

5 Conservative Treatment for Pelvic Floor Disorders

23 Pharmacologic Approach to Urinary Incontinence and Voiding Disorders

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Introduction

The main components of the lower urinary tract, i.e. the urinary bladder, urethra, and striated urethral sphincter, constitute a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors [1–3]. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of emptying [4]. Failure to store urine may lead to various forms of incontinence (mainly urge and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence.

Urinary incontinence is as prevalent as or more prevalent than most other chronic diseases, including asthma, coronary artery disease, and peptic ulcer disease, and is associated with considerable direct and indirect costs [5–7]. Appropriate management can significantly reduce both morbidity and costs. Pharmacological treatment has had varying degrees of success, and there is presently no group of drugs which can be used with consistently successful results. Many drugs have been tried, but the results are often disappointing, owing to poor treatment efficacy and/or side effects [8]. There have been many evaluations of the currently used drugs for treating the disorder. The present review is based on the evaluations made by the 2nd International Consultation on Incontinence, held in Paris 2001 [9].

Drugs have been evaluated using different types of evidence (Table 23.1). Pharmacological and/or physiological efficacy evidence means that a drug has been shown to have desired effects in relevant preclinical experiments or in healthy volunteers (or in experimental situations in patients). Clinical drug

recommendations are based on evaluations made using a modification of the Oxford system, in which emphasis has been given to the quality of the trials assessed (Table 23.2).

Table 23.1 Types of evidence

<i>Pharmacodynamic</i>
In vitro
In vivo
<i>Pharmacokinetic</i>
Absorption
Distribution
Metabolism
Excretion
<i>Physiological</i>
Animal models
Clinical phase I
<i>Clinical</i>
Oxford guidelines

Table 23.2 ICI assessments: Oxford guidelines (modified)

<i>Levels of evidence</i>
Level 1: Randomized controlled clinical trials
Level 2: Good quality prospective studies
Level 3: Retrospective case-control studies
Level 4: Case series
Level 5: Expert opinion
<i>Grades of recommendation</i>
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” (recommended with reservation)
Grade D: Evidence inconsistent/inconclusive (not recommended)

Nervous Control of Micturition

The nervous mechanisms for urine storage and bladder emptying involve a complex pattern of efferent and afferent signaling in *parasympathetic*, *sympathetic* and *somatic* nerves (see Figures 23.1 and 23.2). During storage (at low levels of vesical afferent activity) spinal reflexes are active, mediating contraction of urethral sphincter mechanisms through somatic (striated muscle) and sympathetic (smooth muscle) nerves. Sympathetic and ganglionic nerves may also mediate detrusor and ganglionic inhibition. During storage, there is no activity in the sacral parasympathetic outflow. Micturition is initiated by distension of the bladder, activating mechanorecep-

tors in the bladder wall. This triggers a high level of activity in small myelinated afferent nerves ($A\delta$), which via the dorsal root ganglia reaches the lumbosacral spinal cord. The $A\delta$ afferents connect to a spinobulbospinal reflex consisting of an ascending limb from the lumbosacral spinal cord, integration centers in the rostral brain stem, and a descending limb back to the parasympathetic nucleus in the lumbosacral spinal cord. Afferent information may also be conveyed by small unmyelinated (C-fiber) vesical afferents, which have a high mechanical threshold, but which may be activated by irritation of the bladder mucosa. They may also be active in spinal cord injuries. Efferent micturition reflex pathways reach the bladder through the pelvic nerves.

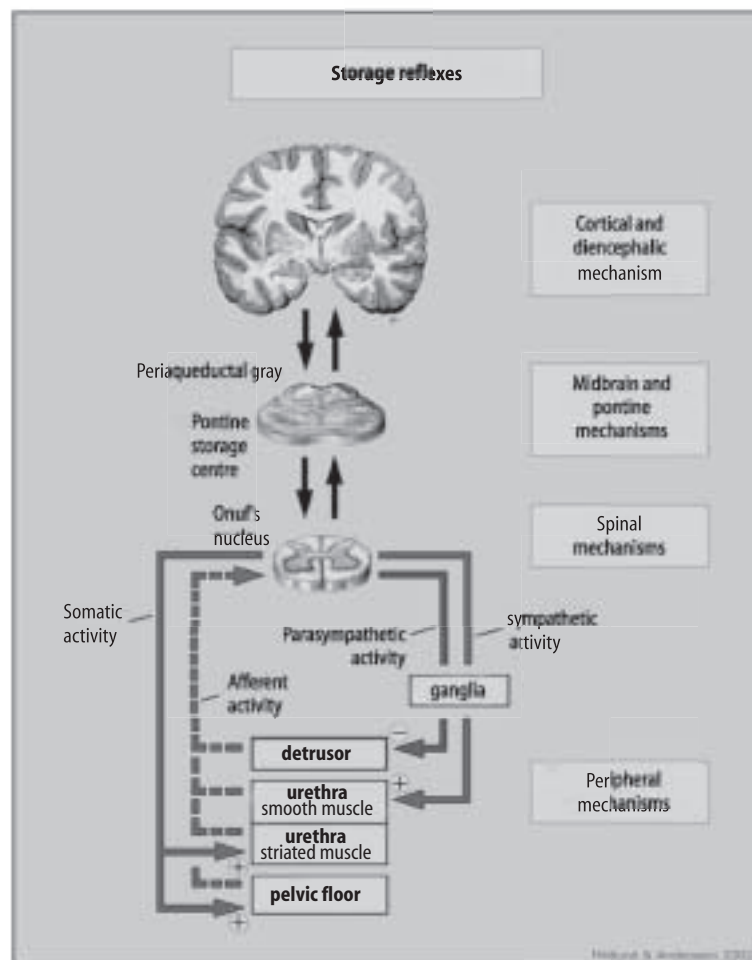


Figure 23.1 During filling, there is continuous and increasing afferent activity from the bladder. There is no spinal parasympathetic outflow that can contract the bladder. The sympathetic outflow to urethral smooth muscle, and the somatic outflow to urethral and pelvic floor striated muscles keep the outflow region closed. Whether or not the sympathetic innervation to the bladder (not indicated) contributes to bladder relaxation during filling in humans has not been established.

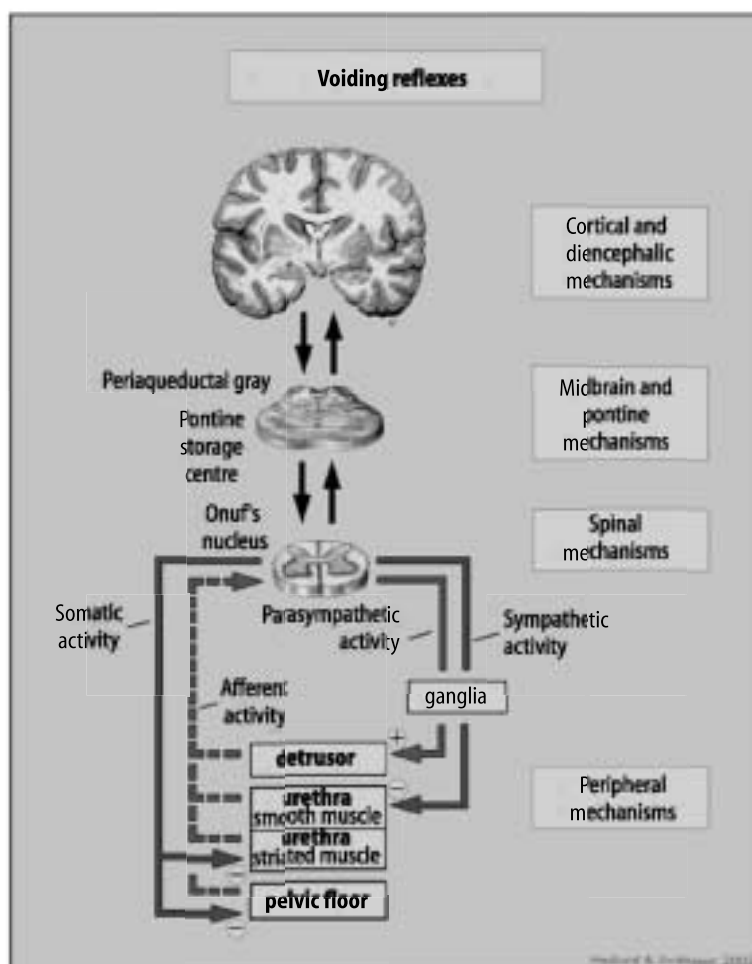


Figure 23.2 Voiding reflexes involve supraspinal pathways, and are under voluntary control. During bladder emptying, the spinal parasympathetic outflow is activated, leading to bladder contraction. Simultaneously, the sympathetic outflow to urethral smooth muscle, and the somatic outflow to urethral and pelvic floor striated muscles are turned off, and the outflow region relaxes.

Bladder Contraction

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle. 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 [1,10] (Figure 23.3). However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused by ATP [1,3]. A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders (Figure 23.4), and has

been reported to occur in hypertrophic bladders [11,12], interstitial cystitis [13], neurogenic bladders [14], and in the aging bladder [15]. The importance of the NANC component to detrusor contraction *in vivo*, normally, and in different micturition disorders, remains to be established.

Muscarinic Receptors

Molecular cloning studies have revealed five distinct genes for muscarinic acetylcholine receptors in rats and humans, and it is now generally accepted that five receptor subtypes correspond to these gene products [16,17]. Muscarinic receptors are coupled to G-proteins (Figure 23.5). The signal transduction systems involved varies, but M_1 , M_3 , and M_5 prefer-

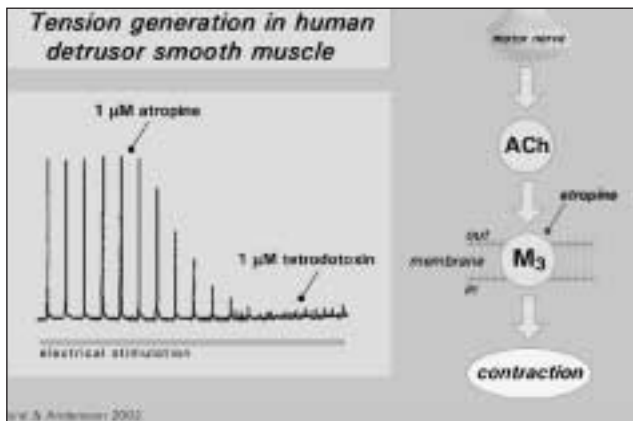


Figure 23.3 Contraction of the normal human bladder. Acetylcholine is released from cholinergic motor nerves and binds to the main contraction-mediating muscarinic (M_3) receptor (see also Figure 23.5). Note that there is practically no atropine resistance. Modified from Bayliss et al. [10].

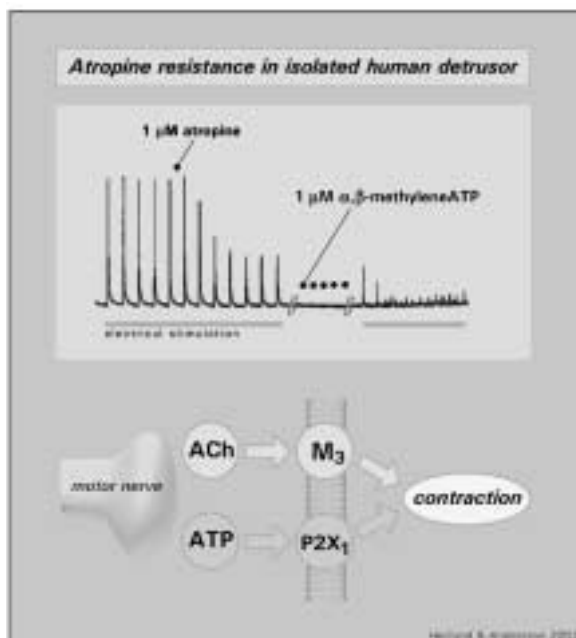


Figure 23.4 Atropine resistance in the human bladder. The contraction remaining after addition of atropine is caused by ATP, and can be abolished by α,β methylene ATP, which causes desensitization of $P2X_1$ receptors.

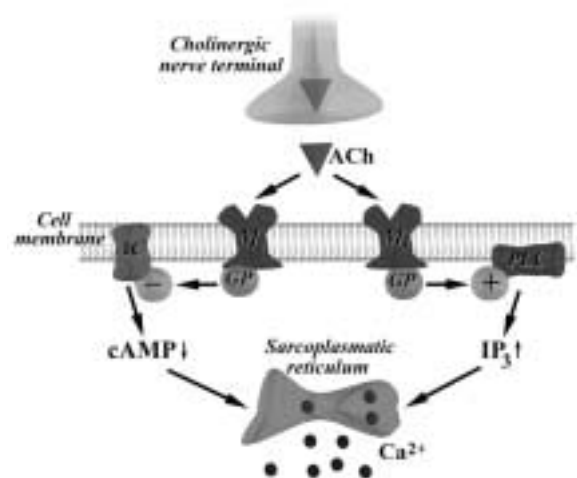


Figure 23.5 Acetylcholine (ACh) is released from cholinergic nerve terminals, and acts on muscarinic receptors (M_2 and M_3) in the detrusor. Both M_2 and M_3 receptors are coupled to G-proteins (GP) and may contribute to bladder contraction, but different signal transduction pathways are involved. M_2 receptors inhibit adenylyl cyclase (AC), which leads to a diminished intracellular level of cyclic AMP (cAMP). cAMP mediates bladder relaxation. Stimulation of M_3 receptors activates phospholipase C (PLC) to generate inositol triphosphate (IP_3). IP_3 can release calcium ions (Ca^{2+}) from the sarcoplasmic reticulum and this Ca^{2+} will activate the contractile machinery within the cell with resulting bladder contraction. The voiding contraction is believed to be mediated mainly through M_3 receptors.

entially couple to phosphoinositide hydrolysis leading to mobilization of intracellular calcium, whereas activation of muscarinic M_2 and M_4 receptors inhibits adenylyl cyclase activity. It has been suggested that muscarinic receptor stimulation may also inhibit K_{ATP} channels in smooth muscle cells from urinary bladder through activation of protein kinase C [18], thereby increasing the open probability of voltage-operated calcium channels and calcium influx.

Bladder Muscarinic Receptors

Detrusor smooth muscle from various species contains muscarinic receptors of the M_2 ($\approx 2/3$) and M_3 ($\approx 1/3$) subtype [19]. The M_3 receptors in the human bladder are believed to cause a direct smooth muscle contraction through phosphoinositide hydrolysis [20], whereas the role for the M_2 receptors has not been clarified. It has been suggested that M_2 receptors may oppose sympatheti-

cally (via β -ARs) mediated smooth muscle relaxation, since activation of M_2 receptors (rats) results in an inhibition of adenylyl cyclase [21].

There is general agreement that M_3 receptors are mainly responsible for the normal micturition contraction [19]. On the other hand, in certain disease states, M_2 receptors may contribute to contraction of the bladder [22,23].

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as M_4 in the human [24] urinary bladders. Prejunctional facilitatory muscarinic receptors appear to be of the M_1 subtype and have been detected in human bladders [25].

The muscarinic receptor functions may be changed in different urological disorders, such as outflow obstruction, neurogenic bladders, bladder overactivity without overt neurogenic cause, and diabetes. However, it is not always clear what the changes mean in terms of changes in detrusor function.

Drugs Used for Treatment of Bladder Overactivity

It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence. Even if it affects 30–60% of patients older than 65 years, it is not a disease exclusive to aging. It appears that detrusor overactivity may be the result of several different mechanisms, both myogenic [26] and neurological [27]. Most probably, both factors contribute to the genesis of the disease.

An abundance of drugs has been used for the treatment of the hyperactive detrusor (Table 23.3). However, for many of them, clinical use is based on the results of preliminary, open studies rather than randomized, controlled clinical trials (RCTs).

Antimuscarinic (Anticholinergic) Drugs

Both voluntary and involuntary bladder contractions are mediated mainly by acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle. Antimuscarinic drugs will therefore depress both types of contraction, irrespective of how the efferent part of the micturition reflex is activated. In patients with involuntary bladder contractions, the volume to the first contraction is increased, the amplitude of the contraction is decreased, and total bladder capacity is increased [28].

Table 23.3 Drugs used in the treatment of detrusor overactivity. Assessments according to the Oxford system (modified)

	Level of evidence	Grade of recommendation
<i>Antimuscarinic drugs</i>		
Tolterodine	1	A
Trospium	1	A
Propantheline	2	B
Atropine, hyoscyamine	2	D
(Darifenacin, solifenacin)	Under investigation	
<i>Drugs acting on membrane channels</i>		
Calcium antagonists	Under investigation	
Potassium channel openers	Under investigation	
<i>Drugs with mixed actions</i>		
Oxybutynin	1	A
Propiverine	1	A
Dicyclomine	4	C
Flavoxate	4	D
<i>Alpha-adrenoceptor antagonists</i>		
Alfuzosin	4	D
Doxazosin	4	D
Prazosin	4	D
Terazosin	4	D
Tamsulosin	4	D
<i>Beta-adrenoceptor agonists</i>		
Terbutaline	4	D
Clenbuterol	4	D
Salbutamol	4	D
<i>Antidepressants</i>		
Imipramine	2	C ^a
<i>Prostaglandin synthesis inhibitors</i>		
Indomethacin	4	C
Flurbiprofen	4	C
<i>Vasopressin analogues</i>		
Desmopressin	1	A
<i>Other drugs</i>		
Baclofen	2 ^b	C ^b
Capsaicin	3	C
Resiniferatoxin	Under investigation	

^a Should be used with caution.

^b Intrathecal use.

Atropine and related antimuscarinics are tertiary amines. They are well absorbed from the gastrointestinal tract and pass into the central nervous system (CNS). CNS side effects may therefore limit their use. Quaternary ammonium compounds are not well absorbed, pass into the CNS to a limited extent, and have a lower incidence of CNS side effects [29]. They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, tachycardia and dryness of mouth. All antimuscarinic drugs are contraindicated in narrow angle glaucoma.

Antimuscarinics are the most widely used treatment for urge and urge incontinence. However, currently used drugs lack selectivity for the bladder [16], and effects on other organ systems may result in side effects which limit their usefulness. 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.

Several antimuscarinic drugs have been used for treatment of bladder overactivity. For many of them, documentation of effects is not based on RCTs satisfying currently required criteria, and some drugs can be considered as obsolete (e.g. emepronium). Information on these drugs has not been included, but can be found elsewhere [30,31].

Atropine and Scopolamine

Atropine (dl-hyoscyamine) is rarely used for treatment of detrusor overactivity because of its systemic side effects, which preclude its use. However, in patients with detrusor hyperreflexia, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [32–35]. The pharmacologically active antimuscarinic half of atropine is l-hyoscyamine. Although still used, few clinical studies are available to evaluate the antimuscarinic activity of l-hyoscyamine sulfate.

Scopolamine (l-hyoscine) has been administered transdermally in a randomized, placebo-controlled clinical trial in 20 female patients with detrusor instability [36]. Although the authors concluded that transdermal scopolamine was effective and safe as a treatment of detrusor instability, further investigations are needed to assess its therapeutic value.

Propantheline

Propantheline bromide is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes, which has a low (5–10%) and individually varying biological availability [37]. 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.

The AHCPR (Agency of Health Care Policy and Research) Clinical Practice Guidelines (Urinary Incontinence Guideline Panel) lists five randomized controlled trials reviewed for propantheline, showing a reduction of urge (percent drug effect minus percent effect on placebo) between 0 and 53%. Controlled randomized trials ($n = 6$) were also reviewed by Thüroff et al. [38], who confirmed a positive, but varying response.

Although the effect of propantheline on detrusor overactivity 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.

Trospium

Trospium chloride is a quaternary ammonium compound with antimuscarinic actions on detrusor smooth muscle. It has no selectivity for muscarinic receptor subtypes. Its biological availability is low, approximately 5% [39,40], and it does not cross the blood–brain barrier. It seems to have no negative cognitive effects [40–42].

In a placebo-controlled, double-blind study on patients with detrusor hyperreflexia [43], 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 a randomized, double-blind multicenter trial in patients with spinal cord injuries and detrusor hyperreflexia, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects [44].

The effect of trospium in urge incontinence has been documented in placebo-controlled, randomized studies. Allousi et al. [45] compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3 weeks' duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first unstable contraction and in maximum bladder capacity. Cardozo et al. [46] investigated 208 patients with bladder instability who were treated with trospium 20 mg twice daily for 2 weeks. Also in this study, significant increases were found in volume at first unstable contraction and in maximum bladder capacity in the trospium treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Höfner et al. [47] compared the effects of oxybutynin 5 mg twice daily with those of trospium 20 mg twice daily in a double-blind, randomized study over 12 months in 358 patients with urge symptoms or urge incontinence. The urodynamic improvements after the two drugs were comparable, but oxybutynin produced a significantly higher rate of side effects, and the drop-out rate was higher in the oxybutynin group.

Jünemann et al. [48] 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 bladder overactivity, sensory urge incontinence 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).

Trospium chloride has a documented effect in detrusor overactivity, and seems to be well tolerated.

Tolterodine

Tolterodine is a new potent and competitive antagonist at muscarinic receptors, developed for treatment of urinary urgency and urge incontinence [49–52]. The drug has no selectivity for muscarinic receptor subtypes, but still shows some selectivity for the bladder over the salivary glands in an animal model [49], and possibly in humans [54]. Tolterodine has a major active metabolite with a similar pharmacological profile as the mother compound [53]. This metabolite contributes significantly to the therapeutic effect of tolterodine [55,56]. Tolterodine is rapidly absorbed and has a half-life of 2–3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. The main metabolite also has a half-life of 2–3 h [56].

The relatively low lipophilicity of tolterodine implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [52,57].

Several randomized, double-blind, placebo-controlled studies, both on patients with idiopathic detrusor instability and on those with detrusor hyperreflexia, have documented a significant reduction in micturition frequency and number of incontinence episodes [51,52]. Tolterodine immediate release seems to be well tolerated when used in the dose range 1–4 mg a day.

A once daily formulation of tolterodine has been developed, and a large-scale (1529 patients) clinical trial compared the effects of this agent to placebo and the twice daily formulation [58]. Tolterodine extended release (ER) 4 mg once daily and tolterodine immediate release (IR) 2 mg twice daily both significantly reduced the mean number of urge incontinence episodes per week compared with placebo. The median reduction in these episodes as a percentage of the baseline values was 71% for tolterodine ER, 60% for tolterodine IR, and 33% for placebo. Treatment with both formulations of tolterodine was also associated with statistically significant improvements in all other micturition diary variables compared with placebo. The rate of dry mouth (of any severity) was 23% for tolterodine ER, 30% for tolterodine IR, and 8% for placebo. The rates of withdrawal were comparable for the two active groups and the placebo group. No safety concerns were noted.

In a placebo-controlled study, comparing tolterodine 2 mg twice daily and oxybutynin 5 mg three times daily in 293 patients with detrusor instability, both drugs were found to be equally effective in reducing frequency of micturition and number of incontinence episodes. However, tolterodine appeared to have a better efficacy/tolerability profile [59]. These findings were largely confirmed by other investigators [60,61]. These data contrast with those of Appell et al. [62] comparing extended release oxybutynin chloride and immediate release tolterodine in a 12-week randomized, double-blind, parallel-group study in 378 patients with overactive bladder. Participants who had between 7 and 50 episodes of urge incontinence per week and 10 or more voids in 24 hours received extended release oxybutynin, 10 mg once daily, or tolterodine, 2 mg twice daily. The outcome measures were the number of episodes of urge incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, extended release oxybutynin was found to be significantly more effective than tolterodine in each of the main outcome measures adjusted for baseline. Dry mouth, the most common adverse event, was reported by 28.1% and 33.2% of participants taking extended release oxybutynin and tolterodine, respectively. Rates of central nervous system and other adverse events were low and similar in both groups. The authors concluded that extended release oxybutynin was more effective than tolterodine and that rates of dry mouth and other adverse events were similar in both treatment groups.

No comparative trials between extended release tolterodine and the extended release form of oxybutynin have been so far been reported. However, comparison of the immediate release forms would seem to indicate that efficacy is no different, whereas the side effect profile of tolterodine is favorable [57,63]. Head to head comparisons between the two extended release preparations are required to adequately compare efficacy and tolerability between the two agents.

Tolterodine, in both the immediate and extended release forms, has a well-documented effect on detrusor overactivity, and the side effect profile seems acceptable.

Drugs in development

Darifenacin. Darifenacin is a selective muscarinic M3 receptor antagonist developed for treatment of bladder overactivity [64]. Published clinical information on its clinical effects is scarce. In a pilot study on patients with detrusor instability, the drug was found to reduce the total number, maximum amplitude, and duration of unstable bladder con-

tractions [65]. A randomized, double-blind trial of 25 patients with detrusor instability compared the effects of darifenacin 15 mg and 30 mg once a day and oxybutynin 5 mg three times daily on ambulatory urodynamic monitoring and salivary flow [66]. Both drugs had similar urodynamic efficacy, but oxybutynin reduced salivary flow significantly more than darifenacin. In another controlled study, on 27 healthy male subjects, the effects of darifenacin 7.5 and 15 mg once a day, dicyclomine 20 mg four times a day, and placebo on cognitive and cardiac functions were investigated [67]. Unlike dicyclomine, darifenacin had no detectable effects on cognitive or cardiovascular function.

Darifenacin is currently being evaluated in a phase III clinical studies.

Solifenacin (YM-905). Solifenacin (YM905) is a long-acting muscarinic receptor antagonist in development for the treatment of overactive bladder. It has some selectivity for M_3 receptors, and it is currently being investigated in phase III clinical studies.

Drugs acting on membrane channels

Calcium antagonists

Activation of detrusor muscle, through both muscarinic receptor and NANC pathways, seems to require influx of extracellular Ca^{2+} through Ca^{2+} channels, as well as via mobilization of intracellular Ca^{2+} [1]. The influx of extracellular calcium can be blocked by calcium antagonists, blocking L-type Ca^{2+} channels, and theoretically, this would be an attractive way of inhibiting detrusor overactivity. However, there have been few clinical studies of the effects of calcium antagonists in patients with detrusor overactivity (see Andersson et al. [31]).

Available information does not suggest that systemic therapy with calcium antagonists is an effective way to treat detrusor overactivity, but controlled clinical trials are lacking. However, the possibility that intravesical therapy with these drugs could be useful should not be ignored, nor the fact that calcium antagonists may enhance the effects of antimuscarinic agents [1].

Potassium Channel Openers

Opening of K^+ channels and subsequent efflux of K^+ will produce hyperpolarization of various smooth muscles, including the detrusor. This leads to a decrease in Ca^{2+} influx by reducing the probability of Ca^{2+} channels opening with subsequent relaxation or inhibition of contraction. Theoretically, such drugs may be active during the filling phase of the

bladder, abolishing bladder overactivity with no effect on normal bladder contraction. K^+ channel openers, such as pinacidil and cromakalim, have been effective in animal models [68], but clinically, the effects have not been encouraging.

The first generation of openers of ATP-sensitive K^+ channels, such as cromakalim and pinacidil, were found to be more potent as inhibitors of vascular than of detrusor smooth muscle, and in clinical trials performed with these drugs, no bladder effects have been found at doses already lowering blood pressure. However, new K_{ATP} channel openers have been described, which may be useful for the treatment of bladder overactivity [9].

K^+ channel opening is an attractive way of treating bladder overactivity, since it would make it possible to eliminate undesired bladder contractions without affecting normal micturition. However, at present there is no evidence from controlled clinical trials to suggest that K^+ channel openers represent a treatment alternative.

Drugs with "Mixed" Actions

Some drugs used to block bladder overactivity 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.

Oxybutynin

Oxybutynin has several pharmacological effects, some of which seem difficult to relate to its effectiveness in the treatment of detrusor overactivity. 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 [69]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug.

Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue. It was shown to have higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors [70], but the clinical significance of this is unclear.

Oxybutynin is a tertiary amine that is well absorbed, but undergoes an extensive first-pass metabolism (biological availability 6% in healthy volunteers). The plasma half-life of the drug is approximately 2 hours, but with wide inter-individual variation [71,72]. Oxybutynin has an active metabolite, N-desethyl oxybutynin, which has pharmacological properties similar to those of the parent compound [73], but which occurs in much higher concentrations [72]. Therefore, it seems reasonable to assume that the effect of oral oxybutynin is exerted to a large extent by the metabolite.

Many controlled studies have shown that oxybutynin is effective in controlling detrusor overactivity, including hyperreflexia (see reviews by Yarker et al. [74], Thüroff et al. [38], Wein [63]). The recommended oral dose of the immediate release form is 5 mg twice daily or four times daily, though lower doses have been used. Thüroff et al. [38] 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 for 24 h was 33%. The overall "subjective improvement" rate was reported as 74% (range 61–100%). The mean percentage of patients reporting side effects was 70 (range 17–93%). Oxybutynin 7.5 to 15 mg/day significantly improved quality of life for patients with overactive bladder in a large open multicenter trial. In this study, patient compliance was 97% and side effects – mainly dry mouth – were reported by only 8% of patients [75].

In nursing home residents ($n = 75$), oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double-blind, crossover trial. On the other hand, in another controlled trial in elderly subjects, oxybutynin with bladder training was found to be superior to bladder training alone. Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit [9].

The therapeutic effect of immediate release oxybutynin on detrusor overactivity 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 [76,77]. Oxybutynin passes the blood-brain barrier and may have effects on the central nervous system [29,41]. The drug can cause cognitive impairment [78,79], and this side effect may be particularly troublesome in the geriatric population [80]. The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence [82]; no changes were found. It

cannot be excluded that the commonly recommended dose $5 \text{ mg} \times 3$ is unnecessarily high in some patients, and that a starting dose of $2.5 \text{ mg} \times 2$ with following dose-titration would reduce the number of adverse effects [75,81].

Once daily formulations of oxybutynin have been developed. The oxybutynin ER (Ditropan XL) uses an osmotic drug delivery system to release the drug at a controlled rate over 24 h. This formulation overcomes the marked peak to trough fluctuations in plasma levels of both drug and the major metabolite that occur with immediate release oxybutynin [83]. A trend towards a lower incidence of dry mouth with oxybutynin ER was attributed to reduced first-pass metabolism and to the maintenance of lower and less fluctuating plasma levels of drugs. Clinical trials on oxybutynin ER have concentrated primarily on comparing this drug with immediate release oxybutynin [84,85]. Anderson et al. [84] reported on a multicenter, randomized, double-blind study on 105 patients with urge incontinence, or mixed incontinence with a clinically significant urge component. Urge urinary incontinence episodes were the primary efficacy parameter. The number of weekly urge incontinence episodes decreased from 27.4 to 4.8 after controlled release and from 23.4 to 3.1 after immediate release oxybutynin, and total incontinence episodes decreased from 29.3 to 6 and from 26.3 to 3.8, respectively. Weekly urge incontinence episodes from baseline to end of study also decreased to 84% after controlled and 88% after immediate release oxybutynin. Since only patients who had previously responded to treatment with oxybutynin were selected for treatment, these figures do not represent what can be considered normal in clinical practice. Dry mouth of any severity was reported by 68% and 87% of the controlled and immediate release groups, respectively, and moderate or severe dry mouth occurred in 25% and 46%, respectively.

Appell et al. [62] compared extended release oxybutynin chloride 10 mg/day and tolterodine 2 mg twice daily in a 12-week randomized, double-blind, parallel-group study in 378 patients with overactive bladder. Extended release oxybutynin was found to be significantly more effective than tolterodine in each of the main outcome measures (number of episodes of urge incontinence, total incontinence, and micturition frequency at 12 weeks) adjusted for baseline, and the rates of dry mouth and other adverse events were similar in both treatment groups.

Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improve-

ment with few side effects, both in hyperreflexia and in other types of bladder overactivity, and in both children and adults [86]. Cognitive impairment can also occur in children treated with intravesical oxybutynin. Since it was reported that these effects may differ from those with oral administration [79], these patients should be closely monitored.

Oxybutynin has a well-documented efficacy in the treatment of detrusor overactivity, and is, together with tolterodine, the drug of first choice in patients with this disorder.

Dicyclomine

Dicyclomine has attributed to it both a direct relaxant effect on smooth muscle and an antimuscarinic action. Favorable results in detrusor overactivity have been demonstrated in several studies, performed more than a decade ago, and which do not satisfy current criteria of good quality RTCs [9].

Even though published experiences of the effect of dicyclomine on detrusor overactivity are favorable, the drug is not widely used, and RTCs documenting its efficacy and side effects are scarce.

Propiverine

Propiverine has been shown to have combined anticholinergic and calcium antagonistic actions [87,88]. The drug is rapidly absorbed, but has a high first-pass metabolism. Several active metabolites are formed, whose pharmacological characteristics remain to be established. It seems most probable that these metabolites contribute to the clinical effects of the drug [89].

Propiverine has been shown in several investigations to have beneficial effects in patients with detrusor overactivity [89]. Thüroff et al. [38] collected 9 randomized studies on a total of 230 patients, and found reductions in frequency (30%) and micturitions per 24 h (17%), 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 hyperreflexia, controlled clinical trials have demonstrated propiverine's superiority over placebo [89]. Controlled trials comparing propiverine, flavoxate and placebo [90], and propiverine, oxybutynin and placebo [91,93], have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin.

Stöhrer et al. [92] reported a double-blind, randomized, prospective, multicenter trial comparing propiverine 15 mg three times a day to placebo in 113 spinal cord injury patients with detrusor

hyperreflexia. Maximal cystometric capacity increased significantly in the propiverine group, by an average of 104 ml. Changes in bladder capacity at first contraction and in maximum bladder contraction were likewise statistically significant. Bladder compliance showed a more pronounced increase under propiverine in comparison to placebo. Sixty-three percent of patients experienced subjective improvement with propiverine in comparison with 23% of the placebo group. Dryness of the mouth (37% in the propiverine and 8% in the placebo group), and accommodation disorders (28% and 2% respectively) were reported side effects.

Madersbacher et al. [93] compared the tolerability and efficacy of propiverine (15 mg three times a day) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urge incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence and the severity of dry mouth were judged to be less with propiverine than with oxybutynin.

Dorschner et al. [94] 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, urge incontinence or mixed urge–stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times a day) or placebo (twice daily) for 4 weeks. Propiverine caused a significant reduction in micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). Resting and ambulatory electrocardiograms indicated no significant changes. The incidence of adverse events was very low (2% dryness of the mouth with propiverine – 2 out of 49 patients).

Propiverine has a documented beneficial effect in the treatment of detrusor overactivity, and seems to have an acceptable side effect profile. Its complex pharmacokinetics with several active, not very well-characterized metabolites, needs more attention.

Flavoxate

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 phosphodiesterase, and to have local anesthetic properties; no anticholinergic effect has been found [95]. It has been suggested that pertussis toxin-sensitive G-proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex in rats [96]. Its main metabolite (3-methylflavone-8-

carboxylic acid, MFCA) has been shown to have low pharmacological activity [95].

The clinical effects of flavoxate in patients with detrusor instability and frequency, urge and incontinence have been studied in both open and controlled investigations, but with varying rates of success [97]. Stanton [98] compared emepromium bromide and flavoxate in a double-blind, cross-over study of patients with detrusor instability and reported improvement rates of 83% and 66% after flavoxate or emepromium bromide, respectively, both administered as 200 mg three times daily. In another double-blind, cross-over study comparing flavoxate 1200 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. [99] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. The lack of placebo arm in these studies reduces the value of the efficacy conclusions.

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 [100–102].

In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared with other therapeutic alternatives, is not well documented.

α -Adrenoceptor antagonists

The normal human detrusor responds to norepinephrine (noradrenaline) by relaxing, probably because of the effect on both α - and β -adrenoceptors (ARs). Stimulation of α_2 -ARs on cholinergic neurons may lead to a decreased release of acetylcholine, and stimulation of postjunctional β -ARs to direct relaxation of the detrusor muscle [1].

Drugs stimulating α -ARs have hardly any contractile effects in isolated, normal human detrusor muscle. However, there is evidence that this may change in bladder overactivity associated with, for example, hypertrophic bladder and outflow obstruction and neurogenic bladders [1]. A significant subtype selective α_{1D} -AR mRNA upregulation was found in rats with outflow obstruction [103], but functional correlates were not reported. It cannot be excluded that factors such as the degree and duration of obstruction have an important influence on the α -ARs in the detrusor, but the functional consequences have not been established.

α -AR antagonists have been used to treat patients with neurogenic bladders and bladder overactivity [104–107]; however, the success has been moderate. Abrams [107] reported results from a placebo-

controlled study (4 weeks' duration) on the effects of tamsulosin in 263 patients with supra-sacral spinal cord lesions and neurogenic lower urinary tract dysfunction. There was a trend, but no statistically significant reduction of maximum urethral pressure with tamsulosin after 4 weeks. In 134 patients who completed a 1-year open-label treatment, significant positive effects, urodynamic as well as symptomatic, were found. At present no definitive conclusions can be drawn on the efficacy of α_1 -AR antagonists in the treatment of neurogenic bladders until further information is available.

Lower urinary tract symptoms in women have been reported to respond favorably to treatment with α -AR antagonists [108,109]. In a prospective open study of 34 women with urgency and frequency, evaluated by an expanded AUA (American Urological Association) symptom score, a combination of doxazosin and hyoscyamine was found to be more effective than either drug given alone [110]. The value of such a combination should be evaluated in a controlled clinical trial.

Although α -AR antagonists may be effective in selected cases of bladder overactivity, convincing effects documented in RCTs are lacking. In women, these drugs may produce stress incontinence [111,112].

β -Adrenoceptor Agonists

In isolated human bladder, non-subtype selective β -AR agonists such as isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in humans. However, the β -ARs of the human bladder were shown to have functional characteristics typical of neither β_1 -, nor β_2 -ARs [1]. On the other hand, receptor binding studies using subtype selective ligands suggested that the β -ARs of the human detrusor are primarily of β_2 subtype [113]. In a double-blind investigation clenbuterol 0.01 mg three times daily was shown to have a good therapeutic effect in 15 of 20 women with motor urge incontinence [114]. Other investigators, however, have not been able to show that β -ARs agonists represent an effective therapeutic principle in elderly patients with unstable bladder [115], or in young patients with myelodysplasia and detrusor overactivity [116].

Atypical β -AR-mediated responses have been shown to be mediated by a β_3 -AR, which has been cloned, sequenced, expressed in model systems, and extensively characterized functionally [117]. Both normal and neurogenic human detrusors were shown to express β_1 -, β_2 -, and β_3 -AR mRNAs, and selective β_3 -AR agonists effectively relaxed both types of detrusor muscle [118–120]. Thus, it seems

that the atypical β -AR of the human bladder may be the β_3 -AR. Whether or not this is of importance in humans, and whether β_3 -AR stimulation will be an effective way of treating the overactive bladder, has yet to be shown in controlled clinical trials.

Antidepressants

Several antidepressants have been reported to have beneficial effects in patients with detrusor overactivity [121,122]. However, imipramine is the only drug that has been widely used clinically to treat this disorder.

Imipramine has complex pharmacological effects, including marked systemic anticholinergic actions [123] and blockade of the reuptake of serotonin and norepinephrine [124], but its mode of action in detrusor overactivity has not been established [125]. Even if it is generally considered that imipramine is a useful drug in the treatment of detrusor overactivity, 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 [125,126].

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 [127,128]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [123].

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 [125], and no good quality RCTs have documented that the drug is effective in the treatment of detrusor overactivity. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

Prostaglandin synthesis inhibitors

Human bladder mucosa has the ability to synthesize eicosanoids, and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [129]. Even if prostaglandins cause contraction of human bladder muscle [1], it is still unclear whether prostaglandins contribute to the pathogenesis of unstable 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. [130] performed a double-blind controlled study of 30 women with detrusor instability 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 detrusor overactivity. There was a high incidence of side effects (43%) including nausea, vomiting, headache and gastrointestinal symptoms. Palmer [131] studied the effects of flurbiprofen 50 mg \times 4 versus placebo in a double-blind, cross-over trial in 37 patients with idiopathic detrusor instability (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 detrusor instability, compared with bromocriptine in a randomized, single-blind, cross-over study [132]. The incidence of side effects was high, occurring in 19 of 32 patients. However, no patient had to stop treatment because of side effects.

The paucity of controlled clinical trials on the effects of prostaglandin synthesis inhibitors in the treatment of detrusor overactivity, and the limited number of drugs tested, makes it difficult to evaluate their therapeutic value. No new information has been published during the last decade.

Vasopressin Analogues

Desmopressin

Desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) is a synthetic vasopressin analogue with a pronounced antidiuretic effect, but practically lacking vasopressor actions. It is now widely used as a treatment for primary nocturnal enuresis [133]. Studies have shown that one of the factors that can contribute to nocturnal enuresis in children, and probably in adults, is lack of a normal nocturnal increase in plasma vasopressin, which results in high nocturnal urine production [134–137]. By decreasing the nocturnal production of urine, beneficial effects may be obtained in enuresis and nocturnal polyuria.

Several, controlled, double-blind investigations have shown intranasal administration of desmo-

pressin to be effective in the treatment of nocturnal enuresis in children [126,138,139]. The dose used in most studies has been 20 µg intranasally at bedtime. However, the drug is orally active, even if the bioavailability is low (less than 1% compared to 2–10% after intranasal administration), and its oral efficacy in primary nocturnal enuresis in children and adolescents has been documented in randomized, double-blind, placebo-controlled studies [140,141].

Positive effects of desmopressin on nocturia in adults have been documented. Nocturnal frequency and enuresis due to bladder instability responded favorably to intranasal desmopressin therapy even when previous treatment with “antispasmodics” had been unsuccessful [142]. In patients with multiple sclerosis, desmopressin was shown in controlled studies to reduce nocturia, and micturition frequency [143–146]. Furthermore, desmopressin was shown to be successful in treating nocturnal enuresis in spina bifida patients with diurnal incontinence [147]. Oral desmopressin has proved to be effective in the treatment of nocturia with polyuric origin. In addition to prolonging sleep duration to first void, desmopressin reduced the number and frequency of nocturnal voids and nocturnal urine volume in both men and women [148,149].

Desmopressin is a well-documented therapeutic alternative in pediatric nocturnal enuresis, and seems to be effective also in adults with nocturia with polyuric origin. Even if side effects are uncommon, there is a risk of water retention and hyponatremia during desmopressin treatment [150,151], and due consideration should be given to this potential side effect, particularly in elderly patients.

Other Drugs

Baclofen

Baclofen is considered to depress monosynaptic and polysynaptic motor neurons and interneurons in the spinal cord by acting as a GABA receptor agonist, and has been used in voiding disorders, including detrusor hyperreflexia secondary to lesions of the spinal cord [37]. The drug may also be an alternative in the treatment of idiopathic detrusor overactivity [152]. However, published experience with the drug is limited.

Intrathecal baclofen may be useful in patients with spasticity and bladder dysfunction [153].

Capsaicin and Resiniferatoxin

Capsaicin, the pungent ingredient of red peppers, has identified a pharmacological classification of

subpopulations of primary afferent neurons innervating the bladder and urethra, the “capsaicin-sensitive nerves”. Capsaicin exerts a biphasic effect on sensory nerves: initial excitation is followed by a long-lasting blockade which renders sensitive primary afferents (C-fibers) resistant to activation by natural stimuli [154]. It is believed that capsaicin exerts these effects by acting on specific receptors, “vanilloid” receptors [155]. It is possible that capsaicin at high concentrations (mM) has additional, nonspecific effects [156].

Intravesical capsaicin has been used with success in bladder overactivity caused by neurological disorders such as multiple sclerosis, or traumatic chronic spinal lesions. The effect of treatment may last for 2 to 7 months [157–159]. However, negative results have also been reported [160].

Side effects of intravesical capsaicin include discomfort and a burning sensation at the pubic/urethral level during instillation, an effect that can be overcome by prior instillation of lidocaine, which does not interfere with the beneficial effects of capsaicin [161]). No premalignant or malignant changes in the bladder have been found in biopsies of patients who had repeated capsaicin instillations for up to 5 years [159].

Resiniferatoxin is a phorbol related diterpene, isolated from some species of *Euphorbia*, a cactus-like plant. It has effects similar to those of capsaicin. Given intravesically, resiniferatoxin has been shown to be approximately 1000 times more potent than capsaicin in stimulating bladder activity [162].

Lazzeri et al. [163] instilled resiniferatoxin intravesically in 15 subjects, including 8 normal subjects and 7 with bladder over activity (6 with hyperreflexia). Resiniferatoxin (10 nM concentration) did not produce any warm or burning sensation suprapubically. In the patients with bladder overactivity, but not in the normal subjects, the mean bladder capacity increased significantly immediately after resiniferatoxin treatment. However, this effect remained in only 2 out of the 7 patients 4 weeks after the instillation. Higher doses (50 and 100 nM) were used by Cruz et al. [164], who treated 7 patients with hyperreflexia with intravesical resiniferatoxin. They found no temporary deterioration of urinary symptoms, as seen with capsaicin, and found improvement in urinary frequency in 5 of the patients that lasted up to 3 months. The beneficial effect of resiniferatoxin has been confirmed in other studies [165,166]. These observations make resiniferatoxin an interesting alternative to capsaicin, but further investigations are needed to explore its clinical potential. Currently it is not in clinical development owing to formulation problems.

Table 23.4 Drugs used in the treatment of stress incontinence. Assessments according to the Oxford system (modified)

	Level of evidence	Grade of recommendation
<i>Alpha-adrenoceptor agonists</i>		
Ephedrine	3	C
Norephedrine (phenylpropanolamine, PPA)	2	NR
<i>Other drugs</i>		
Imipramine	4	C ^a
Clenbuterol (Duloxetine)	4 Under investigation	C
<i>Hormones</i>		
Estrogens	2	D

NR, not recommended.

^a Should be used with caution.

Drugs Used for Treatment of Stress Incontinence

Factors which may contribute to urethral closure include urethral smooth muscle tone and the passive properties of the urethral lamina propria, in particular the vascular submucosal layer. 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 norepinephrine [1]. A contributing factor to stress incontinence, mainly in elderly women with lack of estrogen, may be lack of mucosal function. The role of striated urethral and pelvic floor muscles has not yet been established.

The pharmacological treatment of stress incontinence (Table 23.4) aims at increasing intraurethral pressure by increasing tone in the urethral smooth muscle, or by affecting tone of the striated muscles in the urethra and pelvic floor (see below). Although several drugs may contribute to such an increase in intraurethral pressure, including β -AR antagonists and imipramine, only α -AR agonists and estrogens (see below), alone or together, have been more widely used.

α -Adrenoceptor Agonists

Although several drugs with agonistic effects on α -ARs have been used in the treatment of stress incontinence, for example midodrine [167,168] and norfenefrine [169], ephedrine and norephedrine seem to be the most widely used drugs. Ephedrine,

pseudoephedrine (a stereoisomer of ephedrine), and norephedrine (phenylpropanolamine, PPA) directly stimulate α - as well as β -ARs, but can also release norepinephrine from adrenergic nerve terminals. They have all been reported to be effective in stress incontinence, as found in open and controlled clinical trials, ephedrine at a dose of 25 to 50 mg 3–4 times daily, and PPA at a dose of 50 to 100 mg 2–3 times daily. These drugs lack selectivity for urethral α -ARs, and may increase blood pressure. They also can cause sleep disturbances, headache, tremor and palpitations. Long-term experience with the drugs is lacking. It has been pointed out that individuals taking PPA might have an initial increase in blood pressure that can be dangerous, and it should be noted that the FDA has asked manufacturers to voluntarily stop selling PPA-containing drugs and replace the ingredients with a safer alternative. Judging from the clinical benefit documented with PPA and the possible risks, this drug (and probably drugs with similar action) should not be used [9].

Radley et al. [170] evaluated the effect of the selective α_1 -AR agonist, methoxamine, in a randomized, double-blind, placebo-controlled, cross-over study on a group of women with genuine stress incontinence while measuring maximum urethral pressure (MUP), blood pressure, heart rate, and symptomatic side effects. Methoxamine evoked non-significant increases in MUP and diastolic blood pressure, but caused a significant rise in systolic blood pressure and significant fall in heart rate at maximum dosage. Systemic side effects including piloerection, headache, and cold extremities were experienced in all subjects. The authors suggested that the clinical usefulness of direct, peripherally acting subtype-selective α_1 -AR agonists in the medical treatment of stress incontinence may be limited by side effects.

α -AR agonists has been used in combination with estrogens, and with other nonsurgical treatments of stress incontinence, such as pelvic floor exercises and electrical stimulation. Even if this type of treatment can be effective in women with mild stress incontinence or in those not suitable for surgery, the risks with PPA and related compounds (see above) do not seem to warrant their use as single drug therapy or in combination with estrogen. In carefully selected patients, selective α_1 -AR agonists may be used on an “on demand” basis in certain situations known to provoke leakage.

β -Adrenoceptor Antagonists

The theoretical basis for the use of β -AR antagonists in the treatment of stress incontinence is that block-

ade of urethral β -ARs may enhance the effects of norepinephrine on urethral α -ARs. Even though propranolol has been reported to have beneficial effects in the treatment of stress incontinence [171,172], there are no RCTs supporting such an action.

Imipramine

Imipramine, among several other pharmacological effects, inhibits the reuptake of norepinephrine and serotonin in adrenergic nerve ending. In the urethra, this can be expected to enhance the contractile effects of norepinephrine on urethral smooth muscle. Theoretically, such an action may also influence the striated muscles in the urethra and pelvic floor by effects at the spinal cord level (Onuf's nucleus).

Gilja et al. [173] 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 maximal urethral closure pressure (MUCP) from 34 to 48 mmHg. Lin et al. [174] assessed the efficacy of imipramine (25 mg imipramine three times a day for 3 months) as a treatment for genuine stress incontinence in 40 women with genuine stress incontinence. A 20-minute 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 44.8–75.2). No RCTs on the effects of imipramine seem to be available.

Clenbuterol

Since β -AR antagonists have been used as a treatment for stress incontinence, it seems paradoxical that the selective β_2 -AR agonist, clenbuterol, was found to cause significant clinical improvement and increase in MUCP in 165 women with stress incontinence [175]. The study was double-blind and placebo-controlled. The number of patients reporting any degree of improvement was 56 (out of 77) in the clenbuterol group and 48 (out of 88) in the placebo group, and the changes in MUCP was 3.3 cmH₂O in the clenbuterol and -1.5 cmH₂O in the placebo group. The positive effects were suggested to be the result of an action on urethral striated muscle and/or the pelvic floor muscles.

Ishiko et al. [176] 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 and a combination of drug therapy and pelvic floor exercises. 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. Further well-designed RCTs documenting the effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence as it is possible that this agent may have a novel, as yet undefined mechanism of action.

Duloxetine

Duloxetine, a combined norepinephrine and 5-HT reuptake inhibitor, has been shown, in animal experiments, to increase the neural activity to the external urethral sphincter, and increase bladder capacity through effects on the central nervous system [177]. In a double-blind, placebo-controlled study in women with stress ($n = 140$) or mixed ($n = 146$) incontinence, duloxetine (20–40 mg four times a day) was shown to cause significant improvements in several efficacy measures (ICS 1 h stress pad test, 24 h pad weight, number of incontinence episodes, quality of life assessment [178]). The drug was well tolerated and there were few discontinuations due to side effects (8% for duloxetine, 3% for placebo).

The drug is still undergoing clinical trials.

Drugs Used for Treatment of Overflow Incontinence

According to the definition of the ICS (1997), overflow incontinence is "leakage of urine at greater than normal bladder capacity. It is associated with incomplete bladder emptying due to either impaired detrusor contractility or bladder outlet obstruction". Two types of overflow incontinence are recognized, one as a result of mechanical obstruction, and the other secondary to functional disorders. Occasionally both types can coexist.

The clinical presentation of overflow incontinence may vary depending on the age of the patient and the cause of the incontinence. In children, overflow incontinence can be secondary to congenital obstructive disorders (e.g. urethral valves) or to neurogenic vesical dysfunction (myelomeningocele, Hinman syndrome). In adults, overflow incontinence may be associated with outflow obstruction secondary to benign prostatic hyperplasia (BPH) or can be a consequence of diabetes mellitus. Mixed

Table 23.5 Drugs used in the treatment of overflow incontinence. Assessments according to the Oxford system (modified)

	Level of evidence	Grade of recommendation
<i>Alpha-adrenoceptor antagonists</i>		
Alfuzosin	4	C
Doxazosin	4	C
Prazosin	4	C
Terazosin	4	C
Tamsulosin	4	C
^a (Phenoxybenzamine)	4	NR
<i>Muscarinic receptor agonists</i>		
Bethanechol	4	D
Carbachol	4	D
<i>Anticholinesterase inhibitors</i>		
Distigmine	4	D
<i>Other drugs</i>		
Baclofen	4	C
Benzodiazepines	4	C
Dantrolene	4	C

NR, not recommended.

^a Should be used with caution.

forms may be seen in disorders associated with motor spasticity (e.g. Parkinson's disease).

Pharmacologic treatment (Table 23.5) should be based on previous urodynamic evaluation. The aim of treatment is to prevent damage to the upper urinary tract by normalizing voiding and urethral pressures. Drugs used for increasing intravesical pressure, i.e. "parasympathomimetics" (acetylcholine analogues such as bethanechol, or acetylcholine esterase inhibitors), or β -AR antagonists, have not been documented to have beneficial effects (see Finkbeiner [179], Wein [4]). Stimulation of detrusor activity by intravesical instillation of prostaglandins has been reported to be successful; however, the effect is controversial and no RCTs are available [4].

The "autonomous" contractions in patients with parasympathetic decentralization are probably mediated by α -AR mediated bladder activity, since they can be inhibited by α -AR antagonists [180]. The α -AR antagonist that has been most widely used is probably phenoxybenzamine [181–183]. However, uncertainties about the carcinogenic effects of this drug, and its side effects, have focused interest on selective α_1 -AR antagonists such as prazosin [184].

Other means of decreasing outflow resistance in these patients, particularly if associated with spasticity, are baclofen, benzodiazepines (e.g. diazepam) and dantrolene sodium (see Wein [4]).

Hormonal Treatment of Urinary Incontinence

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 a woman to remain continent the urethral pressure must exceed the intravesical pressure at all times except during micturition. The urethra has four estrogen-sensitive functional layers which all play a part in the maintenance of a positive urethral pressure: (1) epithelium, (2) vasculature, (3) connective tissue, (4) muscle.

Estrogens in the Treatment of Urinary Incontinence

There are a number of reasons why estrogens may be useful in the treatment of women with urinary incontinence. As well as improving the "maturation index" of urethral squamous epithelium [185], estrogens increase urethral closure pressure and improve abdominal pressure transmission to the proximal urethra [186–188]. The sensory threshold of the bladder may also be raised [189].

Lose and Englev [190] evaluated the effect of estrogens in 251 postmenopausal women, with a mean age of 66 years, reporting at least one bothersome lower urinary tract symptom in an open, randomized, parallel group, controlled trial. One hundred and thirty-four women were treated with the estradiol-releasing ring for 24 weeks; 117 women were treated with estriol pessaries 0.5 mg every second day for 24 weeks. Subjective scores of urgency, frequency, nocturia, dysuria, stress incontinence and urge incontinence were evaluated. The two treatments were equally efficacious in alleviating urinary urgency (51% versus 56%), urge incontinence (58% versus 58%), stress incontinence (53% versus 59%) and nocturia (51% versus 54%). The authors concluded that low dose vaginally administered estradiol and estriol are equally efficacious in alleviating lower urinary tract symptoms which appear after the menopause. The lack of a placebo group makes the improvement rates difficult to evaluate.

Estrogens for Stress Incontinence

The role of estrogen in the treatment of stress incontinence has been controversial, even though there are a number of reported studies (see Hextall [191]). Some have given promising results but this may be because they were observational, 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 durations of treatment. Fantl et al. [192] treated 83 hypoestrogenic women with urodynamic evidence of genuine stress incontinence and/or detrusor instability with conjugated equine estrogens 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. [193] treated 57 postmenopausal women with genuine stress incontinence or mixed incontinence with estradiol valerate 2 mg or placebo daily for 6 months. There was no significant change in objective outcome measures although both the active and placebo group reported subjective benefit.

There have been two meta-analyses performed which have helped to clarify the situation further. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee, the use of estrogens to treat all causes of incontinence in postmenopausal women was examined [194]. Of 166 articles identified which were published in English between 1969 and 1992, only 6 were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with genuine stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost. Maximum urethral closure pressure did increase significantly, but this result was influenced by only one study showing a large effect. In the second meta-analysis, Sultana and Walters [195] reviewed 8 controlled and 14 uncontrolled prospective trials and included all types of estrogen treatment. They also found that estrogen therapy was not an efficacious treatment of stress 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 incontinence. However, several studies have shown that it may have a role in *combination* with other therapies (for combination with α -AR agonists, see above). In a randomized trial, Ishiko et al. [196] compared the effects of the combination of pelvic floor exercise and estriol (1 mg/day) in 66 patients with postmenopausal stress 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 incontinence patients in both groups 3 months after the start of therapy and concluded that combination therapy with estriol plus pelvic floor exercise was

effective and capable of serving as first-line treatment for mild stress incontinence.

Estrogens for Urge Incontinence

Estrogen has been used to treat postmenopausal urgency and urge incontinence for many years, but there are few controlled trials confirming that it is of benefit [191].

A double-blind multicenter study of 64 postmenopausal women with the "urge syndrome" has failed to confirm its efficacy [197]. All women underwent pre-treatment urodynamic investigation to establish that they had either sensory urgency or detrusor instability. They were then randomized to treatment with oral estriol 3 mg daily or placebo for 3 months. Compliance 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 it was not significantly better than placebo. Grady et al. [198] determined whether postmenopausal hormone therapy improves the severity of urinary incontinence. in a randomized, blinded trial among 2763 postmenopausal women younger than 80 years with coronary disease and intact uteri. The report included 1525 participants who reported at least one episode of incontinence per week at baseline. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet daily ($n = 768$) or placebo ($n = 757$) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved (decrease of at least two episodes per week), unchanged (change of at most one episode per week), or worsened (increase of at least two episodes per week). The results showed that incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to hormones, while 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 and was observed for both urge and stress incontinence. The number of incontinent 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 progestin therapy was associated with worsening urinary incontinence in older postmenopausal women with weekly incontinence, and did not recommend this therapy for the treatment of incontinence. It cannot be excluded that the progestagen component had a negative influence on the outcome of this study.

Estrogen has an important physiological effect on the female lower urinary tract and its deficiency is

an etiological factor in the pathogenesis of a number of conditions. However, the use of estrogens alone to treat urinary incontinence has given disappointing results.

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