 h), but has a high first pass metabolism, and its biological availability is about 50 %. Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man [801]. Several active metabolites are formed which quantitatively and qualitatively

differ from the mother compound [347, 568, 733, 820, 843]. Most probably these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified [549]. The half-life of propiverine itself is about 11–14 h. An extended release preparation was shown to be effective [409, 535]. Oral absorption of propiverine is site-dependent and influenced by dosage form and circadiantime-dependent elimination processes [535].

Propiverine has combined antimuscarinic and calcium antagonistic actions [343, 766]. The importance of the calcium antagonistic component for the drug's clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes. The effects of propiverine on cardiac ion channels and action potentials were investigated by Christ et al. [170]. Propiverine blocked in a concentration-dependent manner HERG channels expressed in HEK293 cells, as well as native I(Kr) current in ventricular myocytes of guinea pig. However, action potential duration was not prolonged in guinea-pig and human ventricular tissue, and the investigators concluded that their results did not provide evidence for an enhanced cardiovascular safety risk with the drug.

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff et al. [761] collected nine randomized studies on a total of 230 patients and found a 17 % reduction in micturitions per 24 h, a 64 mL increase in bladder capacity, and a 77 % (range 33–80 %) subjective improvement. Side effects were found in 14 % (range 8–42 %). In patients with neurogenic DO, controlled clinical trials have demonstrated propiverine's superiority over placebo [726]. Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate, and placebo [807], and propiverine, oxybutynin and placebo [505, 808] have confirmed the efficacy of propiverine and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared [727]. The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin.

Also in children and adolescents with neurogenic DO, propiverine was found to be effective [328, 680], with a low incidence rate of adverse events: <1.5 % [328]. A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5–10 year was performed by Marschall-Kehrel et al. [524]. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy parameter; secondary endpoints included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine vs. placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well-tolerated: 23 % of side effects were reported for propiverine and 20 % for placebo.

In a randomized, double-blind, multicenter clinical trial, patients with idiopathic DO were treated with 15 mg propiverine twice daily or 2 mg TOLT-IR twice daily over a period of 28 days [408]. The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary endpoint. Secondary endpoints were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, post-void residual urine, and quality of life. It was found that the mean maximum cystometric capacity increased significantly ($p<0.01$) in both groups. The volume at first urgency and the frequency/volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the quality of life improved comparably in both groups.

Madersbacher et al. [505] compared the tolerability and efficacy of propiverine (15 mg three times daily) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic

efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin. Dorschner et al. [241] investigated in a double-blind, multicenter, placebo-controlled, randomized study the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years), suffering from urgency, urgency incontinence, or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2 % dryness of the mouth under propiverine—2 out of 49 patients). Resting and ambulatory ECGs indicated no significant changes. The cardiac safety of propiverine was further studied by Donath et al. [236] in two comprehensively designed mono-centric ECG studies (including 24 healthy females, followed by a second study on 24 male patients with CHD and a pathological Pardee-Q-wave in the ECG). Both studies were placebo-controlled and compared the effects of single (30 mg s.i.d.) and multiple dosing (15 mg TID) of propiverine hydrochloride in a crossover design over 6 and 13 days, respectively. They were performed to investigate the influence of propiverine hydrochloride and its main metabolite propiverine-*N*-oxide on cardiac function with regard to QTc prolongation, QTc dispersion, and T-wave shape. No negative effects on cardiac safety could be demonstrated.

Abrams et al. [3] compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring (AUM) parameters, safety, and tolerability in OABs patients. Patients ($n=77$) received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. They found that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. Oxybutynin had a higher rate of dry mouth, and propiverine had a more pronounced effect on gastrointestinal, cardiovascular, and visual function.

Yamaguchi et al. [824] performed a multicenter, 12-week, double-blind phase III trial in Japanese men and women with OABs (1,593 patients were randomized and 1,584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at endpoint in number of voids/24 h, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence and quality of life (QoL) were examined. It was found that at endpoint, there were greater reductions in mean (SD) voids/24 h with all drug regimens than with placebo. All active treatments improved the volume voided and QoL vs. placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided vs. propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg. Wada et al. [793] performed a prospective nonrandomized crossover study of female OABs patients, assigned alternately to treatment with propiverine (20 mg) for 8 weeks then solifenacin (5 mg) for 8 weeks or solifenacin for 8 weeks then propiverine for 8 weeks. At baseline, eighth week and 16th week symptoms were assessed using OABSS. Of the 121 patients enrolled, 83 were analyzed. Both drugs were effective. Urgency was further improved after switching from propiverine to solifenacin, but not after switching from solifenacin to propiverine. Solifenacin was better tolerated than propiverine.

In another multicenter, prospective, parallel, double-blind, placebo-controlled trial, Lee et al. [482] studied the effects of 30 mg propiverine/day in 264 OABs patients (mean age 52.2 years), 221 of whom had efficacy data available from baseline and at least one on-treatment visit with >75 compliance. The study was focused on improving urgency. Overall, among patients treated with propiverine, 39 % rated their treatment as providing "much benefit," compared with 15 % in the placebo group. Adverse events reported by 32 (22.5 %) and 10 (12.7 %) patients in the propiverine and placebo group were all tolerable.

Masumori et al. [530] examined prospectively the efficacy and safety of propiverine in patients with OABs who poorly responded to previous treatment with solifenacin, tolterodine, or imidafenacin. Of 73 patients enrolled (29 males and 44 females, median age 71 years), 52 completed the protocol treatment. The OABSS was significantly improved by propiverine treatment. The scores of OAB symptoms (nighttime frequency, urgency and urge incontinence) except daytime frequency also improved significantly. No increase in PVR was observed. The most frequent adverse event was dry mouth (13.7 %), followed by constipation (6.8 %).

In a non-controlled study in patients with wet OABs the efficacy of propiverine on symptoms and quality of life was confirmed [463].

Assessment. Propiverine has a documented beneficial effect in the treatment of OABs/DO (Table 13.1) and seems to have an acceptable side effect profile.

Flavoxate Hydrochloride

Flavoxate is often discussed as a drug with mixed actions; however, its main mechanism of action may not be antimuscarinic. Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100 % [334]. The drug is extensively metabolized and plasma half-life was found to be 3.5 h [692]. Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity [111, 132]. The main mechanism of flavoxate's effect on smooth muscle has not been established. The drug has been found to possess a moderate calcium antagonistic activity, to have the ability to inhibit PDE, and to have local anesthetic properties; no antimuscarinic effect was found [333]. Uckert et al. [776], on the other hand, found that in strips of human bladder, the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable, It has been suggested that pertussis toxin-sensitive G-proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, since intracerebroventricularly or intrathecally administered flavoxate abolished isovolumetric rhythmic bladder contractions in anesthetized rats [603].

The clinical effects of flavoxate in patients with DO and frequency, urgency, and incontinence have been studied in both open and controlled investigations, but with varying rates of success [654]. Stanton [714] compared emepronium bromide and flavoxate in a double-blind, cross-over study of patients with detrusor overactivity and reported improvement rates of 83 % and 66 % after flavoxate or emepronium bromide, respectively, both administered as 200 mg three times daily. In another double-blind, cross-over study comparing flavoxate 1,200 mg/day with that of oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency, and utilizing both clinical and urodynamic criteria, Milani et al. [552] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects of flavoxate with those of placebo, have not been able to show any beneficial effect of flavoxate at dosages up to 400 mg three times daily [104, 157, 198]. In general, few side effects have been reported during treatment with flavoxate. On the other hand, its efficacy, compared to other therapeutic alternatives, is not well documented (Table 13.1).

Assessment. No RCTs seem to have been performed with flavoxate during the last decade. The scarcity of documented clinical efficacy should be considered before using the drug.

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