Committee 9

Pharmacological Treatment of Urinary Incontinence

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I. INTRODUCTION

The functions of the lower urinary tract, to store and periodically release urine, are dependent on the activity of smooth and striated muscles in the urinary bladder, urethra, and external urethral sphincter. These structures constitute a functional unit which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors (Andersson 1993, de Groat et al. 1999, de Groat and Yoshimura 2001). Malfunction at various levels may result in bladder control disorders disorders, which roughly can be classified as disturbances of filling/storage or disturbances of emptying (Wein 2001a). 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. Theoretically, a disturbed filling/storage function can be improved by agents that decrease detrusor activity, increase bladder capacity and/or increase outlet resistance (Wein 2001a).

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, and the use of some of the currently prescribed agents is based more on tradition than on evidence based on results from controlled clinical trials (Andersson et al 1999, Wein 2001a).

In this report, we update the recommendations from the previous International Consensus meeting. The most relevant information obtained since the last meeting is reviewed and summarised. Agents specifically used for treatment of urinary tract infections and interstitial cystitis have not been included. Drugs have been evaluated using different types of evidence (Table 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). This information has been considered in our clinical drug recommendations, which 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 1 : Types of evidence

PHARMACODYNAMIC
In vitro
In vivo
PHARMACOKINETIC
Absorption
Distribution
Metabolism
Excretion
PHYSIOLOGICAL
Animal models
Clinical phase I
CLINICAL
Oxford guidelines

II. CENTRAL NERVOUS CONTROL

The normal micturition reflex in the adult individual is mediated by a spinobulbospinal pathway, passing through relay centers in the brain (Figure 1). In infants, the central pathways seem to be organized as on-off switching circuits, but after the age of 4-6 years, voiding is initiated voluntarily by the cerebral cortex (de Groat et al 1999). Studies in humans and animals have identified areas in the brainstem and diencephalon that are specifically implicated in micturition control, namely Barrington's nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum,

which directly excites bladder motoneurons and indirectly inhibits urethral sphincter motoneurons via inhibitory interneurons in the medial sacral cord; the periaqueductal grey (PAG) receiving bladder filling information, and the pre-optic area of the hypothalamus, which is probably involved in the initiation of micturition. According to PET-scan studies in humans, these supraspinal regions are active during micturition (Blok et al 1998, Nour et al 2000).

III. PERIPHERAL NERVOUS CONTROL

Bladder emptying and urine storage involve a complex pattern of efferent and afferent signalling in *parasympathetic*, *sympathetic* and *somatic* nerves (Figures 1 and 2). These nerves are parts of reflex pathways which either maintain the bladder in a relaxed state, enabling urine storage at low intravesical pressure, or which initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Contraction of the detrusor smooth muscle and relaxation of the outflow region result from activation of *parasympathetic* neurones located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2-S4 (de Groat *et al.*, 1993). The postganglionic neurones in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine (ACh) acting on muscarinic receptors. However, an atropine-resistant component has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by release of nitric oxide (Andersson & Persson, 1993), although other transmitters might be involved (Bridgewater & Brading, 1993; Hashimoto *et al.*, 1993; Werkstrom *et al.*, 1995).

Most of the *sympathetic* innervation of the bladder and urethra originates from the intermediolateral nuclei in

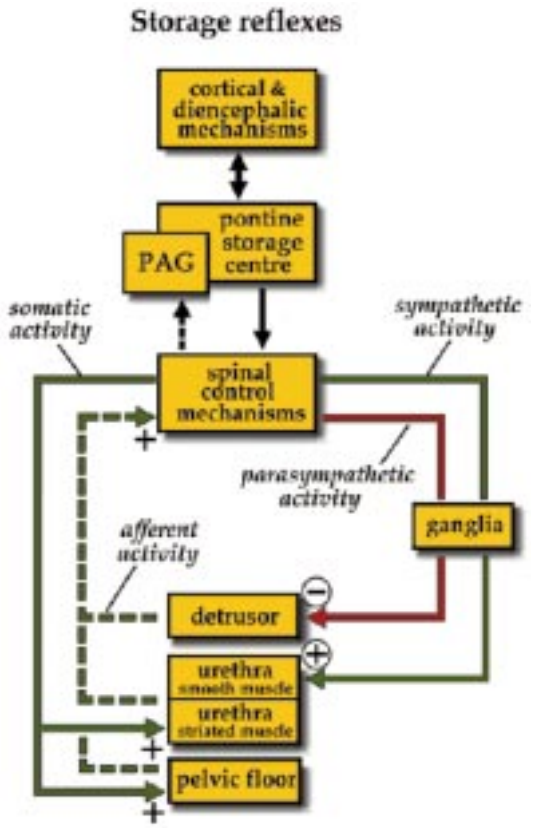

Figure 1 : During filling, there is continuous and increasing afferent activity from the bladder. There is no spinal parasympathetic outflow that can contract the bladder. The sympathetic outflow to urethral smooth muscle, and the somatic outflow to urethral and pelvic floor striated muscles keep the 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.

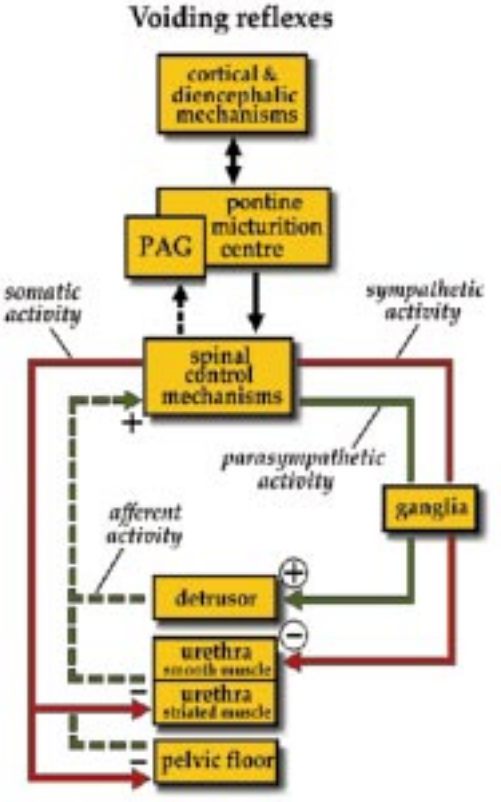

Figure 2 : Voiding reflexes involve supraspinal pathways, and are under voluntary control. During bladder emptying, the spinal parasympathetic outflow is activated, leading to bladder contraction. Simultaneously. the sympathetic outflow to urethral smooth muscle, and the somatic outflow to urethral and pelvic floor striated muscles are turned off, and the outflow region relaxes.

the thoraco-lumbar region (T10-L2) of the spinal cord. The axons travel either through the inferior mesenteric ganglia and the hypogastric nerve, or pass through the paravertebral chain and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric and pelvic nerves (Lincoln & Burnstock, 1993).

The predominant effects of the sympathetic innervation of the lower urinary tract in man are inhibition of the parasympathetic pathways at spinal and ganglion levels, and mediation of contraction of the bladder base and the urethra. However, in several animals, the adrenergic innervation of the bladder body is believed to inactivate the contractile mechanisms in the detrusor directly (Andersson 1993). Noradrenaline is released in response to electrical stimulation of detrusor tissues *in vitro*, and the normal response of detrusor tissues to released noradrenaline is relaxation (Andersson 1993).

Most of the *sensory* innervation of the bladder and urethra reaches the spinal cord via the pelvic nerve and dorsal root ganglia. In addition, some afferents travel in the hypogastric nerve. The sensory nerves of the striated muscle in the rhabdosphincter travel in the pudendal nerve to the sacral region of the spinal cord (Lincoln & Burnstock, 1993). The most important afferents for the micturition process are myelinated Aδ-fibres and unmyelinated C-fibres travelling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall to the spinal cord. The Aδ-fibres respond to passive distension and active contraction, thus conveying information about bladder filling (Janig & Morrison, 1986). C-fibres have a high mechanical threshold and respond primarily to chemical irritation of the bladder mucosa (Habler *et al.*, 1990) or cold (Fall *et al.*, 1990). Following chemical irritation, the C-fibre afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension (Habler *et al.*, 1990). These fibres are normally inactive and are therefore termed ”silent fibres”.

IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS

As pointed out previously, bladder control disorders can be divided into two general categories: disorders of filling/storage and disorders of voiding (Wein 2001). Storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence, which may account for one-third of cases. Failure to store also occurs if the bladder is unstable or overactive, and this may affect > 50 % of incontinent men and 10-15% of incontinent young women. Overactive bladder 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 denervation, or to damage to 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. Overactive bladder may also occur in elderly patients due to changes in the brain or bladder during aging. Urinary retention and overflow incontinence may occur in patients with urethral outlet obstruction (e.g. prostate enlargement), neural injury, and/or diseases that damage nerves (e.g. diabetes mellitus) or in those who are taking drugs that depress the neural control of the bladder (Wein 2001).

V. 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 (Andersson 1993, Bayliss et al 1999; Figure 3). However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused by ATP (Hoyle et al. 1989, Luheshi and Zar 1990, Ruggieri et al. 1990). ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G-protein-coupled receptor family (P2Y). Seven P2X subtypes and eight P2Y subtypes have been identified. In several species (rabbit, cat, rat, and human), various studies suggested that multiple purinergic excitatory receptors are present in the bladder (de Groat and Yoshimura 2001). Immunohistochemical experiments with specific antibodies for different P2X receptors showed that $P2X_1$ receptors are the dominant subtype in membranes of rat detrusor muscle and bladder vascular smooth muscle. Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells (de Groat and Yoshimura 2001). $P2X_3$ receptors, which have been identified in small-diameter afferent neurons in dorsal root ganglia, have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves. In $P2X_3$ knockout mice, afferent activity induced by bladder distension was significantly reduced (Cockayne et al 2000). These data indicate that purinergic receptors are involved in mechanosensory signaling in the bladder.

A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders

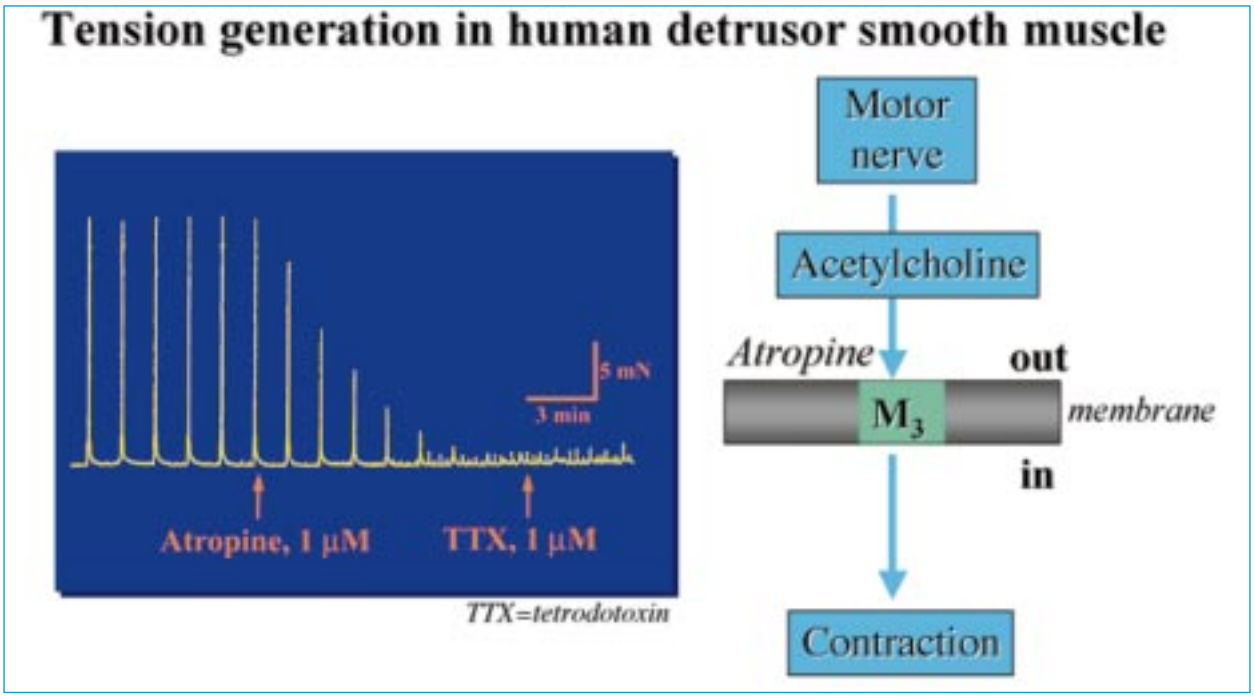

Figure 3: Contraction of the normal human bladder. Acetylcholine is released from cholinergic motor nerves and binds to the main contraction-mediating muscarinic (M_3) receptor (see also Figure 5). Note that there is prcatically no atropine resistance. Modified from Bayliss et al (1999).

(Figure 4), and has been reported to occur in hypertrophic bladders (Sjögren et al. 1982, Smith and Chapple 1994), interstitial cystitis (Palea et al. 1993), neurogenic bladders (Wammack et al. 1995), and in the aging bladder (Yoshida et al 2001). The importance of the NANC component to detrusor contraction in vivo, normally, and in different micturition disorders, remains to be established.

1. Muscarinic Receptors

Molecular cloning studies have revealed five distinct genes for muscarinic ACh receptors in rats and humans, and it is now generally accepted that five receptor subtypes correspond to these gene products (Eglen et al. 1996, Caulfield and Birdsall 1998). Muscarinic receptors are coupled to G-proteins (Figure 5). The signal transduction systems involved varies, but M_1, M_3, and M_5 preferentially couple to phosphoinositide hydrolysis leading to mobilization of intracellular calcium, wheras 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 (Bonev and Nelson 1993).

2. Bladder muscarinic receptors

Detrusor smooth muscle from various species contains muscarinic receptors of the M_1 and M_3 subtype (Hegde and Eglen 1999). In the human bladder, the occurrence of mRNAs encoding M_2 and M_3 subtypes has been demonstrated, whereas no mRNA encoding M_1 receptors was found (Yamaguchi et al 1996). The M_3 receptors in the human bladder are believed to cause a direct smooth muscle contraction through phosphoinositide hydrolysis (Harriss et al 1995), whereas the role for the M_2 receptors is not clarified. However, it has been suggested that M_2 receptors may oppose sympathetically (via β-ARs) mediated smooth muscle relaxation, since in rats activation of M_2 receptors results in an inhibition of adenylyl cyclase (Hegde et al 1997). Contractile mechanisms involving M_2 muscarinic receptors, such as activation of a non-specific cationic channel and inactivation of potassium channels, may be operative in the bladder (Hegde and Eglen 1999). However, there is general agreement that M_3 receptors are mainly responsible for the normal micturition contraction (Hegde and Eglen 1999). Even in the obstructed rat bladder, M_3 receptors were found to play a predominant role in mediating detrusor contraction (Krichevsky et al 1999). On the other hand, in certain disease states, M_2 receptors may contribute to contraction of the bladder. Thus, in the denervated rat bladder, M_2 receptors, or a combination of M_2 and M_3 receptors mediated contractile responses (Braverman et al 1998, 1999). Also in patients with neurogenic bladder dysfunction, detrusor contraction can be mediated by M_2 receptors (Braverman et al 2001).

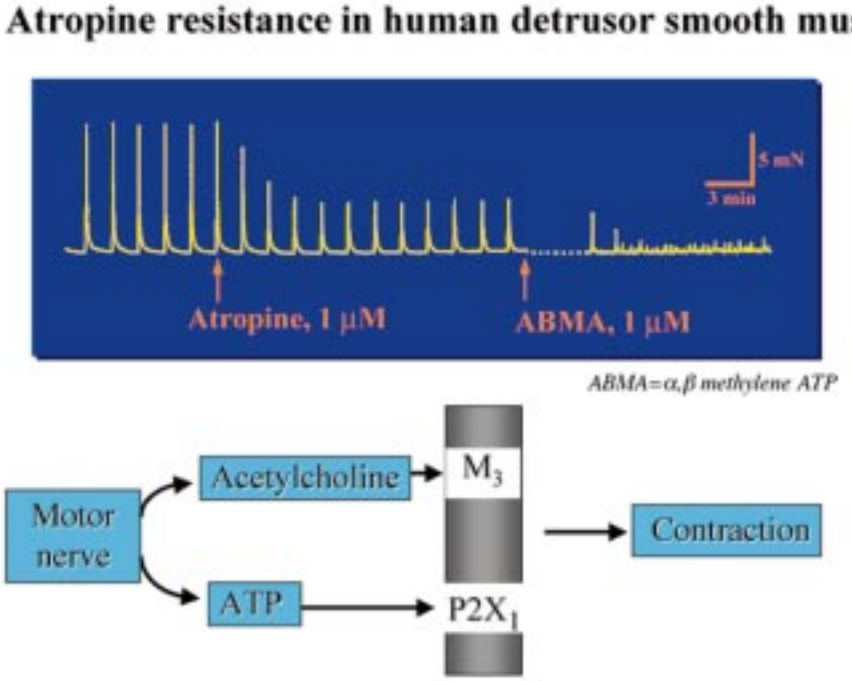

Figure 4 : Atropine resistance in the human bladder. The contraction remaining after addition of atropine is caused by ATP, and can be abolished by α,β methylene ATP, which causes desensitization of P2X receptors. Modified from Bayliss et al (1999).

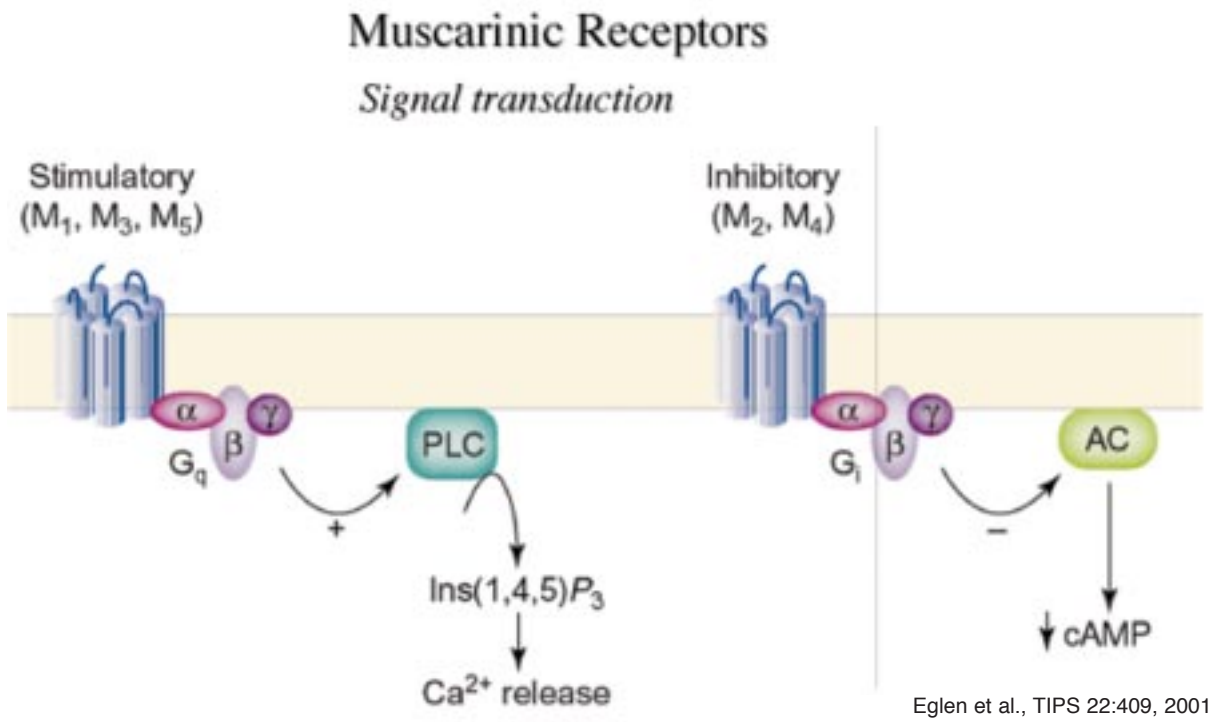

Figure 5 : Acetylcholine (ACh) is released from cholinergic nerve terminals, and acts on muscarinic receptors (M_1 and M_5) in the detrusor. Both M2 and M3 receptors are coupled to G-proteins (G-p) and may contribute to bladder contraction, but different signal transduction pathways are involved. M2 receptors inhibit adenylyl cyclase (AC), which leads to a diminished intracellular level of cyclic AMP (cAMP). cAMP mediates bladder relaxation. Stimulation of M3 receptors activates phospholipase C (PLC) to generate inositol triphosphate (IP3). IP3 can release calcium ions (Ca2+) from the sarcoplasmic reticulum and this Ca2+ will activate the contractile machinery within the cell with resulting bladder contraction. The voiding contraction is believed to be mediated mainly through M3 receptors.

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory pre-junctional muscarinic receptors have been classified as muscarinic M_2 in the rabbit (Tobin and Sjögren 1995) and rat (Somogyi and de Groat 1992), and M_4 in the guinea-pig (Alberts 1995) and human (d'Agostino et al 2000) urinary bladder. Pre-junctional facilitatory muscarinic receptors appears to be of the M_1 subtype in the rat and rabbit urinary bladder (Tobin and Sjögren 1995, Somogyi and de Groat 1992). Prejunctional muscarinic facilitation has also been detected in human bladders (Somogyi and de Groat 1999). The muscarinic facilitatory mechanism seems to be upregulated in hyperactive bladders from chronic spinal cord transected rats. The facilitation in these preparations is primarily mediated by M_1 muscarinic receptors (Somogyi and de Groat 1999).

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.

VI. 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, and 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 (Brading 1997) and neurological (de Groat 1997). Most probably, both factors contibute to the genesis of the the disease.

An abundance of drugs has been used for the treatment of the hyperactive detrusor (Table 2). However, for many of them, clinical use is based on the results of preliminary, open studies rather than randomized, controlled clinical trials (RCTs; for discussion of clinical research criteria, see addendum). It should be stressed that in many trials on both detrusor instability and detrusor hyperreflexia, there has been such a high placebo response that meaningful differences between placebo and active drug cannot be demonstrated (Thüroff et al 1998). However, drug effects in individual patients may be both distinct and useful.

As underlined by several other subcommittees, drugs may be efficacious in some patients, but they do have side effects, and frequently are not continued indefinitely. Hence it would be worth to consider them as an adjunct to conservative therapy. The role of pharmacotherapy is even more contentious in older, and particularly frail older people (see report from Committee no 10).

1. Antimuscarinic (anticholinergic) drugs

Voluntary, but also involuntary, bladder contractions are mediated mainly by ACh –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 (Jensen 1981). However, the "warning time", i.e., the time between the perception of an involuntary contraction about to occur and its occurrence, and the ability to suppress are not increased.

Several studies have supported that antimuscarinics can depress involuntary bladder contractions (Low 1977, Cardozo and Stanton 1979, Blaivas et al. 1980, Naglo et al. 1981). On the other hand, there are several reports of insufficient efficacy of antimuscarinics given orally to patients with unstable detrusor contractions (Ritch et al. 1977, Walther et al. 1982, Bonnesen et al, 1984, Zorzitto et al. 1986). It is unclear to what extent this can be attributed to low bioavailability of the drugs used, side effects limiting the dose that can be given, or to atropine resistance.

Atropine and related antimuscarinics are tertiary amines. They are well absorbed from the gastrointestinal tract and pass into the central nervous system (CNS) well. 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 (Pietzsko et al. 1994). 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 still the most widely used treatment for urge and urge incontinence (Andersson et al 1999). However, currently used drugs lack selectivity for the bladder (Eglen et al. 1996), and effects on other organ systems may result in side effects which limit their usefulness. 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. 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.

Table 2 : Drugs used in the treatment of detrusor overactivity. Assessments according to the Oxford system

	Level of evidence	Grade of recommendation
ANTIMUSCARINIC DRUGS		
Tolterodine	1	A
Trospium	1	A
Propantheline	2	B
Atropine, hyoscyamine	2	D
(Darifenacin, solifenacin)	UNDER INVESTIGATION	
DRUGS ACTING ON MEMBRANE CHANNELS		
Calcium antagonists	UNDER INVESTIGATION	
Potassium channel openers	UNDER INVESTIGATION	
DRUGS WITH MIXED ACTIONS		
Oxybutynin	1	A
Propiverine	1	A
Dicyclomine	4	C
Flavoxate	4	D
ALPHA-ADRENOCEPTOR ANTAGONISTS		
Alfuzosin	4	D
Doxazosin	4	D
Prazosin	4	D
Terazosin	4	D
Tamsulosin	4	D
BETA-ADRENOCEPTOR AGONISTS		
Terbutaline	4	D
Clenbuterol	4	D
Salbutamol	4	D
ANTIDEPRESSANTS		
Imipramine	2	C*
PROSTAGLANDIN SYNTHESIS INHIBITORS		
Indomethacin	4	C
Flurbiprofen	4	C
VASOPRESSIN ANALOGUES		
Desmopressin	1	A
OTHER DRUGS		
Baclofen	2**	C**
Capsaicin	3	C
Resiniferatoxin	UNDER INVESTIGATION	

** SHOULD BE USED WITH CAUTION ** INTRATHECAL USE*

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 (Andersson et al 1999, 2000).

a) Atropine

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 (Ekström et al. 1993, Glickman et al. 1995, Deaney et al 1998, Enskat et al 2001).

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.

b) Propantheline

Propantheline bromide is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes, which has a low (5 to 10%) and individually varying biological availability (Andersson 1988). It is usually given in a dose of 15 to 30 mg 4 times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher dosages. Using this approach in 26 patients with uninhibited detrusor contractions, Blaivas et al. (1980) in an open study obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline 15

mg 4 times daily. The range of dosages varied from 7.5 to 60 mg 4 times daily. In contrast, Thüroff et al. (1991) comparing the effects oxybutynin 5 mg x 3, propantheline 15 mg x 3, and placebo, in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency and incontinence related to detrusor overactivity (154 patients with idiopathic detrusor instability or detrusor hyperreflexia), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic detrusor instability), and with dose titration, Holmes et al. (1989) found no differences in efficacy between oxybutynin and propantheline. The AHCPR (Agency of health Care policy and Research) Clinical practice Guidelines (Urinary Incontinence Guideline Panel) lists 5 randomized controlled trials reviewed for propantheline, showing a reduction of urge (percent drug effect minus percent effect on placebo) between 0 to 53 %. Controlled randomized trials (n=6) were also reviewed by Thüroff et al (1998), who confirmed a positive, but varying response.

Although the effect of propantheline on detrusor overactivity has not been well documented in controlled trials satifying standards of today, it can be considered effective, and may, in individually titrated doses, be clinically useful.

c) Trospium

Trospium chloride is a quaternary ammonium compound with antimuscarinic actions on detrusor smooth muscle, but also with effects on ganglia (Antweiler 1966). However, the clinical importance of the ganglionic effects has not been established. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions (Ückert et al 1998). Trospium has no selectivity for muscarinic receptor subtypes. Its biological availability is low, approximately 5% (Schladitz-Keil et al 1986, Füsgen and Hauri 2000), and it does not cross the blood-brain barrier. It seems to have no negative cognitive effects (Füsgen and Hauri 2000, Todorova et al 2001, Wiedemann et al 2001). Several open studies have indicated that the drug may be useful in the treatment of detrusor overactivity (Lux and Widey 1992, Madersbacher et al 1991, Stöhrer et al. 1991). In a placebo-controlled, double-blind study on patients with detrusor hyperreflexia (Stöhrer et al. 1991), 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 multicentre trial in patients with spinal cord injuries and detrusor hyperreflexia, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects (Madersbacher et al. 1995.

The effect of trospium in urge incontinence has been documented in placebo-controlled, randomized studies. Allousi et al (1998) 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 b.i.d. Significant increases were noted in volume at first unstable contraction and in maximum bladder capacity. Cardozo et al (2000) investigated 208 patients with bladder instability, who were treated with trospium 20 mg b.i.d. for two 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. (2000) compared the effects of oxybutynin 5 mg b. i.d. with those of trospium 20 mg b.i.d. 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 (2000) compared trospium 20 mg b.i.d with tolterodine 2 mg b.i.d 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 were comparable in the trospium and tolterodine groups (7 and 9%, respectively).

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

d) Tolterodine

Tolterodine is a potent and competitive antagonist at muscarinic receptors, developed for treatment of urinary urgency and urge incontinence (Nilvebrant et al. 1997a, b, Hills et al. 1998, Clemett and Jarvis 2001). 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 (Nilvebrant et al. 1997a, and possibly in man (Stahl et al. 1995). Tolterodine has a major active metabolite with a similar pharmacological profile as the mother compound (Nilvebrant et al. 1997 c). This metabolite significantly contributes to the therapeutic effect of tolterodine (Brynne et al. 1997, 1998). 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 (Brynne et al. 1998). 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 (Stahl et al. 1995). However, 5 h after administration, the effects on the urinary bladder were maintained, whereas no significant effects on salivation could be demonstrated.

The relatively low lipophilicity of tolterodine implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects (Chapple 2000, Clemett and Jarvis 2001)

Several randomised, double-blind, placebo-controlled studies, both on patients with idiopathic detrusor instability and detrusor hyperreflexia, have documented a significant reduction in micturition frequency and number of incontinence episodes (see Hills et al. 1998, Clemett and Jarvis 2001). Tolterodine seems to be well tolerated when used in the dosage range 1 to 4 mg a day. Chancellor et al (2000) reported the results of a double-blind randomized study on 1022 patients comparing tolterodine 2 mg b.i.d. to placebo. Active drug reduced urge incontinence episodes by 46% versus base-line, and the effect compared to placebo was also significant. Withdrawals were essentially the same between the two treatment groups.

A once daily formulation of tolterodine has recently been developed, and the first large scale (1529 patients) clinical trial compared the effects of this agent to placebo and the twice daily formulation (van Kerrebroeck et al 2001). Tolterodine extended release 4 mg once daily and tolterodine immediate release 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 bid and oxybutynin 5 mg t.i.d 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 (Abrams et al. 1998). These findings were largely confirmed by other investigators (Drutz et al 1999, Malone-Lee et al 2001). Malone-Lee et al (2001) compared oxybutynin and tolterodine in 378 patients 50 years and older with symptoms of overactive bladder. They received 10 weeks of treatment with tolterodine 2 mg b.i.d. or oxybutynin 5 mg b.i.d (final doses). Patients treated with tolterodine had significantly fewer adverse events (69% versus 81%), notably dry mouth (37% versus 61%), than those in the oxybutynin group. Each agent had comparable efficacy for improving urinary symptoms. The authors concluded that tolterodine was as effective as oxybutynin for improving the symptoms of overactive bladder, but had superior tolerability. These data contrast with those of Appell et al (2001) 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 b.i.d. 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 treament groups.

No comparative trials between extended release tolterodine and the extended release form of oxybutynin have 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 (Chapple 2000, Wein 2001b). 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 in detrusor overactivity, and the side effect profile seems acceptable.

e) Darifenacin

Darifenacin is a selective muscarinic M_3 receptor antagonist developed for treatment of bladder overactivity (Alabaster 1997). In vitro, it is selective for human cloned muscarinic M_3 receptors relative to M_1, M_2, M_4 or M_5. On theoretical grounds, it may be argued that M_3

vs M_1 receptor selectivity may provide an advantage over non-selective agents, since both M_3 and M_1 receptors have been implicated in salivary mucous secretion (Culp et al 1996), and in an anesthetized dog model model, selectivity for the urinary bladder over the salivary gland has been demonstrated (Newgreen et al. 1995, Wallis et al. 1995). M_3 vs M_1 selectivity may be associated with a low rate of cognitive impairment (M_1; Pavia et al 1998). M_3 vs M_2 selectivity can provide little effect on heart rate (M_2), and M_3 vs M_5 selectivity may reduce impairment of visual accommodation (M_5; Eglen and Nahorski 2000, Choppin and Eglen 2000). However, the clinical importance of these potential advantages has not been established.

Published clinical information on the effect of darifenacin 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 contractions (Rosario et al. 1995). In a randomised, double-blind trial of 25 patients with detrusor instability, the effects of darifenacin 15 mg and 30 mg o.d. and oxybutynin 5 mg t.i.d. on ambulatory urodynamic monitoring and salivary flow were compared (Mundy et al 2001). 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 o.d., dicyclomine 20 mg q.d.s, and placebo on cognitive and cardiac functions were investigated (Nichols et al 2001). Unlike dicyclomine, darifenacin had no detectable effects on cognitive or cardiovascular function.

Darifenacin is currently being evaluated in a phase III global clinical evaluation programme for the treatment of bladder overactivity, to identify the optimal dose regimen and to assess its potential clinical benefits.

f) Solifenacin (YM-905)

Solifenacin (YM905) is a long acting muscarinic receptor antagonist developed for the treatment of overactive bladder.

In guinea-pig urinary bladder smooth muscle preparations, solifenacin inhibited cholinergic responses with nanomolar potency. When tested in anaesthetised mice, both solifenacin and oxybutynin potently inhibited carbachol-induced increase of urinary bladder pressure. However, only oxybutynin was associated with potent inhibition of carbachol-stimulated salivary secretion (Ikeda et al. 1998). In cellular systems, solifenacin appears to be more potent as a muscarinic receptor antagonist for bladder smooth muscle than for salivary gland when compared with reference molecules like oxybutynin or tolterodine, indicating a potentially beneficial efficacy/tolerability profile (Ikeda et al. 1999). The clinical relevance of these findings is currently being investigated in phase III clinical studies.

2. Drugs acting on membrane channels

a) Calcium antagonists

Activation of detrusor muscle, both through 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+} (Andersson 1993). 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 (Andersson and Forman 1978). However, there have been few clinical studies of the effects of calcium antagonists in patients with detrusor overactivity (see Andersson et al 1999). Intravesical instillation of verapamil was found to increase bladder capacity and decrease the degree of leakage during cystometry in patients with detrusor hyperreflexia (Mattiasson et al. 1989). The effect was less pronounced in patients with non-neurogenic overactivity (Babu et al. 1990).

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 (Andersson et al. 1986). Oral nifedipine has been used effectively as prophylaxis for autonomic hyperreflexia during urologic instrumentation in spinal cord injured patients (Wein 2001b).

b) Potassium channel openers

Opening of K+channels and subsequent efflux of K^+ will produce hyperpolarization of various smooth muscles, including the detrusor (Andersson 1992, Shieh et al 2000). This leads to a decrease in Ca^{2+} influx by reducing the opening probability of Ca^{2+} channels 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 (Andersson 1992), 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 preparations than of detrusor muscle, and in clinical trials performed with these drugs, no bladder effects have been found at doses already lowering blood pressure (Hedlund et al.

1991, Komersova et al. 1995). However, new drugs with K_{ATP} channel opening properties have been described, which may be useful for the treatment of bladder overactivity (Howe et al. 1995, Masuda et al. 1995, Butera et al 2000, Gilbert et al. 2000, Shieh et al 2000).

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.

3. 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. 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 (Conolly et al. 1991, Stewart et al. 1992).

a) 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 (Kachur et al. 1988). 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 (Nilvebrant et al. 1985, Waldeck et al. 1997). The drug was shown to have higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors (Nilvebrant et al. 1986, Norhona-Blob and Kachur 1991), 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 interindividual variation (Douchamps et al 1988, Hughes et al. 1992). Oxybutynin has an active metabolite, N-desethyl oxybutynin, which has pharmacological properties similar to those of the parent compound (Waldeck et al. 1997), but which occurs in much higher concentrations (Hughes et al. 1992). Considering this, 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. (1988).

Several controlled studies have have shown that oxybutynin is effective in controlling detrusor overactivity, including hyperreflexia (Thompson and Lauvetz 1976, Moisey et al. 1980, Hehir and Fitzpatrick 1985, Gajewski and Awad 1986, Cardozo et al. 1987, Zeegers et al. 1987, Holmes et al 1989, Thüroff et al. 1991, More et al. 1990, Tapp et al. 1990, Iselin et al. 1997, see reviews by Yarker et al. 1995, Thüroff et al 1998, Wein 2001). The recommended oral dose of the immediate release form is 5 mg t.d. or q.i.d., even if lower doses have been used. Thüroff et al (1998) 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 percent of patients reporting side effects was 70 (range 17% - 93%). Oxybutynin 7.5 to 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 - was reported by only 8% of the patients (Amarenco et al. 1998).

In nursing home residents (n=75), Ouslander et al. (1995) 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 (Szonyi et al. 1995).

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit (Szollar and Lee 1996, Kim et al. 1997).

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 (Baigrie et al. 1988, Jonville et al. 1992). Oxybutynin passes the blood-brain barrier and may have effects on the central nervous system

(Pietsko et al 1994, Todorova et al 2001). The drug can cause cognitive impairment (Katz et al, Ferrara et al. 2001), and this side effect may be particularly troublesome in the geriatric population (Ouslander et al 2000).The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence (Hussain et al. 1994); no changes were found. It cannot be excluded that the commonly recommended dose 5 mg x 3 is unnecessarily high in some patients, and that a starting dose of 2.5 mg x 2 with following dose-titration would reduce the number of adverse effects (Malone-Lee et al. 1992, Amarenco et al. 1998).

Once daily formulations of oxybutynin have been developed. The oxybutynin ER (Ditropan XL) uses an innovative osmotic drug delivery system to release the drug at at a controlled rate over 24 h. This formulation overcomes the marked peak to trough fluctuations inplasma levels of both drug and the major metabolite, which occurs with immediate release oxybutynin (Gupta and Sathayan 1999). 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. Anderson et al (1999) 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 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.

Another controlled study comparing efficacy and safety of controlled release oxybutynin with conventional immediate-release oxybutynin, included 226 patients with urge incontinence (Versi et al 2000). They were known to respond to anticholinergic therapy and had seven or more urge incontinence episodes per week. Reductions in urge urinary incontinence episodes from baseline to the end of treatment were 18.6 to 2.9 per week (83% mean decrease) and 19.8 to 4.4 per week (76% mean decrease) in the controlled- and immediate-release oxybutynin groups (difference non-significant), respectively. The incidence of dry mouth increased with dose in both groups, but there was no difference in dry mouth rates between the groups: 47.7% and 59.1% for the controlled- and immediate-release. However, a significantly lower proportion of patients taking controlled-release oxybutynin had moderate to severe dry mouth or any dry mouth compared with those taking immediate-release oxybutynin.

As referred to previously, Appell et al (2001) compared extended-release oxybutynin chloride 10 mg/day and tolterodine 2 mg b.i.d 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.

A different extended release form of oxybutynin was utilized by Birns et al (2000), who reported comparable efficacy of a 10 mg preparation with 5 mg b.i.d. of immediate release oxybutynin. Efficacy was similar, but the extended release formulation was better tolerated, patients only reporting approximately half the total number of adverse effects than with the immediate release preparation. Nilsson et al (1997), however, failed to demonstrated improved tolerability with this controlled release tablet.

Other administration forms of oxybutynin have been introduced. Rectal administration (Collas and Malone-Lee 1997, Winkler and Sand 1998) was reported to have fewer adverse effects than the conventional tablets. A transdermal preparation is in clinical trials.

Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in hypereflexia and in other types of bladder overactivity, and both in children and adults (Brendler et al. 1989, Madersbacher and Jilg 1991, O´Flynn and Thomas 1993, Weese et al 1993, Mizunaga et al. 1994, Buyse et al. 1995, Enzelsberger et al. 1995, Madersbacher and Knoll 1995, Kaplinsky et al. 1996), although adverse effects may occur (Kasabian et al. 1994, Palmer et al. 1997). 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 (Ferrarra et al, 2001), 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.

b) Dicyclomine

Dicyclomine has attributed to it both a direct relaxant effect on smooth muscle and an antimuscarinic action (Downie et al. 1977). Favorable results in detrusor overactivity have been demonstrated in several studies (Beck et al. 1976, Awad et al. 1977, Fischer et al. 1978, Castleden et al. 1987), performed more than a decade ago and which do not satisfy current criteria of good quality RTCs.

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

c) Propiverine

Propiverine has been shown to have combined anticholinergic and calcium antagonistic actions (Haruno et al. 1989, Haruno 1992, Tokuno et al. 1993). The drug is rapidly absorbed, but has a high first pass metabolism. Several active metabolites are formed (Haustein and Hüller 1988, Muller et al. 1993), whose pharmacological characteristics remain to be established. It seems most probable that these metabolites contribute to the clinical effects of the drug.

Propiverine has been shown to have beneficial effects in patients with detrusor overactivity in several investigations. Thüroff et al (1998) 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, showing symptomatic improvement in approximately 50% and 25% of cases, respectively (Takayasu et al. 1990, Richter et al. 1997). Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate and placebo (Wehnert and Sage 1989), and propiverine, oxybutynin and placebo (Wehnert and Sage 1992, Madersbacher et al. 1999), have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin.

Stöhrer et al (1999) reported a double-blind, randomised, prospective, multicentre trial comparing propiverine 15mg t.i.d. 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 per cent of the patients expressed subjectively an improvement under 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 (1999) compared the tolerability and efficacy of propiverine (15 mg t.i.d.) oxybutynin (5 mg b.i.d.) 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 of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin.

Dorschner et al (1999) investigated in a double-blind, multicentre, 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 t.i.d.) or placebo (t.i.d.) 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). Resting and ambulatory electrocardiograms indicated no significant changes. The incidence of adverse events was very low (2% dryness of the mouth under 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.

d) 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 (Guarneri et al. 1994). 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 (Oka et al. 1996). Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity (Cazzulani et al. 1988, Caine et al. 1991).

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 (Ruffman 1988). Stanton (1973) compared emepronium 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 emepronium bromide, respectively, both administered as 200 mg 3 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 utilising both clinical and urodynamic criteria, Milani et al. (1993) 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 flavoxate with those of placebo, have not been able to show any beneficial effect of flavoxate at dosages up to 400 mg 3 times daily (Briggs et al. 1980, Chapple et al. 1990, Dahm et al. 1995).

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.

4. α-Adrenoceptor antagonists

The normal human detrusor responds to noradrenaline by relaxing (Perlberg and Caine 1982, Åmark 1986), 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 (Andersson 1993, 1997).

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 (Perlberg and Caine 1982) and neurogenic bladders (Andersson 1993). A significant subtype selective α_{1D}-AR mRNA upregulation was found in rats with outflow obstruction (Schwinn and Michelotti 2000), 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.

Even if it is well known that α-AR antagonists can ameliorate lower urinary tract symptoms in men with BPH (Andersson et al. 1997), and occasionally can abolish detrusor overactivity in these patients (Perlberg and Caine 1982, Caine 1986, Eri and Tveter 1995), there are no controlled clinical trials showing that they are an effective alternative in the treatment of bladder overactivity in this patient category. In an open label study, Arnold (2001) evaluated the clinical and pressure-flow effects of tamsulosin 0.4 mg once daily in patients with lower urinary tract symptoms (LUTS) caused by benign prostatic obstruction. He found that tamsulosin can produce a significant decrease in detrusor pressure, increase in flow rate and a symptomatic improvement in patients with LUTS and confirmed obstruction.

α-AR antagonists have been used to treat patients with neurogenic bladders and bladder overactivity (Jensen 1981, Petersen et al. 1989, Åmark and Nergård 1991, Abrams 2001); however, the success has been moderate. Abrams (2001) 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 (Jollys et al 1993, Lepor and Machi 1993). In a prospective open study of 34 women with urgency and frequency, evaluated by an expanded AUA symptom score, a combination of doxazosin and hyoscyamine was found to be more effective than either drug given alone (Serels and Stein 1998). 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 (Dwyer and Teele 1992, Marshall and Beevers 1996).

5. β–Adrenoceptor agonists

In isolated human bladder, non-subtype selective β-AR agonists like isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in man (Andersson 1993). However, the β-ARs of the human bladder were shown to have functional characteristics typical of neither β_1-, nor β_2-ARs, since they could be blocked by propranolol, but not by practolol or metoprolol (β_1) or butoxamine (β_2) (Nergårdh et al. 1977, Larsen 1979). 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 (Levin et al. 1988), and favourable effects on bladder overactivity were reported in open studies with selective β_2-AR agonists such as terbutaline (Norlén et al. 1978, Lindholm and Lose 1986). In a double-blind investigation clenbuterol 0.01

mg 3 times daily was shown to have a good therapeutic effect in 15 of 20 women with motor urge incontinence (Grüneberger 1984). Other investigators, however, have not been able to show that β-AR agonists represent an effective therapeutic principle in elderly patients with unstable bladder (Castleden and Morgan 1980), or in young patients with myelodysplasia and detrusor overactivity (Naglo et al. 1981).

Atypical β-AR-mediated responses, reported repeatedly in early studies of β-AR antagonists, have been shown to be mediated by a β3-AR, which has been cloned, sequenced, expressed in model system, and extensively characterized functionally (Lipworth 1996, Strosberg and Pietri-Rouxel 1997). Both normal and neurogenic human detrusors were shown to express β_1, β_2-, and β3-AR mRNAs, and selective β3-AR agonists effectively relaxed both types of detrusor muscle (Igawa et al. 1999, 2001, Takeda et al 1999). Thus, it seems that the atypical β-AR of the human bladder may be the β3-AR. Whether or not this is of importance in humans, and whether β3-AR stimulation will be an effective way of treating the overactive bladder, has yet to be shown in controlled clinical trials.

6. Antidepressants

Several antidepressants have been reported to have beneficial effects in patients with detrusor overactivity (Martin and Schiff 1984, Lose et al. 1989). However, 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 (Baldessarini 1985) and blockade of the reuptake of serotonin and noradrenaline (Maggi et al. 1989a), but its mode of action in detrusor overactivity has not been established (Hunsballe and Djurhuus 2001). Even if imipramine 25 to 75 mg, given intramuscularly to 11 patients with uncontrolled detrusor contractions (Diokno et et al. 1972), had no effect, several investigators have found that the drug can be effective in the treatment of bladder overactivity. Thus, in elderly patients with detrusor instability, who received oral imipramine in doses up to 150 mg daily, good effects were reported (Castleden et al. 1981, 1986). Raezer et al. (1977) found that a combination of propantheline and imipramine was particularly useful. 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 favourable effects in the treatment of nocturnal enuresis in children with a success rate of 10-70 % in controlled trials (Miller et al. 1987, Hunsballe and Djurhuus 2001).

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 (Bigger et al 1977, Giardina et al 1979). Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants (Baldessarini 1985).

The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have have been performed during the last decade (Hunsballe and Djurhuus 2001), and no good quality RCTs have documented that the drug is effective in the treatment detrusor overactivity. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

7. Prostaglandin synthesis inhibitors

Human bladder mucosa has the ability to synthesize eicosanoids (Jeremy et al. 1987), and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma (Downie et al. 1984, Leslie et al. 1984). Even if prostaglandins cause contraction of human bladder muscle (Andersson 1993), 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. (1980) performed a double-blind controlled study of 30 women with detrusor instability using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg 3 times daily. The drug was shown to have favourable 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 (1983) studied the effects of flurbiprofen 50 mg x 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 to 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 (Cardozo and Stanton 1980). The inci-

dence of side effects was high, occurring in 19 of 32 patients. However, no patient had to stop treatment because of side effects.

The few 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.

8. Vasopressin analogues

a) Desmopressin

Desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) is a synthetic vasopressin analogue with a pronounced antidiuretic effect, but practically lacking vasopressor actions (Andersson et al. 1988). It is now widely used as a treatment for primary nocturnal enuresis (Nevéus et al 1999). 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 a high nocturnal urine production (Rittig et al. 1989, Matthiesen et al. 1996, Nørgaard et al. 1997, Hjälmås 1999). By decreasing the nocturnal production of urine, beneficial effects may be obtained in enuresis and nocturia. However, the drug may also have stimulatory effects on the CNS, as found in rats (DiMichele et al. 1996).

Several, controlled, double-blind investigations have shown intranasal administration of desmopressin to be effective in the treatment of nocturnal enuresis in children (Miller et al. 1992, Moffat et al. 1993, Nevéus et al 1999). 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 to 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 (Janknegt et al 1997, Skoog et al 1997).

Positive effects of desmopressin on nocturia in adults have been documented. Nocturnal frequency and enuresis due to bladder instability responded favourably to intranasal desmopressin therapy even when previous treatment with "antispasmodics" had been unsuccessful (Hilton and Stanton 1982). Also in patients with multiple sclerosis, desmopressin was shown in controlled studies to reduce nocturia, and micturition frequency (Hilton et al. 1983, Kinn and Larsson 1990, Eckford et al. 1994, Fredrikson et al. 1996). Furthermore, desmopressin was shown to be successful in treating nocturnal enuresis in spina bifida patients with diurnal incontinence (Horowitz et al. 1997). 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 (Weiss et al 2001, van Kerrebroeck et al 2001).

Desmopressin is a well documented therapeutic alternative in paediatric 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 (Robson et al. 1996, Schwab and Ruder 1997), and due consideration should be given to this potential side effect, particularly in elderly patients.

9. Other drugs

a) Baclofen

Baclofen is considered to depress monosynaptic and polysynaptic motorneurons and interneurons in the spinal cord by acting as a $GABA_B$ receptor agonist, and has been been used in voiding disorders, including detrusor hyperreflexia secondary to lesions of the spinal cord (Andersson 1988, Wein 1995). The drug may also be an alternative in the treatment of idiopathic detrusor overactivity (Taylor and Bates 1979). However, published experience with the drug is limited.

Intrathecal baclofen may be useful in patients with spasticity and bladder dysfunction, and increase bladder capacity (Kums and Delhaas 1991, Steers et al. 1992, Bushman et al. 1993).

10. 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-fibres) resistant to activation by natural stimuli (Maggi 1993). It is believed that capsaicin exerts these effects by acting on specific receptors, "vanilloid" receptors (Szallasi 1994). It is possible that capsaicin at high concentrations (mM) has additional, non-specific effects (Kuo 1997).

Cystometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans was originally presented by Maggi et al. (1989b), who instilled capsaicin (0.1-10 μM) intravesically in five patients with hypersensitivity disorders; with attenuation of their symptoms a few days after administration of capsaicin. Intravesical capsaicin, given in considerably higher concentrations (1-2 mM)

than those administered by Maggi et al. (1989b), has since been used with success in detrusor overactivity associated with neurological disorders such as multiple sclerosis, or traumatic chronic spinal lesions (Igawa et al. 1996). The effect of treatment may last for 2 to 7 months (Fowler et al. 1992, Geirsson et al. 1995, Chandiramani et al. 1996, Cruz et al. 1997, De Ridder et al 1997, Cruz 1998, Wiart et al. 1998 de Ridder and Baert 2000, Fowler 2000). However, negative results have also been reported (Petersen et al (1998). de Ridder et al. (1997) recommended that the drug should not be given to severely disabled, bedridden patients.

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 (Chandiramani et al. 1996). 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 (Dasgupta et al. 1998).

Resiniferatoxin is a phorbol related diterpene, isolated from some species of Eurphorbia, 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 (Ishizuka et al. 1995b). Moreover, resiniferatoxin seems able to desensitize bladder sensory fibers with less C-fos expression in the rat spinal cord (Craft et al. 1995, Cruz et al. 1996). Craft et al. (1995) reported that resiniferatoxin, instilled intravesically, produced a desensitization of bladder afferents that lasted approximately 2 months in a rat behavioral model. The authors also suggested that resiniferatoxin may be superior to capsaicin as an agent for desensitization therapy. Lazzeri et al. (1997), instilled resiniferatoxin intravesically in 15 subjects, including 8 normals 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 patients, 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. (1997) 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 (Lazzeri et al 1998, Silva et al 2000). 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.

VII. DRUGS USED FOR TREATMENT OF STRESS INCONTINENCE

Many factors seem to be involved in the pathogenesis of stress urinary incontinence: urethral support, vesical neck function, and function of the urethral muscles (DeLancey 1977). Such anatomical factors cannot be treated pharmacologically. However women with stress incontinence have lower resting urethral pressures than age-matched continent women (Henriksson et al. 1979, Hilton and Stanton 1983), and since it seems likely that there is a reduced urethral closure pressure in most women with stress incontinence, it seems logical to increase urethral pressure to improve the condition.

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 noradrenaline (Andersson 1993). 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 3) 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

Table 3 : Drugs used in the treatment of stress incontinence Assessments according to the Oxford system

ALPHA-ADRENOCEPTOR AGONISTS		
Ephedrine	3	C
Norephedrine (phenylpropanolamine, PPA)	2	NR
OTHER DRUGS		
Imipramine	4	C*
Clenbuterol	4	C
(Duloxetine)	UNDER INVESTIGATION	
Hormones		
Estrogens	2	D

NR = NOT RECOMMENDED
* SHOULD BE USED WITH CAUTION

contribute to such an increase in intraurethral pressure, including β-AR antagonists and imipramine (see Andersson 1988, Wein 1995), only α-AR agonists and estrogens (see below), alone or together, have been more widely used.

a) α-Adrenoceptor agonists

Although several drugs with agonistic effects on α-ARs have been used in the treatment of stress incontinence, for example midodrine (Jonas 1982, Gnad et al. 1984) and norfenefrine (Lose and Lindholm 1984), ephedrine and norephedrine seem to be the most widely used drugs (Andersson 1988, Wein 1995). Ephedrine, pseudoephedrine (a stereoisomer of ephedrine), and norephedrine (phenylpropanolamine, PPA) directly stimulate α- as well as β-ARs, but can also release noradrenaline from adrenergic nerve terminals. They have all been reported to be effective in stress incontinence, as found in open and controlled clinical trials (Diokno and Taub 1975, Awad et al. 1978, Ek et al. 1978, Collste and Lindskog 1987, Siltberg et al 1999), ephedrine at a dose of 25 to 50 mg 3 to 4 times daily, and PPA at a dose of 50 to 100 mg 2 to 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 (Andersson 1988, Wein 1995). 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 (Vick et al 1994), 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.

Radley et al (2001) evaluated the effect of the selective α_1-AR agonist, methoxamine, in a randomised, double-blind, placebo-controlled, crossover 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 a 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.

Attempts have been made to develop agonists with selectivity for the human urethra. Among the three high affinity α_1-AR subtypes identified in molecular cloning and functional studies (α_{1A}, α_{1B}, α_{1D}), α_{1A} seems to predominate in the human lower urinary tract (Andersson 2001). However, the receptor with low affinity for prazosin (the α_{1L}-AR), which has not been cloned and may represent a functional phenotype of the α_{1A}-AR, was found to be prominent in the human male urethra. In the human female urethra, the expression and distribution of α_1-AR subtypes were determined by in situ hybridisation and quantitative autoradiography. mRNA for the α_{1A} subtype was predominant, and autoradiography confirmed the predominance of the α_{1A}-AR (Nasu et al 1998).

No drug with appropriate sub-type selectivity is currently available, and the role of α-AR agonists in the treatment of stress incontinence has yet to be established.

α-AR agonists has been used used in combination with estrogens (Kinn and Lindskog 1988, Ahlström et al. 1990), and with other nonsurgical treatments of stress incontinence, such as pelvic floor exercises and electrical stimulation. Beisland et al (1984) treated 24 women with genuine stress incontinence using PPA (50 mg twice daily) and estriol (1 mg per day vaginally) separately and in combination. They found that the combination cured 8 women and improved further 9 and was more effective than either drug given alone. Hilton and collegues (1990) used (estrogen vaginal or oral) alone or in combination with PPA to treat 60 postmenopausal women with genuine stress incontinence in a double-blind, placebo controlled study. Subjectively the symptom of stress incontinence improved in all groups, but objectively only in the women given combination therapy. 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 motivate their use as single drug therapy or in combination with estrogen. In carefully selected patients, selective α_1-AR antagonists may be used on an ”on demand” basis in certain situations known to provoke leakage.

b) 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-ARs may enhance the effects of noradrenaline on urethral α-ARs. Even if propranolol has been reported to have beneficial effects in the treatment of stress incontinence (Gleason et al 1974, Kaisary 1984), there are no RCTs supporting such an action.

c) Imipramine

Imipramine, among several other pharmacological effects, inhibits the re-uptake of noradrenaline and serotonin in adrenergic nerve ending. In the urethra, this can

be expected to enhance the contractile effects of noradrenaline 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 (1984) 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 mm Hg. Lin et al (1999) assessed the efficacy of imipramine (25 mg imipramine three times a day for three months) as a treatment of genuine stress incontinence in forty 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.

d) Clenbuterol

Since β-AR antagonists have been used as a treatment of 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 (Yasuda et al 1993). 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 cm H_2O in the clenbuterol and -1.5 cm H_2O 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 (2000) 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. In an open study, Noguchi et al (1997) reported positive results with clenbuterol (20 mg b.i.d for 1 month) in 9 of 14 patients with mild to moderate stress incontinence after radical prostatectomy. Further well-designed RTCs 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.

e) Duloxetine

Duloxetine, a combined noradrenaline 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 (Thor and Katofiasc 1995). In a double-blind, placebo-controlled study in women with stress (n=140) or mixed (n=146) incontinence, duloxetine (20-40 mg q.d.) was shown to cause significant improvements in several efficacy measures (ICS 1 h stress pad test, 24h pad weight, number of incontinence episodes, quality of life assessment; Zinner et al 1998). 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.

VIII. 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 syndrom). In adults, overflow incontinence may be associated with outflow obstruction secondary to BPH or can be a consequence of diabetes mellitus. Mixed forms may be seen in disorders associated with motor spasticity (e.g., Parkinson´s disease).

Pharmacologic treatment (Table 4) 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 1985, Wein et al 1994). Stimulation of detrusor activity by intravesical instillation of prostaglandins have been reported to be successful; however, the effect is controversial and no RCTs are available (Andersson 1988, Wein et al. 1994, Wein, 2001a).

The “autonomous” contractions in patients with para-

Table 4 : Drugs used in the treatment of overflow incontinence. Assessments according to the Oxford system

ALPHA-ADRENOCEPTOR ANTAGONISTS		
Alfuzosin	4	C
Doxazosin	4	C
Prazosin	4	C
Terazosin	4	C
Tamsulosin	4	C
*(Phenoxybenzamine)	4	NR
MUSCARINIC RECEPTOR AGONISTS		
Bethanechol	4	D
Carbachol	4	D
ANTICHOLINESTERASE		
Distigmine	4	D
OTHER DRUGS		
Baclofen	4	C
Benzodiazepines	4	C
Dantrolene	4	C

NR = NOT RECOMMENDED

sympathetic decentralisation are probably caused by α-AR mediated bladder activity, since they can be inhibited by α-AR antagonists (Sundin et al 1977). The α-AR antagonist that has been most widely used is probably phenoxybenzamine (Hachen 1980, Krane and Olsson 1973, McGuire et al 1976). However, uncertainties about the carcinogenic effects of this drug, and its side effects (Caine 1986) have focused interest on selective α_1-AR antagonists such as prazosin (Andersson et al 1991).

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 et al 1994, Wein 2001a).

IX. HORMONAL TREATMENT OF URINARY INCONTINENCE

1. 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 (Abrams et al 1990). 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.

a) 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 (Bergman et al 1990), estrogens increase urethral closure pressure and improve abdominal pressure transmission to the proximal urethra (Hilton et al 1983, Bhatia et al 1989, Karram et al 1989). The sensory threshold of the bladder may also be raised (Fantl et al 1988). Salmon et al (1941) were the first to report the successful use of estrogens to treat urinary incontinence over fifty years ago. Intramuscular estrogen therapy was administered to 16 women with dysuria, frequency, urgency and incontinence for 4 weeks. Symptomatic improvement occurred in 12 women until treatment was discontinued, at which time the symptoms recurred. Further studies on larger numbers of patients (Musiani 1972, Schleyer-Saunders 1976) also showed impressive subjective improvement rates of between 39-70%.

There are a number of different causes of lower urinary tract disorders in postmenopausal women (Bent et al 1983). It is well recognized that there is a poor correlation between a woman´s symptoms and the subsequent diagnosis following appropriate investigation (Jarvis et al 1980). Unfortunately, initial trials took place before the widespread introduction of urodynamic studies and therefore almost certainly included a heterogenous group of individuals with a number of different pathologies. Lack of objective outcome measures also limit their interpretation.

Lose and Englev (2000) evaluated the effect of estrogens in two hundred and fifty-one postmenopausal women, with a mean age of 66 years, reporting at least one bothersome lower urinary tract symptom in an open, randomised, parallel group trial. One hundred and thirty-four women were treated with an oestradiol-releasing ring for 24 weeks; 117 women were treated with oestriol 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% vs 56%), urge incontinence (58% vs 58%), stress incontinence (53% vs 59%) and nocturia (51% vs 54%). The authors concluded that low dose vaginally administered oestradiol and oestriol 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.

b) 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 2000). 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 (1996) treated 83 hypo-estrogenic 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 (1996) 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 (Fantl et al 1994). 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 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 (1990) 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 (2001) compared the effects of the combination of pelvic floor exercise and estriol (1mg/day) in sixty-six patients with postmenopausal stress incontinence. Efficacy was evaluated every three 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 three 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.

c) 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 (Hextall 2000).

A double blind multi-center study of 64 postmenopausal women with the "urge syndrome" has failed to confirm its efficacy (Cardozo et al 1993). All women underwent pre-treatment urodynamic investigation to establish that they either had 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 (2001) 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 =.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 <.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 incon-

tinence. 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.

ADDENDUM 1

Clinical Research Criteria

The Committee has included a section on clinical research criteria to encompass general considerations relating to design of clinical trails and appropriate assessments of efficacy of pharmacotherapy for incontinence (see also Blaivas et al 1997).

Existing pharmacotherapies are designed to reduce symptoms and improve quality of life and we therefore feel that these measures should, wherever possible, be considered to be primary efficacy parameters. It is obviously important to document as secondary endpoints the mechanistic aspects of any therapy and for this reason it is essential that objective urodynamic parameters are measured including data relating to frequency and volumes voided (the frequency volume chart), urgency and degree of urgency, number of urge incontinent episodes and wherever possible data relating to volume at first unstable contraction and amplitude of unstable contractions.

It is important that therapies should be administered for adequate lengths of time to allow a steady state situation to be established and also bearing in mind the existing literature base which suggests that drugs may take up to 2 months to produce optimum efficacy often as a consequences of the concomitant bladder retraining and behavioural aspects relating to improvement of symptoms which occur on treatment.

It is important to provide long term follow up data and to appreciate the relevance of data relating to real life practice as well as the essential randomised control data.

The limitations of both approaches however should be adequately taken into account and interpretation of data. Whenever possible pragmatic study designs should be used. It is essential that both cost benefit and cost efficacy should be adequately addressed at an early stage in development of any new therapy.

Whenever a new therapeutic modality is being introduced then the limitations of in vitro and in vivo pharmacological data particularly when based on animal models should be recognised and appropriate proof of concept studies conducted. The role of innovative clinical investigative approaches is to be encouraged including the use of ambulatory urodynamic assessment using a cross-over design.

Adequate patient selection criteria should be utilised which reflect the nature of the population to be treated with particular reference to not excluding the specific population groups which will be a principle target of future therapy. For instance many studies exclude the frail elderly and those with concomitant medical problems. These groups are often in particular risk of being troubled by incontinence.

It is essential that randomised placebo controlled study designs are used wherever possible and that the studies are adequately powered. Peer reviewed journals should be strongly encouraged not to publish studies which do not stick to these criteria. Studies utilising symptoms as an inclusion criterion require greater numbers of patients than those using specific criteria with a clearly identifiable disease entity; therefore studies using overactive bladder criteria require larger numbers than those using detrusor instability.

It may be recommended that all future studies stratify for age, taking into consideration age-related changes in bladder function. Future research with drugs should consider a conservative arm in the study design.

ADDENDUM 2

Placebo

A placebo response refers to the change that may occur in response to the administration of an inactive drug, also called a dummy drug. The placebo effect is defined as the difference between the response with the placebo versus the changes that occur without the administration of any drug. This change may be due to spontaneous remission of the disease, regression toward the mean, life changes, the passage of time, or factors as subtle as the value of more frequent interaction with the provider and the expectancy of a result. The patient's expectations of what is going to happen can lead to self-cure.

The origin of placebo controlled trials probably began with Cornell Conference on Therapy in 1946 and advocacy for the use of placebos in randomized controlled trials (RCT) is generally credited to Dr. Harry Gold. At this conference Dr. Eugene F DuBois noted "If you take three groups, one given no treatment, a second given placebo, and a third given the test drug, you will very often find that the group given the placebos get along very much better, have a much higher percentage of cures than those without treatment, and perhaps, almost as many as those with the test drug, in some cases more".

Today the results of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs and antibiotics. Well-designed clinical trials allow investigators to distinguish the effect of active drug from other influences such as a spontaneous change in the course of the disease, the placebo effect, or even biased observations. Adverse effects caused by a drug can be separated from those resulting from underlying disease.

It is now over fifty years since the first paper that looked at the 'powerful placebo' response and a wide range of clinical studies have reported a placebo response averaging 32 percent (Beecher, 1955). Recently this placebo response has been questioned by Hrobjartsson and Gotzsche (2001), who suggested that the reported large effects of placebo could therefore, at least in part, be artifacts of inadequate research methods. These authors, using Cochrane techniques, found little evidence in general that placebos had powerful clinical effects. However, it is believed that the "uncompromising condemnation of placebos is a bit too sweeping" (Bailer, 2001). There is still evidence that placebo benefits are demonstrable in these studies especially in the treatment of pain.

The use of placebo controlled clinical trials is not required by most regulatory agencies. What is required is adequate and well controlled investigations. By regulation, the Food and Drug Administration (FDA) has described these as placebo control, dose-comparison studies; no treatment concurrent controls, active treatment concurrent controls; and even historical controls (from www.fda.gov/cderCommittee for Advanced Scientific Education Seminar, 1999). (This document lists examples of studies where you cannot do placebo control trials.) Active control trials are to be used "when the condition treated is such that the administration of placebo, or no treatment would be contrary to the interests of the patient." When a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo. Many placebo-controlled trials are conducted as add-on-trials where all patients receive a specified standard therapy or therapy left to the choice of the treating physician or institution.). Even when placebo or a no-treatment control arm is used this does not imply that the patient does not get any treatment at all. For example, in cases of oncology trials when no active drug is approved the patient will still receive standard of care palliative therapy.

Use of a placebo control may raise problems of ethics, acceptability, and feasibility, when an effective treatment is available for the condition under study in a proposed trial. In cases, where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. There are occasional exceptions, however, such as cases in which standard therapy has toxicity so severe that many patients have refused to receive it (FDA Guidance). The use of placebos is not acceptable or ethical in most instances for assessing and managing pain as stated by most professional organizations.

One should also consider the possibility of an increased risk of adverse events during the treatment cycle, e.g. 12 weeks or longer if patients are not receiving the active therapeutic intervention.

It is estimated that more placebos have been administered to participants in clinical trials than any single experimental drug, which should provide a wealth of substantial knowledge that almost no one evaluates. Traditionally, most studies of a new molecular entity for the treatment of urge and mixed incontinence have used a placebo arm in the clinical trials for the approval process or a comparator arm. In some cases the placebo response in the 12-week studies have made it difficult to detect significant differences between the active drug and the placebo. One possibility is that there is a bladder training effect developing with the completion of multiple frequency-volume charts resulting in this 'placebo' response.

It is difficult to compare the placebo response between different studies since the inclusion criteria and severity of disease may not be comparable. The planning of these studies must take into consideration this placebo response in order to adequately detect statistical significant differences between drug and placebo.

Variability of individual responses and response to inactive drug in each of these studies must be considered in the planning of future trials. Most studies are 12 weeks in duration and do not provide long term data on the outcome of patients on placebo. In addition data is not separated by severity of disease. Most importantly there is a learning response probably associated with the patient's beliefs and expectations that must be considered in any of these clinical trials.

REFERENCES

Abrams P and The European Tamsulosin NLUTD Study Group. Tamsulosin efficacy and safety in neurogenic lower urinary tract dysfunction (NLUTD). J Urol 165 Suppl:276 (abstract 1137)

Abrams P, Blaivas JG, Stanton SL et al. The standardisation of terminology of lower urinary tract function. Br J Obstet Gynecol 97:1, 1990

Abrams P, Freeman R, Anderstrom C et al. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol 81:801, 1998

Ahlström K, Sandahl B, Sjöberg B et al. Effect of combined treatment with phenylpropanolamine and estriol, compared with estriol treatment alone, in postmenopausal women with stress urinary incontinence. Gynecol Obstet Invest 30:37, 1990

Alabaster VA. Discovery & development of selective M3 antagonists for clinical use. Life Sci 60:1053, 1997

Alberts P. Classification of the presynaptic muscarinic receptor that regulates 3H-acetylcholine secretion in the guinea pig urinary bladder in vitro. J Pharmacol Exp Ther 274:458, 1995

Allousi S, Laval K-U, Eckert R. Trospium chloride (Spasmo-lyt) in patients with motor urge syndrome (detrusor instability): a double-blind, randomised, multicentre, placebo-controlled study. J Clin Res 1:439, 1998

Amarenco G, Marquis P, McCarthy C et al. Qualité de vie des femmes souffrant d´impériosité mictionelle avec ou sans fuites: étude prospective aprés traitement par oxybutinine (1701 cas). Presse Medicale 27:5, 1998

Åmark P, Nergårdh A. Influence of adrenergic agonists and antagonists on urethral pressure, bladder pressure and detrusor hyperactivity in children with myelodysplasia. Acta Paed Scand 80:824, 1991

Åmark P. The effect of noradrenaline on the contractile response of the urinary bladder. Scand J Urol Nephrol 20:203, 1986

Anderson RU, Mobley D, Blank B et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. OROS Oxybutynin Study Group. J Urol 161:1809, 1999

Andersson KE, Appell R, Cardozo LD et al. Pharmacological treatment of urinary incontinence. In: Incontinence, 1st International Consultation on Incontinence. Abrams P, Khoury S & Wein A (eds), Plymbridge Distributors Ltd, UK, pp447-486, 1999

Andersson KE, Appell R, Cardozo LD et al. The pharmacological treatment of urinary incontinence. BJU Int 84:923, 1999

Andersson K-E, Bengtsson B, Paulsen O. Desamino-8-D-Arginine vasopressin (DDAVP): Pharmacology and clinical use. Drugs of Today 24:509, 1988

Andersson K-E, Ek A, Hedlund H et al. Effects of prazosin on isolated human urethra and in patients with lower motor neuron lesions. Invest Urol 19:39, 1981.

Andersson K-E, Forman A. Effects of calcium channel blockers on urinary tract smooth muscle. Acta Pharmacol Toxicol Suppl II: 90, 1978

Andersson K-E, Fovaeus M, Morgan E et al. Comparative effects of five different calcium channel blockers on the atropine resistant contraction in electrically stimulated rabbit urinary bladder. Neurourol Urodyn 5:579, 1986

Andersson K-E, Lepor H, Wyllie M. Prostatic α1-adrenoceptors and uroselectivity. Prostate 30:202, 1997

Andersson KE, Persson K. The L-arginine/nitric oxide pathway and non-adrenergic, non-cholinergic relaxation of the lower urinary tract. Gen Pharmacol 24:833, 1993.

Andersson K-E. Clinical pharmacology of potassium channel openers. Pharmacol Toxicol 70:244, 1992

Andersson K-E. Current concepts in the treatment of disorders of micturition. Drugs 35:477 1988

Andersson KE. Neurotransmission and drug effects in urethral smooth muscle. Scand J. Urol. Nephrol. Suppl. 207: 26, 2001.

Andersson K-E. The pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev 45: 253, 1993

Antweiler H. Zur Pharmakologie und Toxikologie von Azoniaspiranen in der Nortropin- bzw. Pseudonortropin-Reihe. Arzneimittel Forsch/Drug Res 16: 1581, 1966

Appell RA, Sand P, Dmochowski R et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc 76:358, 2001

Arnold EP. Tamsulosin in men with confirmed bladder outlet obstruction: a clinical and urodynamic analysis from a single centre in New Zealand. BJU Int 87:24, 2001

Awad SA, Bryniak S, Downie JW et al. The treatment of the uninhibited bladder with dicyclomine. J Urol 117:161, 1977

Awad SA, Downie JW, KirilutaHG. Alpha-adrenergic agents in urinary disorders of the proximal urethra, part I: sphincteric incontinence. Br J Urol 50: 332, 1978

Babu R, Vaidyanathan S, Sankaranarayan A et al. Effect of intravesical instillation of varying doses of verapamil (20 mg, 40 mg, 80 mg) upon urinary bladder function in chronic traumatic paraplegics with overactive detrusor function. Int J Clin Pharmacol 28:350, 1990

Baigrie RJ, Kelleher JP, Fawcett DP et al. Oxybutynin: is it safe? Br J Urol 62: 319, 1988

Bailer J C. The powerful placebo and the wizard of Oz. New England Journal of Medicine 344:21, 2001

Baldessarini KJ. Drugs in the treatment of psychiatric disorders. In: Gilman et al. (Eds.) The pharmacological basis of therapeutics, 7th ed., McMillan Publishing Co., pp 387-445,1985

Bayliss M, Wu C, Newgreen D et al. A quantitative study of atropine-resistant contractile responses in human detrusor smooth muscle, from stable, unstable and obstructed bladders. J Urol 162:1833, 1999

Beck RP, Arnausch T, King C. Results of treating 210 patients with detrusor overactivity incontinence of urine. Am J Obstet Gynecol 125:593, 1976

Beecher H K. The powerful placebo. JAMA 159:1602, 1955

Beisland HO, Fossberg E, Moer A et al. Urethral insufficiency in postmenopausal females:treatment with phenylpropanolamine and estriol separately and in combination. Urol Int 39:211, 1984

Bent AE, Richardson DA, Ostergard DR. Diagnosis of lower urinary tract disorders in postmenopausal patients. Am J Obstet Gynecol 145:218, 1983

Bergman A, Karram MM, Bhatia NN. Changes in urethral cytology following estrogen administration. Gynecol Obstet Invest 29:211, 1990

Bhatia NN, Bergman A, Karram MM. Effects of estrogen on urethral function in women with urinary incontinence. Am J Obstet Gynecol 160:176, 1989

Bigger JT, Giardina EG, Perel JM et al . Cardiac antiarrhythmic effect of imipramine hydrochloride. N Engl J Med 296: 206, 977.

Birns J, Lukkari E, Malone-Lee JG. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. BJU Int 85:793, 2000

Blaivas JG, Appell RA, Fantl JA et al. Standards of efficacy for evaluation of treatment outcomes in urinary incontinence: Recommendations of the Urodynamic Society. Neurourol Urodyn 16:145, 1997

Blaivas JG Labib KB, Michalik J et al. Cystometric response to propantheline in detrusor hyperreflexia: therapeutic implications. J Urol 124:259, 1980

Blok BF, Sturms LM, Holstege G.Brain activation during micturition in women. Brain 121: 2033, 1948.

Bonev AD, Nelson MT. Muscarinic inhibition of ATP-sensitive K+ channels by protein kinase C in urinary bladder smooth muscle. Am J Physiol 265:C1723, 1993

Bonnesen T, Tikjøb G, Kamper AL et al. Effect of emepronium bromide (Cetiprin) on symptoms and urinary bladder function after transurethral resection of the prostate. A double-blind randomized trial. Urol Int 39:318, 1984

Brading AF. A myogenic basis for the overactive bladder. Urology 50 (Suppl 6A):57, 1997

Braverman A, Legos J, Young W et al. M2 receptors in genito-urinary smooth muscle pathology. Life Sci 64:429, 1999.

Braverman AS, Luthin GR, Ruggieri MR. M2 muscarinic receptor contributes to contraction of the denervated rat urinary bladder. Am J Physiol 275:R1654, 1998

Braverman, AS, Ruggieri MR, Pontari MA. The M2 muscarinic receptor subtype mediates cholinergic bladder contractions in patients with neurogenic bladder dysfunction. J Urol 165 Suppl:36 (abstract 147)

Brendler CB, Radebaugh LC, Mohler JL. Topical oxybutynin chloride for relaxation of dysfunctional bladders. J Urol 141:1350, 1989

Bridgewater M, MacNeil HF, Brading AF. Regulation of tone in pig urethral smooth muscle. J Urol 150:223, 1993.

Briggs KS, Castleden CM, Asher MJ. The effect of flavoxate on uninhibited detrusor contractions and urinary incontinence in the elderly. J Urol 123:665, 1980

Brynne N, Dalen P, Alvan G. Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. Clin Pharmacol Ther 63:529, 1998

Brynne N, Stahl MMS, Hallén B. Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 35:287, 1997

Bushman W, Steers WD, Meythaler JM. Voiding dysfunction in patients with spastic paraplegia: urodynamic evaluation and response to continuous intrathecal baclofen. Neurol Urodyn 12:163, 1993

Butera JA, Antane MM, Antane SA et al. Design and SAR of novel potassium channel openers targeted for urge urinary incontinence. 1. N-Cyanoguanidine bioisosteres possessing in vivo bladder selectivity. J Med Chem 43:1187, 2000

Buyse G, Verpoorten C, Vereecken R et al. Treatment of neurogenic bladder dysfunction in infants and children with neurospinal dysraphism with clean intermittent (self)catheterisation and optimized intraversical oxybutynin hydrochloride therapy. Eur J Pediatr Surg 5 Suppl 1: 31, 1995

Caine M, Gin S, Pietra C et al. Antispasmodic effects of flavoxate, MFCA, and Rec 15/2053 on smooth muscle of human prostate and urinary bladder. Urology 37:390, 1991

Caine M. The present role of alpha-adrenergic blockers in the treatment of benign prostatic hyperplasia. J Urol 136:1, 1986

Cardozo L, Chapple CR, Toozs-Hobson P et al. Efficacy of trospium chloride in patients with detrusor instability: a placebo-controlled, randomized, double-blind, multicentre clinical trial. BJU Int 85:659, 2000

Cardozo L, Rekers H, Tapp A et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. Maturitas 18:47, 1993

Cardozo LD, Cooper D, Versi E. Oxybutynin chloride in the management of idiopathic detrusor instability. Neurourol Urodyn 6:256, 1987

Cardozo LD, Kelleher CJ. Sex hormones, the menopause and urinary problems. Gyn Endocrinol 9:75, 1995

Cardozo LD, Stanton SL, Robinson H et al. Evaluation on flurbiprofen in detrusor instability. Br Med J 280:281, 1980

Cardozo LD, Stanton SL. A comparison between bromocriptine and indomethacin in the treatment of detrusor instability. J Urol 123:399, 1980

Cardozo LD, Stanton SL. An objective comparison of the effects of parenterally administered drug in patients suffering from detrusor instability. J Urol 122:58, 1979

Castleden CM, Duffin HM, Gulati RS. Double-blind study of imipramine and placebo for incontinence due to bladder instability. Age Ageing 15:299, 1986.

Castleden CM, Duffin HM, Millar AW. Dicyclomine hydrochloride in detrusor instability: A controlled clinical pilot study. J Clin Exper Gerontol 9:265, 1987

Castleden CM, George CF, Renwick AG et al. Imipramine - a possible alternative to current therapy for urinary incontinence in the elderly. J Urol 125: 318, 1981

Castleden CM, Morgan B. The effect of ß-adrenoceptor agonists on urinary incontinence in the elderly. Br J Clin Pharmacol 10:619, 1980

Caulfield MP, Birdsall NJ. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 50:279, 1998

Cazzulani P, Pietra C, Abbiati GA et al. Pharmacological activities of the main metabolite of flavoxate 3-methylflavone-8-carboxylic acid. Arzneim Forsch /Drug Res 38:379, 1988

Chancellor M, Freedman S, Mitcheson HD et al. Tolterodine, an effective and well tolerated treatment for urge incontinence and othe overactive bladder symptoms. Drug Invest 19:83, 2000

Chandiramani VA, Peterson T, Duthie GS et al. Urodynamic changes during therapeutic intravesical instillations of capsaicin. Br J Urol 77:792, 1996

Chapple CR, Parkhouse H, Gardener C et al Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. Br J Urol 66:491, 1990

Chapple CR. Muscarinic receptor antagonists in the treatment of overactive bladder.Urology (Suppl 5A):33, 2000

Choppin A, Eglen RM. Pharmacological characterisation of muscarinic receptors in feline and human isolated ciliary muscle. Br J Pharmacol 129:206P, 2000

Clemett D, Jarvis B. Tolterodine a review of its use in the treatment of overactive bladder. Drugs Aging 18:277, 2001

Cockayne DA, Hamilton SG, Zhu QM et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. Nature 407:1011, 2000

Collas D, Malone-Lee JG. The pharmacokinetic properties of rectal oxybutynin - a possible alternative to intravesical administration. Neurourol Urodyn 16:346, 1997

Collste L, Lindskog M. Phenylpropanolamine in treatment of female stress urinary incontinence. Double-blind placebo controlled study in 24 patients. Urology 40:398, 1987

Connolly MJ, Astridge PS, White EG et al. Torsades de pointes complicating treatment with terodiline. Lancet 338:344, 1991

Craft RM, Cohen SM, Porreca F. Long-lasting desensitization of bladder afferents following intravesical resiniferatoxin and capsaicin in the rat. Pain 61: 317, 1995

Cruz F, Avelino A, Coimbra A. Desensitization follows excitation of bladder primary afferents by intravesical capsaicin, as shown by c-fos activation in the spinal cord. Pain 64:553, 1996

Cruz F, Guimaraes M, Silva C et al. Desensitization of bladder sensory fibers by intravesical capsaicin has long lasting clinical and urodynamic effects in patients with hyperactive or hypersensitive bladder dysfunction. J Urol 157:585, 1997

Cruz F, Guimaraes M, Silva C et al. Suppression of bladder hyperreflexia by intravesical resiniferatoxin. Lancet 350:640, 1997

Cruz F. Desensitization of bladder sensory fibers by intravesical capsaicin or capsaicin analogs. A new strategy for treatment of urge incontinence in patients with spinal detrusor hyperreflexia or bladder hypersensitivity disorders. Inter Urogynecol J Pelvic Floor Dysfunct 9: 214, 1998.

Culp DJ, Luo W, Richardson LA et al. Both M1 and M3 receptors regulate exocrine secretion by mucous acini. Am J Physiol 271:C1963, 1996

D'Agostino G, Bolognesi ML, Luchelli A et al. Prejunctional muscarinic inhibitory control of acetylcholine release in the human isolated detrusor : involvement of the M_4 receptor serotype. Br J pharmacol 129: 493, 2000.

Dahm TL, Ostri P, Kristensen JK et al Flavoxate treatment of micturition disorders accompanying benign prostatic hypertrophy: a double-blind placebo-controlled multicenter investigation. Urol Int 55:205, 1995

Dasgupta P, Chandiramani V, Parkinson MC et al. Treating the human bladder with capsaicin: is it safe? Eur Urol 33:28, 1998

de Groat WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: The Autonomic Nervous System. Vol. 6, Chapter 8, Nervous Control of the Urogenital System, ed. by C.A. Maggi. Harwood Academic Publishers, London, U.K., pp. 227-89, 1993

de Groat WC, Downie JW, Levin RM et al. Basic Neurophysiology and Neuropharmacology. In Incontinence, 1st International Consultation on Incontinence, Abrams P, Khoury S, Wein A (eds), Plymbridge Distributors Ltd, UK, pp 105-154, 1999.

de Groat WC, Yoshimura N. Pharmacology of the lower urinary tract. Annu Rev Pharmacol Toxicol 41:691, 2001

de Groat WC. A neurological basis for the overactive bladder. Urology 50 (Suppl 6A):36, 1997

De Ridder D, Baert L. Vanilloids and the overactive bladder. BJU Int 86:172, 2000

De Ridder D, Chandiramani V, Dasgupta P et al. Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: a dual center study with long-term followup. J Urol 158:2087, 1997

Deaney C, Glickman S, Gluck T et al. Intravesical atropine suppression of detrusor hyperreflexia in multiple sclerosis. J Neurol Neurosurg Psychiatry 65:957, 1998

DeLancey JOL. The pathophysiology of stress urinary incontinence in women and its implications for surgical treatment. World J Urol 15:268, 1997

DiMichele S, Sillén U, Engel JA et al. Desmopressin and vasopressin increase locomotor activity in the rat via a central mechanism: implications for nocturnal enuresis. J Urol 156:1164, 1996

Diokno AC, Hyndman CW, Hardy DA et al. Comparison of action of imipramine (Tofranil) and propantheline (Probanthine) on detrusor contraction. J Urol 107:42, 1972

Diokno AC, Taub M. Ephedrine in treatment of urinary incontinence. Urology 5: 624, 1975

Dorschner W, Stolzenburg JU, Griebenow R et al. Efficacy and cardiac safety of propiverine in elderly patients - a double-blind, placebo-controlled clinical study. Eur Urol 37:702, 2000

Douchamps J, Derenne F, Stockis A et al. The pharmacokinetics of oxybutynin in man. Eur J Clin Pharmacol 35:515, 1988

Downie JW, Twiddy DAS, Awad SA. Antimuscarinic and noncompetitive antagonist properties of dicyclomine hydrochloride in isolated human and rabbit bladder muscle. J Pharmacol Exp Ther 201:662, 1977

Downie, JW, Karmazyn M. Mechanical trauma to bladder epithelium liberates prostanoids which modulate neurotransmission in rabbit detrusor muscle. J Pharmacol Exp Ther 230:445, 1984

Drutz HP, Appell RA, Gleason D et al. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 10:283, 1999

Dwyer PL, Teele JS. Prazosin: a neglected cause of genuine stress incontinence. Obstet Gynecol 79: 117, 1992.

Eckford SD, Swami KS, Jackson SR et al. Desmopressin in the treatment of nocturia and enuresis in patients with multiple sclerosis. Br J Urol 74:733, 1994

Eglen RM, Hegde SS, Watson N. Muscarinic receptor subtypes and smooth muscle function. Pharmacol Rev 48:531, 1996

Eglen RM, Nahorski SR. The muscarinic M5 receptor: a silent or emerging subtype? Br J Pharmacol 130:13, 2000

Ek A, Andersson K-E, Gullberg B et al. The effects of long-term treatment with norephedrine on stress incontinence and urethral closure profile. Scand J Urol Neprol 12:105, 1978

Ekström B, Andersson K-E, Mattiasson A. Urodynamic effects of intravesical instillation of atropine and phentolamine in patients with detrusor hyperactivity. J Urol 149:155, 1992

Enskat R, Deaney CN, Glickman S. Systemic effects of intravesical atropine sulphate. BJU Int 87:613, 2001

Enzelsberger H, Helmer, H, Kurz C. Intravesical instillation of of oxybutynin in woman with idiopathic detrusor instability: a randomised trial. Br J Obstet Gynaecol 102:929, 1995

Eri L M, Tveter K J. α-Blockade in the treatment of symptomatic benign prostatic hyperplasia. J Urol 154:923, 1995

Fall M, Lindstrom S, Mazieres L. A bladder-to-bladder cooling reflex in the cat. J Physiol 427:281, 1990

Fantl JA, Bump RC, Robinson D et al. Efficay of estrogen supplementation in the treatment of urinary incontinence. Obstet Gynecol 88:745, 1996

Fantl JA, Cardozo LD, McClish DK et al. Estrogen therapy in the management of urinary incontinence in postmenopausal women:a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 83:12, 1994

Fantl JA, Wyman JF, Anderson RL et al. Postmenopausal urinary incontinence: comparison between non-estrogen and estrogen supplemented women. Obstet Gynecol 71:823, 1988

Ferrara P, D'Aleo CM, Tarquini E et al. Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. BJU Int 87:674, 2001.

Finkbeiner AE. Is bethanechol chloride clinically effective in promoting bladder emptying : a literature review. J Urol 134:443, 1985

Fischer CP, Diokno A, Lapides J. The anticholinergic effects of dicyclomine hydrochloride for uninhibited neurogenic bladder dysfunction. J Urol 120:328, 1978

Fowler CJ, Jewkes D, McDonald WI et al. Intravesical capsaicin for neurogenic bladder dysfunction. Lancet 339:1239, 1992

Fowler CJ. Intravesical treatment of overactive bladder. Urology 55(Suppl 5A):60, 2000

Fredrikson S. Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. Acta Neurol Scand 94:31, 1996

Fusgen I, Hauri D. Trospium chloride: an effective option for medical treatment of bladder overactivity. Int J Clin Pharmacol Ther 38:223, 2000

Gajewski JB, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. J Urol 135:966, 1986

Geirsson G, Fall M, Sullivan L. Clinical and urodynamic effects of intravesical capsaicin treatment in patients with chronic traumatic spinal detrusor hypereflexia. J Urol 154:1825, 1995

Giardina EG, Bigger JT Jr, Glassman AH et al. The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 60:1045, 1979

Gilbert AM, Antane MM, Argentieri TM et al. Design and SAR of novel potassium channel openers targeted for urge urinary incontinence. 2. Selective and potent benzylamino cyclobutenediones. J Med Chem 43:1203, 2000

Gilja I, Radej M, Kovacic M et al. Conservative treatment of female stress incontinence with imipramine. J Urol 132: 909, 1984

Gleason DM, Reilly SA, Bottacini MR et al. The urethral continence zone and its relation to stress incontinence. J Urol 112:81, 1974

Glickman S, Tsokkos N, Shah PJ. Intravesical atropine and suppression of detrusor hypercontractility in the neuropathic bladder. A preliminary study. Paraplegia 33:36, 1995

Gnad H, Burmucic R, Petritsch P et al. Conservative therapy of female stress incontinence. Double-blind study with the alpha-sympathomimetic midodrin. Fortschr Med 102:578, 1984 (in German)

Grady D, Brown JS, Vittinghoff E et al. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstet Gynecol 97:116, 2001

Grüneberger A. Treatment of motor urge incontinence with clenbuterol and flavoxate hydrochloride. Br J Obstet Gynaecol 91:275, 1984

Guarneri L, Robinson E, Testa R. A review of flavoxate: pharmacology and mechanism of action. Drugs Today 30:91, 1994

Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. J Clin Pharmacol 39: 289, 1999.

Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. J Physiol 425:545, 1990

Hachen HJ. Clinical and urodynamic assessment of alpha adrenolytic therapy in patients with neurogenic bladder function. Paraplegia 18:229, 1980

Harriss DR, Marsh KA, Birmingham AT et al. Expression of muscarinic M3-receptors coupled to inositol phospholipid hydrolysis in human detrusor cultured smooth muscle cells. J Urol 154:1241, 1995

Haruno A, Yamasaki Y, Miyoshi K et al. Effects of propiverine hydrochloride and its metabolites on isolated guinea pig urinary bladder. Folia Pharmacol Japon 94:145, 1989

Haruno A. Inhibitory effects of propiverine hydrochloride on the agonist-induced or spontaneous contractions of various isolated muscle preparations. Arzneim-Forsch /Drug Res 42:815, 1992

Hashimoto S, Kigoshi S, Muramatsu I. Nitric oxide-dependent and -independent neurogenic relaxation of isolated dog urethra. Eur J Pharmacol 231:209, 1993

Haustein KO, Huller G. On the pharmacokinetics and metabolism of propiverine in man. Eur J Drug Metab Pharmacokinet 13:81, 1988

Hedlund H, Andersson K-E, Mattiasson A. Effects of pinacidil on detrusor instability in men with outlet obstruction. J Urol 146:1345, 1991

Hegde SS, Choppin A, Bonhaus D et al. Functional role of M2 and M3 muscarinic receptors in the urinary bladder of rats in vitro and in vivo. Br J Pharmacol 120:1409, 1997

Hegde SS, Eglen RM. Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. Life Sci 64:419, 1999

Hehir M, Fitzpatrick JM. Oxybutynin and prevention of urinary incontinence in spina bifida. Eur Urol 11:254, 1985

Henriksson L, Andersson K-E, Ulmsten U. The urethral pressure profiles in continent and stress incontinent women. Scand J Urol Nephrol 13:5, 1979

Hextall A. Oestrogens and lower urinary tract function. Maturitas 36:83, 2000

Hills CJ, Winter SA, Balfour JA. Tolterodine. Drugs 55:813, 1998

Hilton P, Hertogs K, Stanton SL. The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. J Neurol Neurosurg Psychiatry 46: 854, 1983

Hilton P, Stanton SL. The use of intravaginal oestrogen cream in genuine stress incontinence. Br J Obstet Gynecol 90:940, 1983

Hilton P, Stanton SL. The use of desmopressin (DDAVP) in nocturnal frequency in the female. Br J Urol 54:252, 1982

Hilton P, Stanton SL. Urethral pressure measurement by microtransducer: the results in symptom-free women and in those with genuine stress incontinence. Br J Obstet Gynaecol 90:919, 1983

Hilton P, Tweddel AL, Mayne C. Oral and intravaginal estrogens alone and in combination with alpha adrenergic stimulation in genuine stress incontinence. Int Urogyn J 12:80, 1990

Hjalmas K. Desmopressin treatment: current status. Scand J Urol Nephrol Suppl. 202:70, 1999.

Höfner K, Halaska M, Primus G et al. Tolerability and efficacy of Trospium chloride in a long-term treatment (52 weeks) in patients with urge-syndrome: a double-blind, controlled, multicentre clinical trial. Neurourol Urodyn 19:487, 2000.

Holmes DM, Montz FJ, Stanton SL. Oxybutinin versus propantheline in the management of detrusor instability. A patient-regulated variable dose trial. Br J Obstet Gynaecol 96:607, 1989

Horowitz M, Combs AJ, Gerdes D. Desmopressin for nocturnal incontinence in the spina bifida population. J Urol 158:2267, 1997

Howe BB, Halterman TJ, Yochim CL et al. ZENECA ZD6169: A novel KATP channel opener with in vivo selectivity for urinary bladder. J Pharmacol Exp Ther 274:884, 1995

Hoyle CHV, Chapple C, Burnstock G. Isolated human bladder: evidence for an adenine dinucleotide acting on P2X-purinoceptors and for purinergic transmission. Eur J Pharmacol 174:115 1989

Hrobjartsson A, Gotzsche C. Is the Placebo Powerless? New England Journal of Medicine 344:1594, 2001

Hughes KM, Lang JCT, Lazare R et al. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica 22:859, 1992

Hunsballe JM, Djurhuus JC. Clinical options for imipramine in the management of urinary incontinence. Urol Res 29:118, 2001

Hussain RM, Hartigan-Go K, Thomas SHL et al. Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence. Br J Clin Pharmacol 37:485P, 1994

Igawa Y, Komiyama I, Nishizawa S et al. Intravesical capsaicin inhibits autonomic dysreflexia in patients with spinal cord injury. Neurourol Urodyn 15: 374, 1996

Igawa Y, Yamazaki Y, Takeda H et al. Functional and molecular biological evidence for a possible beta3-adrenoceptor in the human detrusor muscle. Br J Pharmacol 126:819, 1999

Igawa Y, Yamazaki Y, Takeda H et al. Relaxant effects of isoproterenol and selective beta3-adrenoceptor agonists on normal, low compliant and hyperreflexic human bladders. J Urol 165:240, 2001

Ikeda K, Kobayashi S, Suzuki M et al. Effect of YM905, a novel muscarinic receptor antagonist, on salivary gland and bladder. Japan J Pharmacol 76 (Suppl1):243, 1998.

Ikeda K, Suzuki M, Kobayashi S et al. YM905, a novel antimuscarinic agent displays tissue preference for the urinary bladder M3 receptor. FASEB J 13: A157, 1999.

Iselin CE, Schmidlin F, Borst F et al. Oxybutynin in the treatment of early detrusor instability after transurethral resection of the prostate. Br J Urol 79: 915, 1997

Ishiko O, Hirai K, Sumi T et al. Hormone replacement therapy plus pelvic floor muscle exercise for postmenopausal stress incontinence. A randomized, controlled trial. J Reprod Med 46:213, 2001

Ishiko O, Ushiroyama T, Saji F et al. beta(2)-Adrenergic agonists and pelvic floor exercises for female stress incontinence. Int J Gynaecol Obstet 71:39, 2000

Ishizuka O, Mattiasson A, Andersson K-E. Urodynamic effects of intravesical resiniferatoxin and capsaicin in conscious rats with and without outflow obstruction. J Urol 154:611, 1995

Jackson S, Shepherd A, Abrams P. The effect of oestradiol on objective urinary leakage in postmenopausal stress incontinence; a double blind placebo controlled trial. Neurourol Urodyn 15:322, 1996

Janig W, Morrison JF. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Prog Brain Res 67:87, 1986

Janknegt RA, Zweers HMM, Delaere KPJ et al. Oral desmopressin as a new treament modality for primary nocturnal enuresis in adolescents and adults: a double-blind, randomized, multicenter study. J Urol 157:513, 1997

Jarvis GJ, Hall S, Stamp S et al. An assessment of urodynamic investigation in incontinent women. Br J Obstet Gynecol 87:184, 1980

Jensen D Jr. Pharmacological studies of the uninhibited neurogenic bladder. II. The influence of cholinergic excitatory and inhibitory drugs on the cystometrogram of neurological patients with normal and uninhibited neurogenic bladder. Acta Neurol Scand 64:175, 1981

Jensen D. Uninhibited neurogenic bladder treated with prazosin. Scand J Urol Nephrol 15:229, 1981.

Jeremy JY, Tsang V, Mikhailidis DP et al. Eicosanoid synthesis by human urinary bladder mucosa: pathological implications. Br J Urol 59:36, 1987

Jollys JV, Jollys JC, Wilson J et al. Does sexual equality extend to urinary symptoms? Neurourol. Urodyn 12:391, 1993

Jonas D. Treatment of female stress incontinence with midodrine: preliminary report. J Urol 118:980, 1982

Jonville AP, Dutertre JP, Autret E et al. Effets indésirables du chlorure d´oxybutynine (Ditropan®). Therapie 47:389, 1992

Jünemann KP, Al-Shukri S. Efficacy and tolerability of trospium chloride and tolterodine in 234 patients with urge-syndrome: a double-blind, placebo-controlled multicentre clinical trial. Neurourol Urodyn 19:488, 2000

Kachur JF, Peterson JS, Carter JP et al. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. J Pharmacol Exp Ther 247: 867, 1988

Kaisary AV. Beta-adrenoceptor blockade in the treatment of female stress urinary incontinence. J d´Urol (Paris) 90:351, 1984

Kaplinsky R, Greenfield S, Wan J et al. Expanded followup of intravesical oxybutynin use in children with neurogenic bladder. J Urol 156:753, 1996

Karram MM, Yeko TR, Sauer MV et al. Urodynamic changes following hormone replacement therapy in women with premature ovarian failure. Obstet Gynecol 74:208, 1989

Kasabian NG, Vlachiotis JD, Lais A et al. The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyperreflexia. J Urol 151:944, 1994

Katz IR, Sands LP, Bilker W et al. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc 46:8, 1998

Kim YH, Bird ET, Priebe M et al. The role of oxybutynin in spinal cord injured patients with indwelling catheters. J Urol 158:2083, 1996

Kinn A-C, Larsson PO. Desmopressin: a new principle for symptomatic treatment of urgency and incontinence in patients with multiple sclerosis. Scand J Urol Nephrol 24:109, 1990

Kinn AC, Lindskog. Estrogens and phenylpropanolamine in combination for stress urinary incontinence in postmenopausal women. Urology 32:273, 1988

Komersova K, Rogerson JW, Conway EL et al. The effect of levcromakalim (BRL 38227) on bladder function in patients with high spinal cord lesions. Br J Pharmacol 39:207, 1995

Krane RJ, Olsson CA. Phenoxybenzamine in neurogenic bladder dysfunction, part II: clinical considerations. J Urol 104:612, 1973

Krichevsky VP, Pagala MK, Vaydovsky I et al. Function of M3 muscarinic receptors in the rat urinary bladder following partial outlet obstruction. J Urol 161:644, 1999

Kums JJM, Delhaas EM. Intrathecal baclofen infusion in patients with spasticity and neurogenic bladder disease. Preliminary results. World J Urol 9: 99, 1991

Kuo H-C. Inhibitory effect of capsaicin on detrusor contractility: Further study in the presence of ganglionic blocker and neurokinin receptor antagonist in the rat urinary bladder. Urol Int 59:95, 1997

Larsen JJ. a- and ß-Adrenoceptors in the detrusor muscle and bladder base of the pig and ß-adrenoceptors in the detrusor of man. Br J Urol 65:215, 1979

Lazzeri M, Beneforti P, Spinelli M et al. Intravesical resiniferatoxin for the treatment of hypersensitive disorder: a randomized placebo controlled study. J Urol 164:676, 2000

Lazzeri M, Beneforti P, Turini. Urodynamic effects of intravesical resiniferatoxin in humans: preliminary results in stable and unstable detrusor. J Urol 158:2093, 1997

Lepor, H., Machi, G. Comparison of the AUA symptom index in unselected males and females between 55 and 79 years of age. Urology 42:36, 1993

Leslie CA, Pavlakis AJ, Wheeler JS et al. Release of arachidonate cascade products by the rabbit bladder: neurophysiological significance? J Urol 132:376, 1984

Levin RM, Ruggieri MR, Wein AJ. Identification of receptor subtypes in the rabbit and human urinary bladder by selective radioligand binding. J Urol 139:844, 1988

Lin HH, Sheu BC, Lo MC et al. Comparison of treatment outcomes for imipramine for female genuine stress incontinence. Br J Obstet Gynaecol 106:1089, 1999

Lincoln J, Burnstock G. Autonomic innervation of the urinary bladder and urethra. In: The Autonomic Nervous System. Vol. 6, Chapter 2, Nervous Control of the Urogenital System, ed. CA Maggi, London: Harwood Academic Publisher, pp 33-68, 1993

Lindholm P, Lose G. Terbutaline (Bricanyl®) in the treatment of female urge incontinence. Urol Int 41:158, 1986

Lipworth BJ. Clinical pharmacology of ß3-adrenoceptors. Br J Clin Pharmacol 43:291, 1996

Lose G, Englev E. Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. 107:1029, 2000

Lose G, Jorgensen L, Thunedborg P. Doxepin in the treatment of female detrusor overactivity: A randomized double-blind crossover study. J Urol 142: 1024, 1989

Lose G, Lindholm D. Clinical and urodynamic effects of norfenefrine in women with stress incontinence. Urol Int 39:298, 1984

Low JA. Urethral behaviour during the involuntary detrusor contraction. Am J Obstet Gynecol 128:321977

Luheshi GN, Zar MA. Presence of non-cholinergic motor transmission in human isolated bladder. J Pharm Pharmacol 42:223, 1990

Lux B, Wiedey K D. Trospium chloride (Spasmex ®) in the treatment of urine incontinence. Therapiewoche 42:302, 1992

Madersbacher H, Halaska M, Voigt R et al. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int 84:646, 1999

Madersbacher H, Jilg G. Control of detrusor hyperreflexia by the intravesical instillation of oxybutynin hydrochloride. Paraplegia 29:84, 1991

Madersbacher H, Knoll M. Intravesical application of oxybutynin: Mode of action in controlling detrusor hyperreflexia. Eur Urol 28:340, 1995

Madersbacher H, Stöhrer M, Richter R et al. High-dose administration of trospium chloride in the treatment of detrusor hyperreflexia. Urologe Ausg A 30: 260, 1991

Madersbacher H, Stöhrer M, Richter R et al. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia. Br J Urol 75:452, 1995

Maggi CA, Barbanti G, Santicioli P et al. Cystometric evidence that capsaicin-sensitive nerves modulate the afferent branch of micturition reflex in humans. J Urol 142:150, 1989

Maggi CA, Borsini F, Lecci A et al. The effect of acute and chronic administration of imipramine on spinal and supraspinal micturition reflexes in rats. J Pharmacol Exp Ther 248:278, 1989

Maggi CA. The dual, sensory and "efferent" function of the capsaicin-sensitive primary sensory neurons in the urinary bladder and urethra. In: The Autonomic Nervous System, vol. 3, Nervous control of the urogenital system. Chapter 11, p 227, Maggi, C. A. (ed.) Harwood Academic Publishers, Chur, Switzerland, pp 383-422, 1993

Malone-Lee J, Lubel D, Szonyi G. Low dose oxybutynin for the unstable bladder. Br Med J 304:1053, 1992

Malone-Lee J, Shaffu B, Anand C et al. Tolterodine: superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: a randomized controlled trial. J Urol 165:1452, 2001

Marshall HJ, Beevers DG. Alpha-adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility. Br J Clin Pharmacol 42:507, 1996

Martin MR, Schiff AA. Fluphenazine/nortriptyline in the irritative bladder syndrome: a double-blind placebo-controlled study. Br J Urol 56:178, 1984.

Masuda N, Uchida W, Shirai Y et al. Effect of the potassium channel opener YM934 on the contractile response to electrical field stimulation in pig detrusor smooth muscle. J Urol 154:1914, 1995

Matthiesen TB, Rittig S, Norgaard JP et al. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. J Urol 79:825, 1996

Mattiasson A, Ekström B, Andersson K-E. Effects of intravesical instillation of verapamil in patients with detrusor hyperactivity. J Urol 141:174, 1989

McGuire EJ, Wagner FM, Weiss RM. Treatment of autonomic dysreflexia with phenoxybenzamine. J Urol 115:53, 1976

Milani R, Scalambrino S, Milia R et al. Double-blind crossover comparison of flavoxate and oxybutynin in women affected by urinary urge syndrome. Int Urogynecol J 4:3, 1993

Miller K, Atkin B, Moody ML. Drug therapy for nocturnal enuresis. Drugs 44: 47, 1992

Mizunaga M, Miyata M, Kaneko S et al. Intravesical instillation of oxybutynin hydrochloride therapy for patients with a neurogenic bladder. Paraplegia 32:25, 1994

Moffat ME, Harlos S, Kirshen AJ et al. Desmopressin acetate and nocturnal enuresis: how much do we know? Pediatrics 92:420, 1993

Moisey CU, Stephenson TP, Brendler CB. The urodynamic and subjective results of treatment of detrusor instability with oxybutynin chloride. Br J Urol 52:472, 1980

Moore KH, Hay DM, Imrie AE et al. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol 66:479, 1990

Muller C, Siegmund W, Huupponen R et al. Kinetics of propiverine as assessed by radioreceptor assay in poor and extensive metabolizers of debrisoquine. Eur J Drug Metab Pharmacokinet 18:265, 1993

Mundy AR, Abrams P, Chapple CR et al. Darifenacin, the first selective M3 antagonist for overactive bladder: comparison with oxybutynin on ambulatory urodynamic monitoring and salivary flow. International Continence Society 2001.

Musiani U. A partially successful successful attempt at medical treatment of urinary stress incontinence in women. Urol Int 27:405, 1972

Naglo AS, Nergårdh A, Boréus LO. Influence of atropine and isoprenaline on detrusor hyperactivity in children with neurogenic bladder. Scand J Urol Nephrol 15:97, 1981

Nasu K, Moriyama N, Fukasawa R et al. Quantification and distribution of alpha1-adrenoceptor subtype mRNAs in human proximal urethra. Br J Pharmacol 123:1289, 1998

Nergårdh A, Boréus LO, Naglo AS. Characterization of the adrenergic beta-receptors in the urinary bladder of man and cat. Acta Pharmacol Toxicol 40:14, 1977

Neveus T, Lackgren G, Tuvemo T et al. Enuresis--background and treatment. Scand J Urol Nephrol Suppl 206:1, 2000

Newgreen DT, Anderson CWP, Carter AJ et al. Darifenacin - a novel bladder-selective agent for the treatment of urge incontinence. Neurourol Urodyn 14:95, 1995

Nichols D, Colli E, Goka J et al. Darifenacin demonstrates no effect on cognitive and cardiac function: results from a double-blind, randomised, placebo controlled study. International Continence Society 2001

Nilsson CG, Lukkari E, Haarala M et al. Comparison of a 10-mg controlled release oxybutynin tablet with a 5-mg oxybutynin tablet in urge incontinent patients. Neurourol Urodyn 16:533, 1997

Nilvebrant L, Andersson K-E, Gillberg P-G et al. Tolterodine - a new bladder selective antimuscarinic agent. Eur J Pharmacol 327:195, 1997a

Nilvebrant L, Andersson K-E, Mattiasson A. Characterization of the muscarinic cholinoceptors in the human detrusor. J Urol 134: 418, 1985

Nilvebrant L, Gillberg PG, Sparf B. Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine. Pharmacol Toxicol 81:169, 1997c

Nilvebrant L, Hallén B, Larsson G. Tolterodine - A new bladder selective muscarinic receptor antagonist: preclinical pharmacological and clinical data. Life Sci 60:1129, 1997b

Nilvebrant L, Sparf B. Dicyclomine, benzhexol and oxybutynin distinguish between subclasses of muscarinic binding sites. Eur J Pharmacol 123:133, 1986

Noguchi M, Eguchi Y, Ichiki J et al. Therapeutic efficacy of clenbuterol for urinary incontinence after radical prostatectomy. Int J Urol 4:480, 1997

Nørgaard JP, Djurhuus JC, Watanabe H et al. Experience and current status of research into the pathophysiology of nocturnal enuresis. Br J Urol 79:825, 1997

Norhona-Blob L, Kachur, JF. Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. J Pharmacol Exp Ther 256:562, 1991

Norlén L. Sundin T, Waagstein F. Effect of beta-adrenoceptor stimulation on the human bladder in vivo. Urol Int 33:355, 1978

Nour S, Svarer C, Kristensen JK et al. Cerebral activation during micturition in normal men. Brain 123:781, 2000.

O´Flynn K J, Thomas D G. Intravesicular instillation of oxybutinin hydrochloride for detrusor hyperreflexia. Br J Urol 72:566, 1993

Oka M, Kimura Y, Itoh Y et al. Brain pertussis toxin-sensitive G proteins are involved in the flavoxate hydrochloride-induced suppression of the micturition reflex in rats. Brain Res 727:91, 1996

Ouslander JG, Blaustein J, Connor A et al. Pharmacokinetics and clinical effects of oxybutynin in geriatric patients. J Urol 140:47, 1988

Ouslander JG, Schnelle JF, Uman G et al. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial. J Am Geriatr Soc 43:610, 1995

Ouslander JG, Shih YT, Malone-Lee J et al. Overactive bladder: special considerations in the geriatric population. Am J Manag Care 6(11 Suppl):S599, 2000

Palea S, Artibani W, Ostardo E et al. Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis. J Urol 150:2007, 1993

Palmer J. Report of a double-blind crossover study of flurbiprofen and placebo in detrusor instability. J Int Med Res 11 Supplement 2:11, 1983

Palmer LS, Zebold K, Firlit CF et al. Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. J Urol 157:638, 1997

Pavia J de Ceballos ML, Sanchez de la Cuesta F. Alzheimer's disease: relationship between muscarinic cholinergic receptors, beta-amyloid and tau proteins. Fundam Clin Pharmacol 12:473, 1998.

Perlberg S, Caine M. Adrenergic response of bladder muscle in prostatic obstruction. Urology 20:524, 1982

Petersen T, Husted S, Sidenius P. Prazosin treatment of neurological patients with detrusor hyperreflexia and bladder emptying disability. Scand J Urol Nephrol 23:189, 1989

Petersen T, Nielsen JB, Schroder HD. Intravesical capsaicin in patients with detrusor hyper-reflexia--a placebo-controlled cross-over study. Scand J Urol Nephrol 33:104, 1999

Pietzko A, Dimpfel W, Schwantes U et al. Influence of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. Eur J Clin Pharmacol 47: 337, 1994

Radley SC, Chapple CR, Bryan NP et al. Effect of methoxamine on maximum urethral pressure in women with genuine stress incontinence: a placebo-controlled, double-blind crossover study. Neurourol Urodyn 20:43, 2001

Raezer DM, Benson GS, Wein AJ et al. The functional approach to the management of the pediatric neuropathic bladder: a clinical study. J Urol 177: 649, 1977

Richter R, Madersbacher H, Stohrer M et al. Double-blind, placebo-controlled clinical study of propiverine in patients suffering from detrusor hyperreflexia. International Medical Society of Paraplegia, 36th Annual Scientific Meeting, May 14-16, 1997, Innsbruck

Ritch AES, Castleden CM, George CFet al. A second look at emepronium bromide in urinary incontinence. Lancet 1:504, 1977

Rittig S, Knudsen UB, Nørgaard JP et al. Abnormal diurnal rhythm of plasma vasopressin andurinary output in patients with enuresis. Am J Physiol 256:F664, 1989

Robson WL, Nørgaard JP, Leung AK. Hyponatremia in patients with nocturnal enuresis treated with DDAVP. Eur J Pediatr 155:959, 1996

Rosario DJ, Leaker BR, Smith DJ et al. A pilot study of the effects of mutiple doses of the M3 muscarinic receptor antagonist darifenacin on ambulatory parameters of detrusor activity in patients with detrusor instability. Neurourol Urodyn 14:464, 1995

Ruffmann R. A review of flavoxate hydrochloride in the treatment of urge incontinence. J Int Med Res 16:317, 1988

Ruggieri MR, Whitmore KE, Levin RM. Bladder purinergic receptors. J Urol 144:176, 1990

Salmon UL, Walter RI, Gast SH. The use of estrogens in the treatment of dysuria and incontinence in postmenopausal women. Am J Obstet Gynecol 14:23, 1941

Schladitz-Keil G, Spahn H, Mutschler E. Determination of bioavailability of the quaternary ammonium compound trospium chloride in man from urinary excretion data. Arzneimittel Forsch/Drug Res 36:984, 1986

Schleyer-Saunders E. Hormone implants for urinary disorders in postmenopausal women. J Am Geriar Soc 24:337, 1976

Schwab M, Ruder H. Hyponatraemia and cerebral convulsion due to DDAVP administration in patients with enuresis nocturna or urine concentration testing. Eur J Pediatr 156:668, 1997

Schwinn DA, Michelotti GA. alpha1-adrenergic receptors in the lower urinary tract and vascular bed: potential role for the alpha1d subtype in filling symptoms and effects of ageing on vascular expression. BJU Int 85 Suppl 2:6, 2000

Serels, S., Stein M. Prospective sydy comparing hyoscyamine, doxazosin, and combination therapy for the treatment of urgency and frequency in women. Neurourol Urodyn 17:31, 1998

Shieh C, Feng J, Buckner SA et al. Functional implication of spare ATP-sensitive K(+) channels in bladder smooth muscle cells. J Pharmacol Exp Ther 296:669, 2001

Siltberg H, Larsson G, Hallen B et al. Validation of cough-induced leak point pressure measurement in the evaluation of pharmacological treatment of stress incontinence. Neurourol Urodyn 18:591, 1999

Silva C, Rio ME, Cruz F. Desensitization of bladder sensory fibers by intravesical resiniferatoxin, a capsaicin analog: long-term results for the treatment of detrusor hyperreflexia. Eur Urol 38:444, 2000

Sjögren C, Andersson K-E, Husted S et al. Atropine resistance of the transmurally stimulated isolated human bladder. J Urol 128:1368, 1982

Skoog SJ, Stokes A, Turner KL. Oral desmopressin: a randomized double-blind placebo controlled study of effectiveness in children with primary nocturnal enuresis. J Urol 158:1035, 1997

Smith DJ, Chapple CR. In vitro response of human bladder smooth muscle in unstable obstructed male bladders: a study of pathophysiological causes? Neurourol Urodyn 134:14, 1994

Somogyi GT, de Groat WC. Evidence for inhibitory nicotinic and facilitatory muscarinic receptors in cholinergic nerve terminals of the rat urinary bladder. J Auton Nerv Syst 37: 89, 1992

Somogyi GT, de Groat WC. Function, signal transduction mechanisms and plasticity of presynaptic muscarinic receptors in the urinary bladder. Life Sci 64:411, 1999

Stahl MMS, Ekström B, Sparf B et al. Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity. Neurourol Urodyn 14:647, 1995

Stanton SL. A comparison of emepronium bromide and flavoxate hydrochloride in the treatment of urinary incontinence. J Urol 110:529, 1973

Steers WD, Meythaler JM, Haworth C et al. Effects of acute bolus and chronic continuous intrathecal baclofen on genitourinary dysfunction due to spinal cord pathology. J Urol 148:1849, 1992

Stewart DA, Taylor J, Ghosh S etv al. Terodiline causes polymorphic ventricular tachycardia due to reduced heart rate and prolongation of QT interval. Eur J Clin Pharmacol 42:577, 1992

Stöhrer M, Bauer P, Giannetti BM et al. Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries: a multicentre placebo controlled double-blind trial. Urol Int 47:138, 1991

Stohrer M, Madersbacher H, Richter R et al. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia--a double-blind, placebo-controlled clinical trial. Spinal Cord 37:196, 1999

Strosberg D, Pietri-Rouxel F. Function and regulation of the ß3-adrenoceptor. Trends Pharmacol Sci 17:273, 1997

Sultana CJ, Walters MD. Estrogen and urinary incontinence in women. Maturitas 20:129, 1990

Sundin, T., Dahlström, A., Norlén et al. The sympathetic innervation and adrenoreceptor function of the human lower urinary tract in the normal state and after parasympathetic denervation. Invest Urol 14:322, 1977

Szallasi A. The vanilloid (capsaicin) receptor: receptor types and species differences. Gen Pharmacol 25:223, 1994

Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. Spinal Cord 34:284, 1996

Szonyi G, Collas DM, Ding YY et al. Oxybutynin with bladder retraining for detrusor instability in elderly people: a randomized controlled trial. Age Aging 24:287, 1995

Takayasu H, Ueno A, Tuchida S et al. Clinical Effects of propiverine hydrochloride in the treatment of urinary frequency and incontinence

associated with detrusor overctivity: A double-blind, parallel, placebo-controlled, multicenter study. Igaku no Ayumi 153:459, 1990 (in Japanese)

Takeda M, Obara K, Mizusawa T et al. Evidence for beta3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. J Pharmacol Exp Ther 288:1367, 1999

Tapp AJS, Cardozo LD, Versi E et al. The treatment of detrusor instability in post menopausal women with oxybutynin chloride: a double blind placebo controlled study. Br J Obstet Gynaecol 97:521, 1990

Taylor MC, Bates CP. A double-blind crossover trial of baclofen - a new treatment for the unstable bladder syndrome. Br J Urol 51:504, 1979

Thompson IM, Lauvetz R. Oxybutynin in bladder spasm, neurogenic bladder, and enuresis. Urology 8:452, 1976

Thor KB, Katofiasc MA. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized femal cat. J Pharmacol Exp Ther 274:1014, 1995

Thuroff JW, Bunke B, Ebner A et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. J Urol 145: 813, 1991.

Thuroff JW, Chartier-Kastler E, Corcus J et al. Medical treatment and medical side effects in urinary incontinence in the elderly. World J Urol 16 Suppl 1:S48, 1998

Tobin G, Sjögren C. In vivo and in vitro effects of muscarinic receptor antagonists on contractions and release of [3H]acetylcholine in the rabbit urinary bladder. Eur J Pharmacol 28:1, 1995

Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol 41:636, 2001

Tokuno H, Chowdhury JU, Tomita T. Inhibitory effects of propiverine on rat and guinea-pig urinary bladder muscle. Naunyn-Schmiedeberg´s Arch Pharmacol 348:659, 1993

Ückert S, Stief CG, Odenthal KP et al. Responses of isolated normal human detrusor muscle to various spasmolytic drugs commonly used in the treatment of the overactive bladder. Arzneimittelforschung 50:456, 2000

Van Kerrebroeck P, Bäckström T, Blaivas JG et al. Oral desmopressin (Miririn, DDAVP) in the treatment of nocturia in women. J Urol 165 Suppl:250 (abstract 1031)

Van Kerrebroeck P, Kreder K, Jonas U et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder.Urology 57:414, 2001

Versi E, Appell R, Mobley D et al. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. The Ditropan XL Study Group. Obstet Gynecol 95:718, 2000

Vick J, Weiss L, Ellis S. Cardiovascular studies of phenylpropanolamine. Arch Int Pharmacodyn Ther 327; 13, 1994

Waldeck K, Larsson B, Andersson K-E. Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. J Urol 157:1093, 1997

Wallis RM, Burges RA, Cross PE et al. Darifenacin, a selective muscarinic M3 antagonist. Pharmacol Res 31suppl:54, 1995

Walther S, Hansen J, Hansen L et al. Urinary incontinence in old age. A controlled trial of emepronium bromide. Br J Urol 54:249, 1982

Wammack R, Weihe E, Dienes H-P et al. Die Neurogene Blase in vitro. Akt Urol 26:16, 1995

Weese DL, Roskamp DA, Leach GE et al. Intravesical oxybutynin chloride: experience with 42 patients. Urology 41:527, 1993

Wehnert J, Sage S. Comparative investigations to the action of Mictonorm (propiverin hydrochloride) and Spasuret (flavoxat hydrochloride) on detrusor vesicae. Z Urol Nephrol 82:259, 1989

Wehnert J, Sage S. Therapie der Blaseninstabilität und Urge-Inkontinenz mit Propiverin hydrochlorid (Mictonorm®) und Oxybutynin chlorid (Dridase®) - eine randomisierte Cross-over-Vergleichsstudie. Akt Urol 23: 7, 1992

Wein AJ, Longhurst PA, Levin RM. Pharmacologic treatment of voiding dysfunction. In Urodynamics, Principles, Practice, and Application, ed by Mundy A.R., Stephenson T.P., Wein, A.J. 2nd ed., pp 43-70, 1994

Wein AJ. Neuromuscular dysfunction of the lower urinary tract and its treatment. In Campbells Urology 8th ed, 2001a

Wein AJ. Pharmacological agents for the treatment of urinary incontinence due to overactive bladder. Exp Opin Invest Drugs 10:65, 2001b

Weiss J, Blaivas JG, Abrams P et al. Oral desmopressin (Miririn, DDAVP) in the treatment of nocturia in men. J Urol 165 Suppl:250 (abstract 1030)

Werkstrom V, Persson K, Ny L et al. Factors involved in the relaxation of female pig urethra evoked by electrical field stimulation. Br J Pharmacol 116:1599, 1995

Wiart L, Joseph PA, Petit H et al. The effects of capsaicin on the neurogenic hyperreflexic detrusor. A double blind placebo controlled study in patients with spinal cord disease. Preliminary results. Spinal Cord 36:95,1998

Wiedemann A, Füsgen I, Hauri D. New aspects of therapy with trospium chloride for urge incontinence. Eur J Geriatrics 3:41, 2001

Winkler HA, Sand PK. Treatment of detrusor instability with oxybutynin rectal suppositories. Int Urogynecol J Pelvic Floor Dysfunct 9:100, 1998

Yamaguchi O, Shisda K, Tamura K et al. Evaluation of mRNAs encoding muscarinic receptor subtypes in human detrusor muscle. J Urol 156:1208, 1996

Yarker YE, Goa KL, Fitton A. Oxybutynin: A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging 6:243, 1995

Yasuda, K., Kawabe, K., Takimoto et al., and the Clenbutrol Clinical Research Group. A double-blind clinical trial of a b2-adrenergic agonist in stress incontinence. Int Urogynecol J 4: 146, 1993

Yoshida M, Homma Y, Inadome A et al. Age-related changes in cholinergic and purinergic neurotransmission in human isolated bladder smooth muscles. Exp Gerontol 39: 99, 2001

Zeegers AGM, Kiesswetter H, Kramer AEJ et al. Conservative therapy of frequency, urgency and urge incontinence: a double-blind clinical trial of flavoxate hydrochloride, oxybutinin chloride, emepronium bromide and placebo. World J Urol 5:57, 1987

Zinner N, Sarshik S, Yalcin I et al. Efficacy and safety of duloxetine in stress urinary incontinent patients: double-blind, placebo-controlled multiple dose study. ICS 28th Annual Meeting, Jerusalem, Israel, September 14-17, 1998

Zorzitto ML, Jewett MAS, Fernie GRet al. Effectiveness of propantheline bromide in the treatment of geriatric patients with detrusor instability. Neurourol Urodyn 5:133, 1986