

CHAPTER 14

Committee 10

Pharmacological Treatment of Urinary Incontinence

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CONTENTS

I. INTRODUCTION

II. CENTRAL NERVOUS CONTROL

III. PERIPHERAL NERVOUS CONTROL

IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS

V. THE ELDERLY PATIENT

VI. BLADDER CONTRACTION

VII. MUSCARINIC RECEPTORS

VIII. DRUGS USED FOR TREATMENT OF OVERACTIVE BLADDER SYMPTOMS/DETRUSOR OVERACTIVITY

1. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS
2. DRUGS ACTING ON MEMBRANE CHANNELS
3. DRUGS WITH “MIXED” ACTION
4. α -ADRENOCEPTOR ANTAGONISTS
5. β -ADRENOCEPTOR AGONISTS
6. ANTIDEPRESSANTS
7. PROSTAGLANDIN SYNTHESIS INHIBITORS
8. VASOPRESSIN ANALOGUES
9. OTHER DRUGS

IX. DRUGS USED FOR TREATMENT OF STRESS INCONTINENCE

1. α -ADRENOCEPTOR AGONISTS
2. β -ADRENOCEPTOR ANTAGONISTS
3. IMIPRAMINE
4. CLENBUTEROL
5. DULOXETINE

X. DRUGS USED FOR TREATMENT OF OVERFLOW INCONTINENCE

XI. HORMONAL TREATMENT OF URINARY INCONTINENCE

1. ESTROGENS AND THE CONTINENCE MECHANISM
2. ESTROGENS FOR STRESS INCONTINENCE
3. ESTROGENS FOR URGE INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS

REFERENCES

ADDENDUM 1

Clinical Research Criteria

ADDENDUM 2

Ethical Issues Regarding the use of Placebos in Clinical Trials

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 lower urinary tract and pelvic floor. The bladder and the urethra constitute a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors [1-3]. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of emptying. 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. A disturbed filling/storage function can, at least theoretically, be improved by agents which decrease detrusor activity, increase bladder capacity, and/or increase outlet resistance [4].

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 [5].

In this report, we update the recommendations from the 2001 International Consensus meeting [5]. 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. The terminology used is that recommended by the International Continence Society [6].

Table 1. ICI assessments 2004: Oxford guidelines (modified)

Levels of evidence

Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs)

Level 2: RCTs, good quality prospective cohort studies

Level 3: Case-control studies, case series

Level 4: Expert opinion

Grades of recommendation

Grade A: Based on level 1 evidence (highly recommended)

Grade B: Consistent level 2 or 3 evidence (recommended)

Grade C: Level 4 studies or "majority evidence" (optional)

Grade D: Evidence inconsistent/inconclusive (no recommendation possible)

II. CENTRAL NERVOUS CONTROL

In the adult individual, the normal micturition reflex is mediated by a spinobulbospinal pathway, which passes 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 [7].

Studies in humans and animals have identified areas in the brainstem and diencephalon that are specifically implicated in micturition control, including Barrington's nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum [8]. These structures directly excite bladder motoneurons and indirectly inhibit urethral sphincter motoneurons via inhibitory interneurons in the medial sacral cord. The periaqueductal grey (PAG) receives bladder filling information, and the pre-optic area of the hypothalamus is probably involved in the initiation of micturition. According to PET-scan and functional imaging studies in humans, these supraspinal regions are active during micturition [8-11].

III. PERIPHERAL NERVOUS CONTROL

Bladder emptying and urine storage involve a complex pattern of efferent and afferent signalling in parasympathetic, sympathetic, somatic, and sensory 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 [12]. 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 [13], although other transmitters might be involved [14-16].

Most of the *sympathetic* innervation of the bladder and urethra originates from the intermediolateral nuclei in 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 [17].

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 [1]. 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 [1].

The *somatic* innervation of the urethral rhabdosphincter and of some perineal muscles (for example compressor urethrae and urethrovaginal sphincter), is provided by the pudendal nerve. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2-S4) in a region called Onuf's (Onufrowicz's) nucleus (Figure 3).

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 [17]. The most important afferents for the micturition process are myelinated A δ -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 A δ -fibres respond to passive distension and active contraction, thus conveying information about bladder filling [18]. C-fibres have a high mechanical threshold and respond primarily to chemical irritation of the bladder mucosa [19] or cold [20]. Following chemical irritation, the C-fibre afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension [19]. These fibres are normally inactive and are therefore termed "silent fibres".

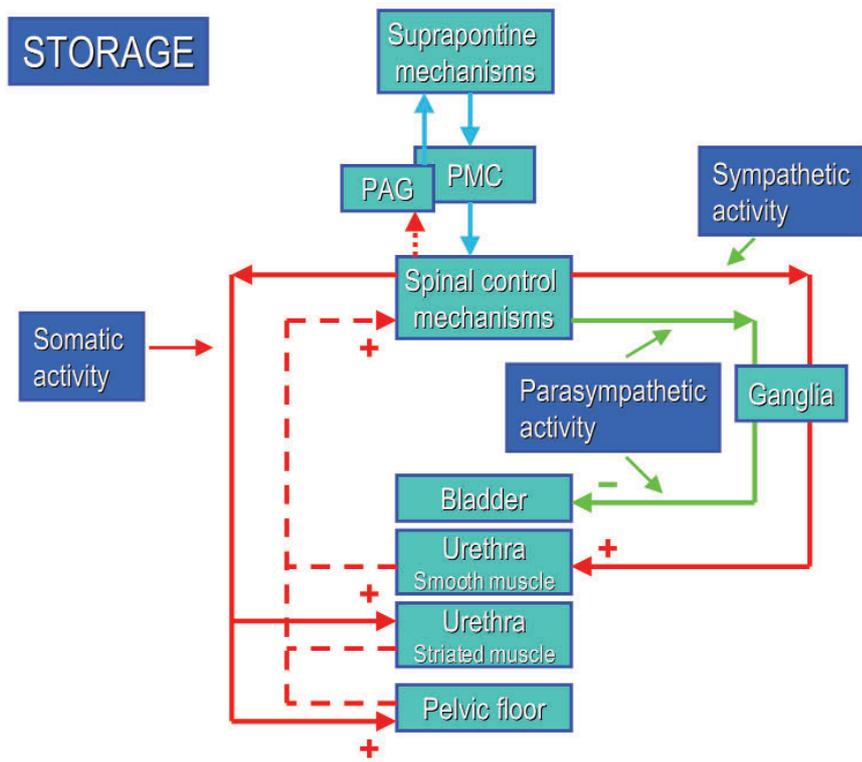


Figure 1. During filling, there is continuous and increasing afferent activity from the bladder. There is no spinal parasympathetic outflow that can contract the bladder. The sympathetic outflow to urethral smooth muscle, and the somatic outflow to urethral and pelvic floor striated muscles keep the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

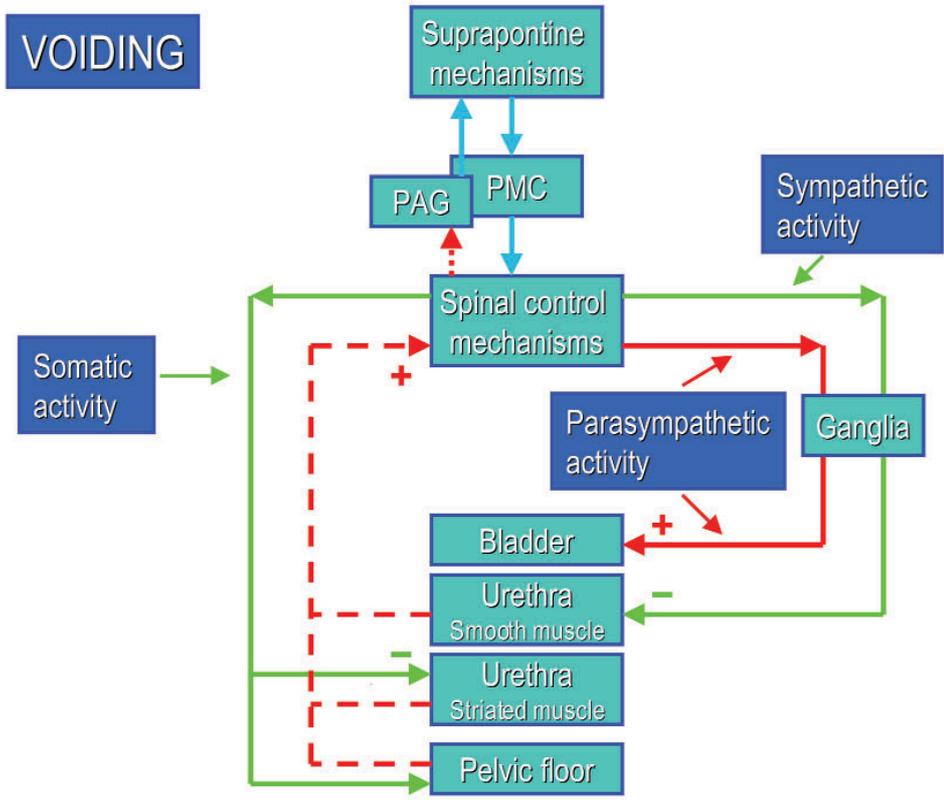


Figure 2. Voiding reflexes involve supraspinal pathways, and are under voluntary control. During bladder emptying, the spinal parasympathetic outflow is activated, leading to bladder contraction. Simultaneously, the sympathetic outflow to urethral smooth muscle, and the somatic outflow to urethral and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

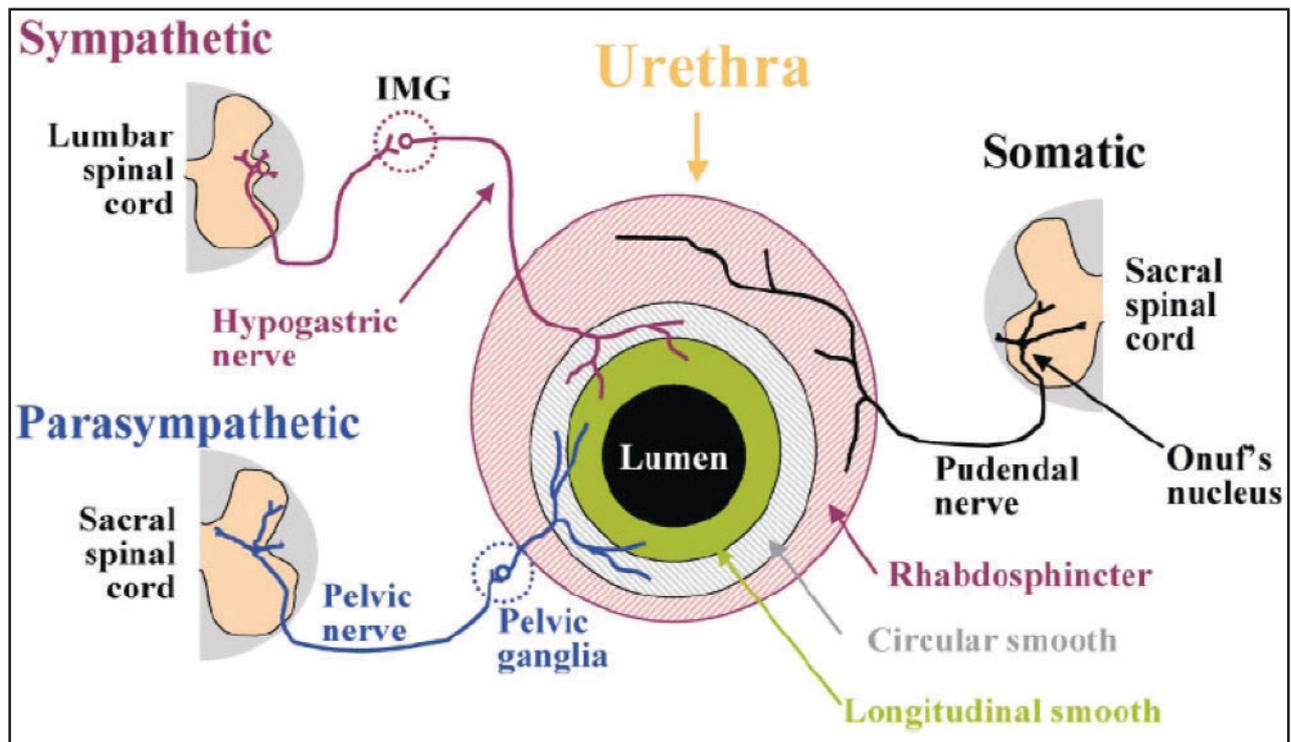


Figure 3. Extrinsic efferent innervation of urethra showing three urethral muscle layers, sympathetic, parasympathetic and somatic innervation, and location of Onufrowicz's (Onuf's) nucleus in sacral spinal cord. IMG, inferior mesenteric ganglion (From ref. 273)

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 [4]. 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 [21]. Overactive bladder symptoms (OAB) and/or detrusor overactivity (DO) [6] may also occur in elderly patients due to changes in the brain or bladder during aging (Figure 4). Urina-

ry retention and overflow incontinence can be observed 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 [4].

V. THE ELDERLY PATIENT

In the aging patient many non-urinary pathologic, anatomic, physiologic, and pharmacologic factors may serve as co-morbidities in the development of acute incontinence or the aggravation of chronic incontinence. Potentially reversible pathologies must be appreciated by the treating physician: infection, atrophic vaginitis and urethritis, fecal impaction, limited mobility, cognitive dysfunction, hyperglycemia, and urinary retention or a large residual urine [22, 23]. Elderly patients are frequently taking many drugs, and iatrogenic incontinence may result from pharmacologic side effects of well-intentioned therapy. Sedative hypnotics and alcohol may depress general behavior and sensorium; they may also depress bladder contractility and reduce the attention normally given to bladder cues. Diuretics produce

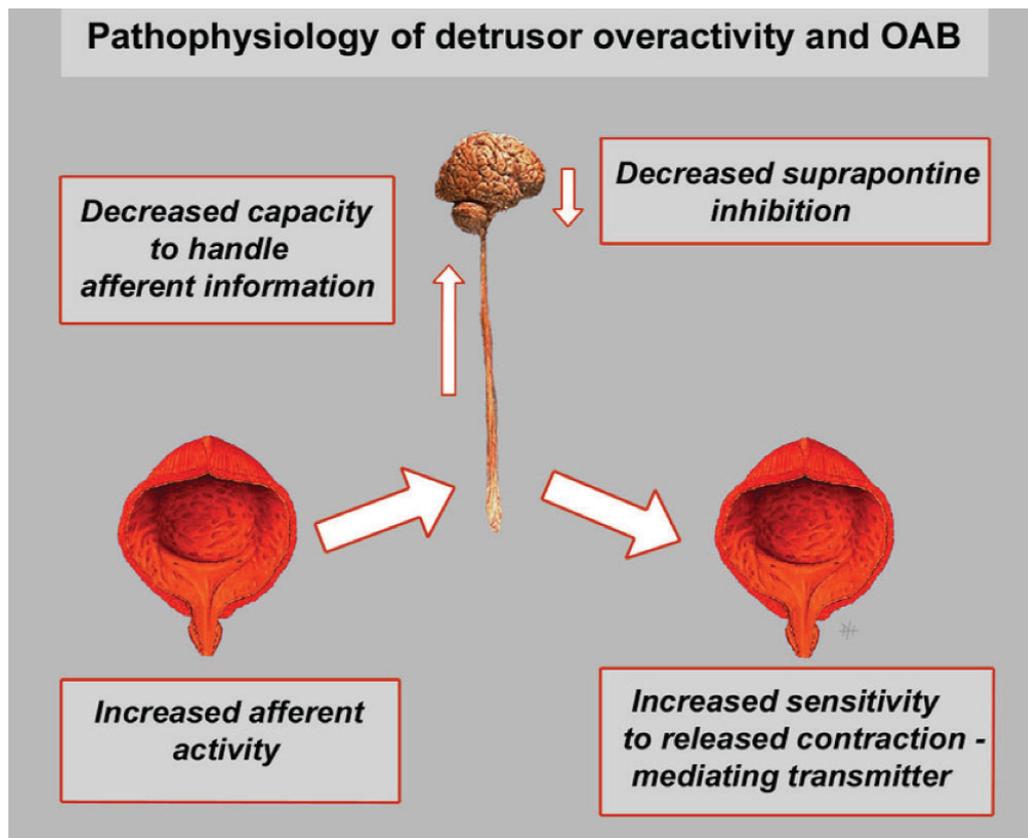


Figure 4. Pathophysiology of detrusor overactivity and the overactive bladder (OAB) syndrome

polyuria and may be the source of complaints of urgency, frequency and nocturia. Agents with antimuscarinic properties may significantly decrease detrusor contractility and thereby increase residual urine and reduce bladder capacity. These can include antihistamines, antidepressants, antipsychotics, opiates, gastrointestinal antispasmodics, and anti-Parkinsonian drugs. Agents which exert an α -adrenoceptor stimulating effect, contained in many decongestants and cold remedies, can increase bladder neck tone and may promote urinary retention. α -Adrenoceptor antagonists may predispose to sphincter incontinence. Calcium channel blockers for hypertension or coronary artery disease, being smooth muscle relaxants, may contribute to urinary retention and overflow incontinence. Finally, drug-drug metabolic interactions are more important to consider in this population.

Because factors outside of the lower urinary tract may affect not only incontinence itself but also the feasibility and efficacy of therapy, successful treatment of established incontinence in the elderly must be multifactorial, more so than in younger individuals, requiring that factors outside the urinary tract be simultaneously addressed [22, 23].

VI. BLADDER CONTRACTION

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle. Atropine resistance, i.e. contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species, but seems to be of little importance in normal human bladder muscle [1, 24]. However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused by ATP [1, 24]. 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 [2]. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that P2X₁ receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder.

Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells [2]. P2X₃ 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 P2X₃ knockout mice, afferent activity induced by bladder distension was significantly reduced [25]. 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, and has been reported to occur in hypertrophic bladders [26], interstitial cystitis [27], neurogenic bladders [28], and in the aging bladder [29]. The importance of the NANC component to detrusor contraction *in vivo*, normally, and in different micturition disorders, remains to be established.

VII. MUSCARINIC RECEPTORS

In the human bladder, where the mRNAs for all the five pharmacologically defined receptors, M₁ – M₅, have been demonstrated [30], there is a predominance of mRNAs encoding M₂ and M₃ receptors [30, 31]. This seems to be the case also in the animal species investigated [32-34]. Both M₂ and M₃ receptors can be found on detrusor muscle cells, where M₂ receptors predominate at least 3:1 over M₃ receptors, but also in other bladder structures, which may be of importance for detrusor activation. Thus, muscarinic receptors can be found on urothelial cells, on suburothelial nerves and on other suburothelial structures, possibly interstitial cells [33, 35].

In human as well as animal detrusor, the M₃ receptors are believed to be the most important for contraction [1, 33]. No differences between genders could be demonstrated in rat and human bladders [36]. The functional role for the M₂ receptors has not been clarified, and even in M₃ receptor knockout mice, they seem responsible for less than 5 % of the carbachol-mediated detrusor contraction [37]. Stimulation of M₂ receptors has been shown to oppose sympathetically mediated smooth muscle relaxation, mediated by β -ARs [38]. However, based on animal experiments, M₂ receptors have been suggested to directly contribute to contraction of the bladder in certain disease states (denervation, outflow obstruction). Preliminary experiments on human detrusor muscle could not confirm

this [39, 40]. On the other hand, Pontari et al. [41] analyzed bladder muscle specimens from patients with neurogenic bladder dysfunction to determine whether the muscarinic receptor subtype mediating contraction shifts from M₃ to the M₂ receptor subtype, as found in the denervated, hypertrophied rat bladder. They concluded that normal detrusor contraction is mediated by the M₃ receptor subtype, whereas contractions can be mediated by the M₂ receptors in patients with neurogenic bladder dysfunction.

Muscarinic receptors are coupled to G-proteins, but the signal transduction systems may vary. Generally, M₁, M₃, and M₅ receptors are considered to couple preferentially to G_{q/11}, activating phosphoinositide hydrolysis, in turn leading to mobilization of intracellular calcium. M₂ and M₄ receptors couple to pertussis toxin-sensitive G_{i/o}, resulting in inhibition of adenylyl cyclase activity (**Figure 5**). In the human detrusor, Schneider et al. [42] confirming that the muscarinic receptor subtype mediating carbachol-induced contraction is the M₃ receptor, also demonstrated that the phospholipase C inhibitor U 73,122 did not significantly affect carbachol-stimulated bladder contraction, despite blocking IP₃ generation. They concluded that carbachol-induced contraction of human urinary bladder is mediated via M₃ receptors and largely depends on Ca²⁺ entry through nifedipine-sensitive channels and activation of the Rho-kinase pathway.

Thus, it may be that the main pathways for muscarinic receptor activation of the detrusor via M₃ receptors are calcium influx via L-type calcium channels, and increased sensitivity to calcium of the contractile machinery via inhibition of myosin light chain phosphatase through activation of Rho-kinase (**Figure 6**).

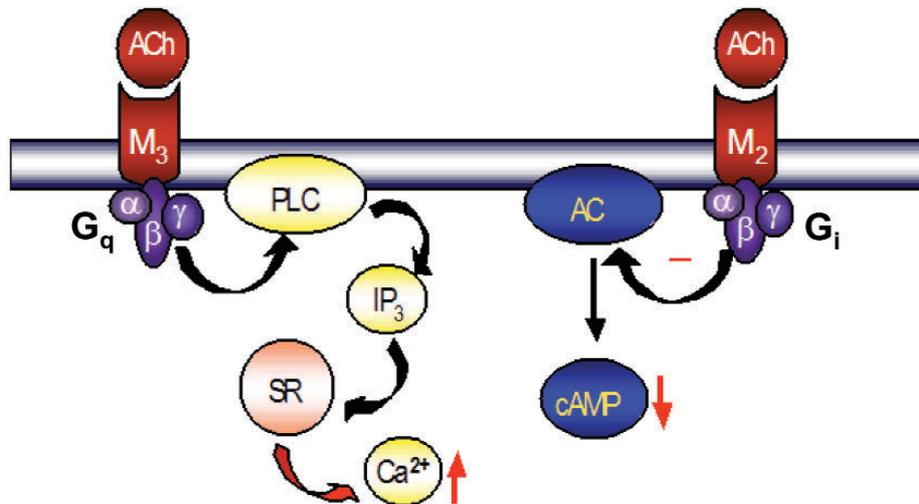
The signaling mechanisms for the M₂ receptors are less clear than those for M₃ receptors. As mentioned previously, M₂ receptor stimulation may oppose sympathetically induced smooth muscle relaxation, mediated by β -ARs via inhibition of adenylyl cyclase [38]. In agreement with this, Matsui et al. [43] suggested, based on results obtained in M₂ receptor KO mice, that a component of the contractile response to muscarinic agonists in smooth muscle involves an M₂ receptor-mediated inhibition of the relaxant effects of agents that increase cAMP levels. M₂ receptor stimulation can also activate non-specific cation channels and inhibit K_{ATP} channels through activation of protein kinase C [44, 45].

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regula-

Signal pathways for muscarinic receptors

Stimulatory: M₁, M₃, M₅

Inhibitory: M₂, M₄



ACh = Acetylcholine, PLC=phospholipase C; IP₃ = inositol trisphosphate, AC=adenylyl cyclase; SR=sarcoplasmic reticulum, G_q, G_i = G-proteins

Figure 5. Muscarinic receptors and their signal pathways. The effects of released acetylcholine (ACh), acting at muscarinic M₃ (and M₁ and M₅) receptors, are believed to stimulate phospholipase C, generation of inositol trisphosphate, and release of Ca²⁺. ACh stimulation of M₂ (and M₄) is believed to inhibit adenylyl cyclase with consequent reduction of the intracellular content of cyclic AMP.

AC = adenylyl cyclase; cAMP = cyklistiskt AMP; PLC = phospholipase C; IP₃ = inositol trisphosphate; G = G-proteins

Signal pathways for muscarinic receptors in the detrusor

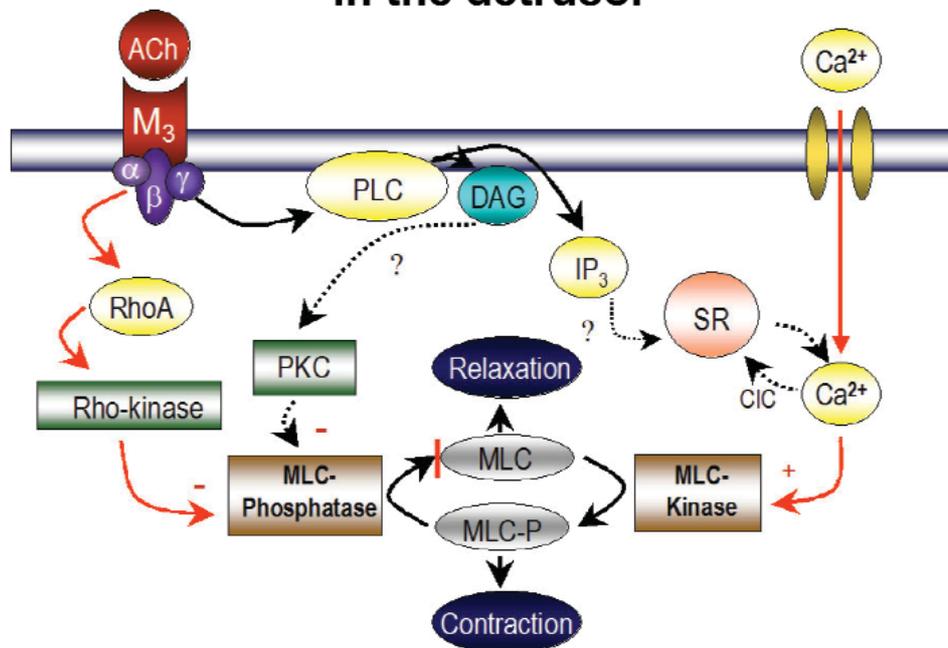


Figure 6. Signal pathways for muscarinic receptors in the human detrusor (according to Fleishmann et al 2004). Myosine light chain (MLC) phosphorylation is regulated by a phosphatase and a kinase. Only phosphorylated MLC can react with myosin and produce contraction. Stimulation of Rho kinase inhibits MLC phosphatase, and influx of Ca²⁺ stimulates MLC kinase resulting in detrusor contraction. PLC = phospholipase C; IP₃ = inositol trisphosphate; DAG = diacylglycerol; PKC = protein kinase C; SR sarcoplasmic reticulum

tion of transmitter release. The inhibitory pre-junctional muscarinic receptors have been classified as muscarinic M₂ in the rabbit [46] and rat [47], and M₄ in the guinea pig [48], and human bladder [49]. Pre-junctional facilitatory muscarinic receptors appear to be of the M₁ subtype in the bladders of rat, rabbit [46, 47], and humans [50]. 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 M₃ muscarinic receptors [50].

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 [51]. However, it is not always clear what the changes mean in terms of changes in detrusor function.

VIII. DRUGS USED FOR TREATMENT OF OVERACTIVE BLADDER SYMPTOMS/DETRUSOR OVERACTIVITY

It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence. Even if it affects 30-60% of patients older than 65 years, it is not a disease exclusive to aging. It appears that OAB/DO may be the result of several different mechanisms, both myogenic and neurological [52]. Most probably, both factors contribute to the genesis of the disease.

An abundance of drugs has been used for the treatment of OAB/DO (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 OAB/DO, there has been such a high placebo response that meaningful differences between placebo and active drug cannot be demonstrated [53]. 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 considering them as an adjunct to conservative therapy. The role of pharmacotherapy is even more contentious in older, and particularly frail older people (see Committee no 13).

1. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS

Antimuscarinics block, more or less selectively, muscarinic receptors. The common view is that in OAB/DO, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine, released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urge and increasing bladder capacity, and during this phase, there is normally no parasympathetic input to the lower urinary tract (Figure 2) [52]. Furthermore, antimuscarinics are usually competitive antagonists (Figure 7). This implies that when there is a massive release of acetylcholine, as during micturition, the effects of the drugs should be decreased, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinics can produce urinary retention in humans, but in the dose range needed for beneficial effects in OAB/DO, there is little evidence for a significant reduction of the voiding contraction. The question is whether there are other effects of antimuscarinics that can contribute to their beneficial effects in the treatment of OAB/DO [54]. Muscarinic receptor functions may change in bladder disorders associated with OAB/DO, implying that mecha-

Effects of antimuscarinics

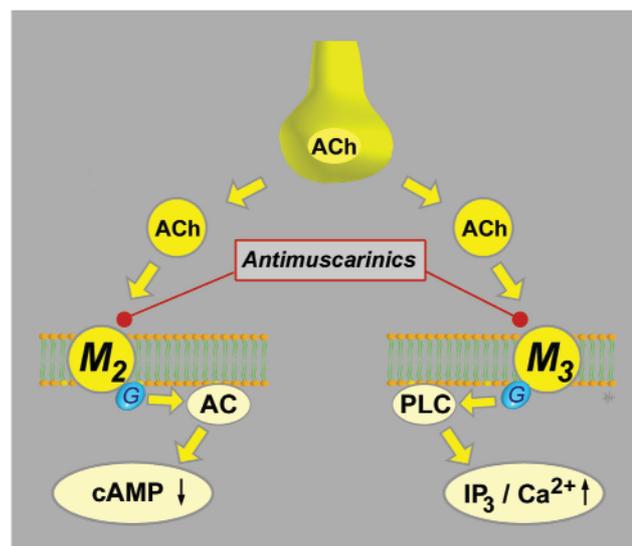


Figure 7. Antimuscarinics block competitively muscarinic receptors.

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

Antimuscarinic drug	Level of evidence	Grade of recommendation
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Dicyclomine	3	C
Flavoxate	2	D
Antidepressants		
Imipramine	3	C
Alpha-AR antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Beta-AR antagonists		
Terbutaline	3	C
Salbutamol	3	C
COX-inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Other drugs		
Baclofen*	3	C
Capsaicin**	2	C
Resiniferatoxin**	2	C
Botulinum toxin***	2	B
Estrogen	2	C
Desmopressin****	1	A

* intrathecal; ** intravesical; *** bladder wall; **** nocturia

nisms, which normally have little clinical importance, may be upregulated and contribute to the pathophysiology of OAB/DO [55].

Muscarinic receptors are found on bladder urothelial cells where their density can be even higher than in detrusor muscle. The role of the urothelium in bladder activation has attracted much interest [56], but whether the muscarinic receptors on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues [57] found that there is basal acetylcholine release in human detrusor muscle. This release was resistant to tetrodotoxin and much diminished when the urothelium was removed; thus, the released acetylcholine was probably of non-neuronal origin and, at least partly, generated by the urothelium. There is also indirect clinical evidence for release of acetylcholine during bladder filling. Smith and co-workers [58] found that in patients with recent spinal-cord injury, inhibition of acetylcholine breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch and colleagues [59] inhibited acetylcholine breakdown with edrophonium in a series of patients with disturbed voiding or urinary incontinence. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly

decreased detrusor compliance in 78% of the patients with the symptom pattern of overactive bladder, but in no patients without specific complaints suggesting DO. Thus, during the storage phase, acetylcholine may be released from both neuronal and non-neuronal sources (eg, the urothelium) and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor (**Figure 8**). This mechanism may be important in the pathophysiology of overactive bladder and a possible target for antimuscarinic drugs (**Figure 9**).

Generally, antimuscarinics can be divided into tertiary and quaternary amines [60]. They differ with regards to lipophilicity, molecular charge, and even molecular size, tertiary compounds generally having higher lipophilicity and molecular charge than quaternary agents. Atropine, tolterodine, oxybutynin, propiverine, darifenacin, and solifenacin are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the central nervous system (CNS), dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and low charge will increase the possibilities to pass the blood brain barrier. Quaternary ammonium compounds, like propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and

Bladder Effects of Antimuscarinics

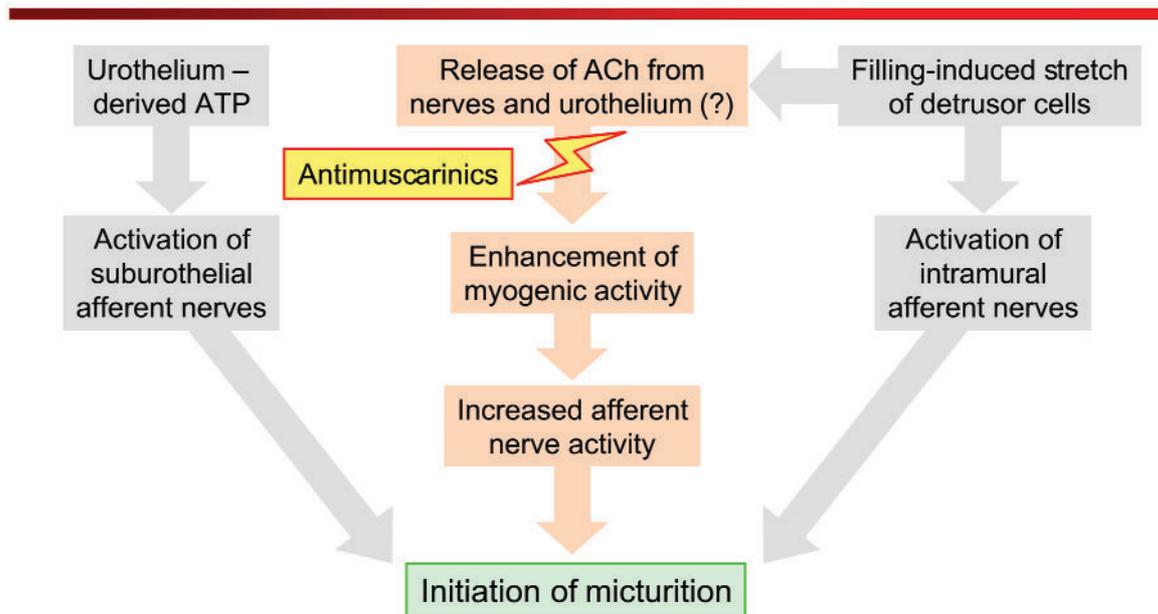


Figure 8. By inhibiting the effects of acetylcholine, generated from non-nervous sources (urothelium) or leaking from cholinergic nerves during the filling phase, antimuscarinics may inhibit detrusor overactivity and urgency.

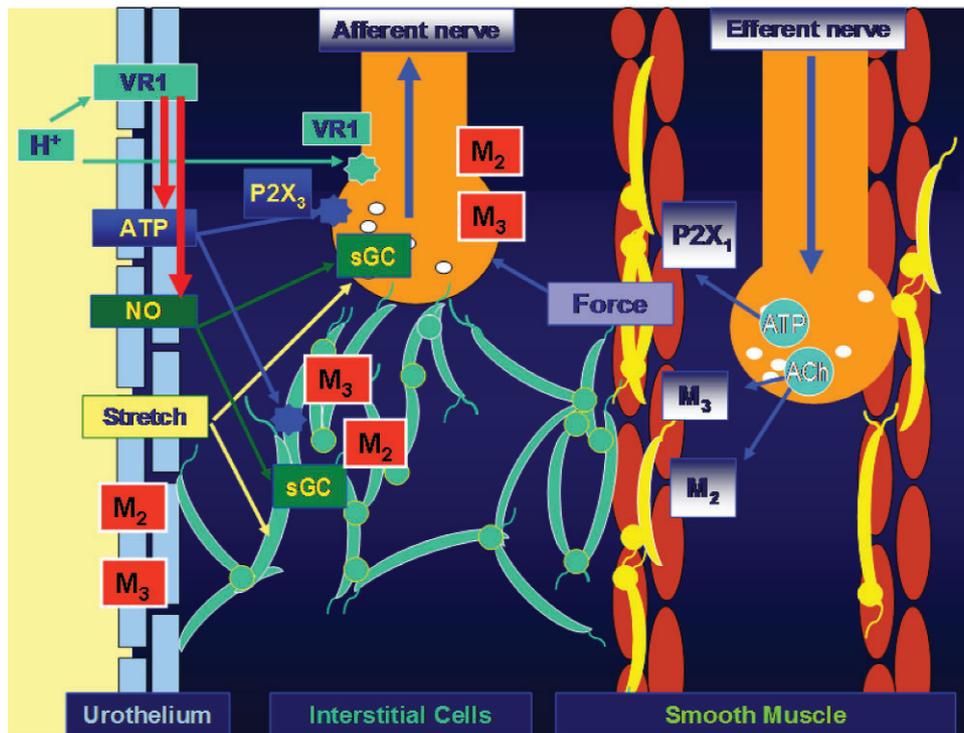


Figure 9. Non-detrusor and detrusor muscle sites (M₂, M₃) in the bladder where antimuscarinics may act. Muscarinic receptors can be found on urothelial cells, on interstitial cells, and on afferent nerves. VR1 = vanilloid receptor; sGC = soluble guanylyl cyclase; ATP = adenosine triphosphate; NO = nitric oxide; ACh = acetylcholine; P2X₃ = purinergic receptor

have a low incidence of CNS side effects [60]. They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, tachycardia, and dryness of mouth.

Many antimuscarinics (all currently used tertiary amines) are metabolized by the P450 enzyme system to active and/or inactive metabolites [60]. The most commonly involved P450 enzymes are CYP2D6, and CYP3A4. The metabolic conversion creates a risk for drug-drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration/effect of the antimuscarinic and /or interacting drug. Antimuscarinics secreted by the renal tubules (eg trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism.

Antimuscarinics are still the most widely used treatment for urge and urge incontinence [55]. However, currently used drugs lack selectivity for the bladder, and effects on other organ systems (Figure 10) may result in side effects, which limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained, if the subtype(s) mediating bladder contraction, and those producing the main side

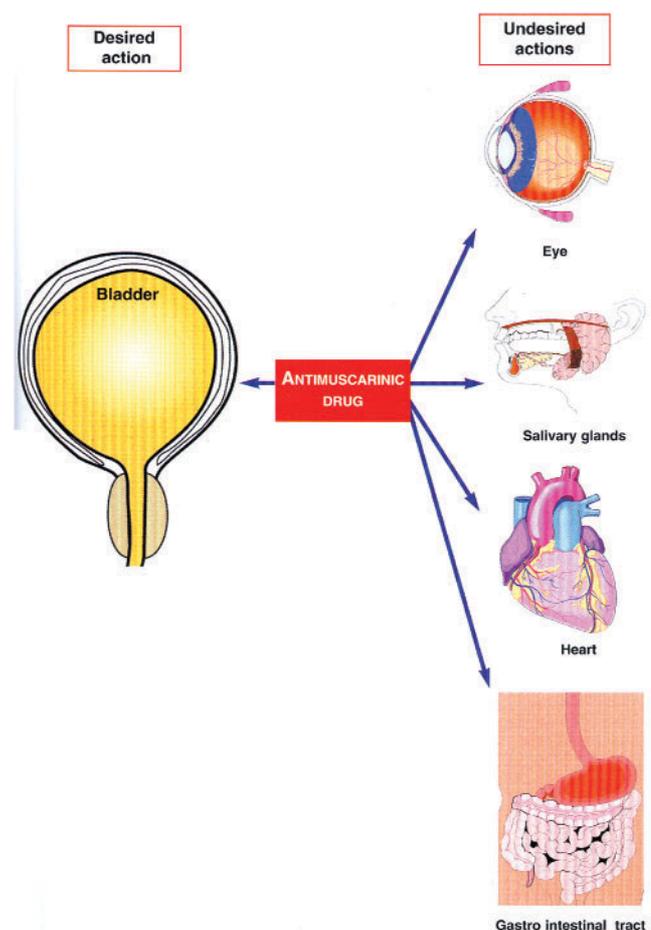


Figure 10. Desired and non-desired effects of antimuscarinics.

effects of antimuscarinic drugs, were different. Unfortunately, this does not seem to be the case. One way of avoiding many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical only in a limited number of patients.

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 [61, 62].

a) Atropine

Atropine (dl-hyoscyamine) is rarely used for treatment of OAB/DO because of its systemic side effects, which preclude its use. However, in patients with neurogenic DO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [63-66].

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 [67].

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. It is metabolized (metabolites inactive) and has a short half-life (less than 2 h) [68]. 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 are required. Using this approach in 26 patients with uninhibited detrusor contractions, Blaivas et al. [69] 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. [70] 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 DO (154 patients), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic DO), and with dose titration, Holmes et al. [71] found no differences in effi-

cacy between oxybutynin and propantheline. Controlled randomized trials (n=6) reviewed by Thüroff et al [53], confirmed a positive, but varying, response to the drug.

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

c) Trospium

Trospium. Trospium chloride is a quaternary ammonium compound with a biological availability less than 10% [72]. It is expected to cross the blood-brain to a limited extent and seems to have no negative cognitive effects [72-74]. The drug has a plasma half-life of approximately 20 h, and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. It is not metabolized by the cytochrome P450 enzyme system [75].

Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions [76].

Several RCTs have documented positive effects of trospium both in neurogenic DO [77-78] and non-neurogenic DO [79-84]. In a placebo-controlled, double blind study on patients with neurogenic DO [77], the drug was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects [78].

The effect of trospium in urge incontinence has been documented in RCTs. Allousi et al [79] 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 [80] investigated 208 patients with DO, 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.

Jünemann et al [81] 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 DO, sensory urge incontinence or mixed incontinence. Trospium reduced the frequency of micturition, which was the primary endpoint, more than tolterodine and placebo, and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7 and 9%, respectively).

Halaska et al [82] studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urge syndrome. The trial comprised a total of 358 patients with urge syndrome or urge incontinence. After randomisation in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily). Urodynamic measurements were performed at the beginning, and at 26 and 52 weeks to determine the maximal cystometric bladder capacity. The frequencies of micturition, incontinence and number of urgency events were recorded in patient diary protocols in weeks 0, 2, 26 and 52. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgencies in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 ml after 26 weeks and 115 ml after 52 weeks ($P=0.001$). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 64.8% of the patients treated with trospium chloride and 76.7% of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the mouth. An overall assessment for each of the drugs reveals a comparable efficacy level and a better benefit-risk ratio for trospium chloride than for oxybutynin due to better tolerability.

Zinner et al. [83] treated 523 patients with symptoms associated with OAB and urge incontinence with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo controlled trial. Dual primary end points were change in average number of toilet voids and change in urge incontinent episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urge severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire. Trospium signi-

ficantly decreased average frequency of toilet voids and urge incontinent episodes compared to placebo. It significantly increased average volume per void, and decreased average urge severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%), constipation (9.5%) and headache (6.5%).

Trospium is a well documented alternative for treatment of OAB/DO, and seems to be well tolerated. In a large US multicenter trial with the same design, and including 658 patients with OAB, Rudy et al [84] confirmed the data by Zinner et al [83], both with respect to efficacy and adverse effects.

d) Tolterodine

Tolterodine is a tertiary amine, rapidly absorbed and extensively metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite has a similar pharmacological profile as the mother compound [85], and significantly contributes to the therapeutic effect of tolterodine [86, 87]. Both tolterodine and its metabolite have plasma half-lives 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 relatively low lipophilicity of tolterodine implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [88, 89]. Tolterodine has no selectivity for muscarinic receptor subtypes, but is claimed to have functional selectivity for the bladder over the salivary glands [90, 91]. 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 [90]. However, 5 h after administration, the effects on the urinary bladder were maintained, whereas no significant effects on salivation could be demonstrated.

Tolterodine is available as immediate-release (IR; 1 or 2 mg; twice daily dosing) and extended-release (ER) forms (2 or 4 mg; once daily dosing). The extended release form seems to have advantages over the immediate-release form in terms of both efficacy and tolerability [92].

Several randomised, double blind, placebo-controlled studies, on patients with OAB/DO (both idiopathic and neurogenic DO), have documented a significant reduction in micturition frequency and number

of incontinence episodes [5, 88, 89]. Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment), and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness.

The OBJECT trial compared oxybutynin ER 10 mg once daily with tolterodine IR 2 mg twice daily [93] in a 12-week randomized, double blind, parallel-group study including 378 patients with OAB. Participants had between 7 and 50 episodes of urge incontinence per week and 10 or more voids in 24 hours. 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% and 33% of participants taking extended-release oxybutynin and tolterodine IR, respectively. Rates of central nervous system and other adverse events were low and similar in both groups. The authors concluded that oxybutynin-ER was more effective than tolterodine IR and that the rates of dry mouth and other adverse events were similar in both treatment groups.

In the OPERA study [94], oxybutynin ER at 10 mg/d or tolterodine ER at 4 mg/d were given for 12 weeks to women with 21 to 60 urge incontinence episodes per week and an average of 10 or more voids per 24 hours. Episodes of incontinence episodes (primary end point), total (urge and non urge) incontinence, and micturition were recorded in 24-hour urinary diaries at baseline and at weeks 2, 4, 8 and 12 and compared. Adverse events were also evaluated. Improvements in weekly urge incontinence episodes were similar for the 790 women who received oxybutynin ER (n=391) or tolterodine ER (n=399). Oxybutynin ER was significantly more effective than tolterodine ER in reducing micturition frequency, and 23.0% of women taking oxybutynin ER reported no episodes of urinary incontinence compared with 16.8% of women taking tolterodine ER. Dry mouth, usually mild, was more common with oxybutynin ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urge incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with oxybutynin ER, but tolera-

bility was otherwise comparable; including adverse events involving the central nervous system.

The ACET (Antimuscarinic Clinical Effectiveness Trial) [95] study, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOL-ER and in the other to 5 mg or 10mg of extended-release oxybutynin (OXY-ER). A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial in the TOL-ER 4 mg group (12%) than either the OXY-ER 5 mg (19%) or OXY-ER 10 mg groups (21%). More patients in the OXY-ER 10 mg group than the TOL-ER 4 mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOL-ER 4 mg group perceived an improved bladder condition, compared with 60% in the TOL-ER 2 mg group, 59% in the OXY-ER 5 mg group and 60% in the OXY-ER 10 mg group. Dry mouth was dose-dependent with both agents, although differences between doses only reached statistical significance in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; $p=0.05$). Patients treated with TOL-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of tolterodine ER (4 mg) than of oxybutynin ER (10 mg) may be weakened by the open label design of the study.

Zinner et al [96] evaluated the efficacy, safety, and tolerability of a tolterodine ER in treating OAB in older (> or =65) and younger (<65) patient in a 12-week double-blind, placebo-controlled clinical trial including 1015 patients (43.1% aged > or =65) with urge incontinence and urinary frequency. Patients were randomized to treatment with tolterodine ER 4 mg once daily (n = 507) or placebo (n = 508) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments, safety, and tolerability endpoints were evaluated, relative to placebo, according to two age cohorts: younger than 65 and 65 and older. Compared with placebo, significant improvements in micturition chart variables with tolterodine ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the tolterodine ER and placebo treatment arms, irrespective of age (<65: ER 22.7%, placebo 8.1%; > or =65: ER 24.3%, placebo 7.2%). Few patients (<2%) experienced severe dry mouth. No central nervous system, visual, cardiac (including electrocardiogram), or laboratory safety concerns were noted. Withdrawal

rates due to adverse events on tolterodine ER 4 mg qd were comparable in the two age cohorts (<65: 5.5%; ≥65: 5.1%).

The central symptom in the OAB syndrome is urgency. Freeman et al [97] presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily, ER tolterodine on urinary urgency in patients with OAB. Patients with urinary frequency (eight or more micturitions per 24 hours) and urge incontinence (five or more episodes per week) were randomized to oral treatment with tolterodine ER 4 mg once daily (n=398) or placebo (n=374) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with tolterodine ER, 44% reported improved urgency symptoms (compared with 32% for placebo), and 62% reported improved bladder symptoms (placebo, 48%). The odds of reducing urgency and improving bladder symptoms were 1.68 and 1.78 times greater, respectively, for patients in the tolterodine ER group than for patients receiving placebo. In response to urgency, there was a more than six-fold increase in the proportion of patients able to finish a task before voiding in the tolterodine extended release group. The proportion of patients unable to hold urine upon experiencing urgency was also decreased by 58% with tolterodine, compared with 32% with placebo (P<.001).

Mattiasson et al. [98] compared the efficacy of tolterodine 2 mg twice daily plus simplified bladder training (BT) with tolterodine alone in patients with OAB in a multicenter single blind study. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine + BT than with tolterodine alone (33% vs. 25%), while the median percentage increase in volume voided per void was 31% with tolterodine + BT and 20% with tolterodine alone. There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine + BT (-87%). It was concluded that the effectiveness of tolterodine 2mg twice daily can be augmented by a simplified BT regimen.

Millard et al [99] investigated whether the combination of tolterodine plus a simple pelvic floor muscle exercise program would provide improved treatment benefits compared with tolterodine alone in 480 patients with OAB. Tolterodine therapy for 24 weeks resulted in significant improvement in urgency, frequency, and incontinence, however, no additional benefit was demonstrated for a simple pelvic floor muscle exercise program.

Tolterodine, in both the immediate and extended release forms, has a well-documented effect in OAB/DO. It is well tolerated and is currently, together with oxybutynin, first line therapy for patients with this disorder.

e) *Darifenacin*

Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolised in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6. The metabolism of darifenacin by CYP3A4 suggests that co-administration of a potent inhibitor of this enzyme (e.g. ketoconazole) may lead to an increase in the circulating concentration of darifenacin [100]. Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg/d.

Darifenacin is a selective muscarinic M₃ receptor antagonist. In vitro, it is selective for human cloned muscarinic M₃ receptors relative to M₁, M₂, M₄ or M₅ receptors. Theoretically, drugs with selectivity for the M₃ receptor can be expected to have clinical efficacy in OAB/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes [101]. However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

The clinical effectiveness of darifenacin has been documented in several RCTs [102, 103]. Haab et al [102] reported a multicentre, double-blind, placebo-controlled, parallel-group study which enrolled 561 patients (19–88 years; 85% female) with OAB symptoms for >6 months, and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were randomised (1:4:2:3) to once-daily oral darifenacin controlled-release tablets: 3.75 mg (n=53), 7.5 mg (n=229) or 15 mg (n=115) or matching placebo (n=164) for 12 weeks. Patients recorded daily incontinence episodes, micturition frequency, bladder capacity (mean volume voided), frequency of urgency, severity of urgency, incontinence episodes resulting in change of clothing or pads and nocturnal awakenings due to OAB using an electronic diary during weeks 2, 6 and 12 (directly preceding clinic visits). Tolerability data were evaluated from adverse event reports.

Darifenacin 7.5 mg and 15 mg had a rapid onset of

effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). Darifenacin 7.5 mg and 15 mg, respectively, was significantly superior to placebo for improvements in micturition frequency, bladder capacity, frequency of urgency, severity of urgency, and number of incontinence episodes leading to a change in clothing or pads. There was no significant reduction in nocturnal awakenings due to OAB.

The most common adverse events were mild-to-moderate dry mouth and constipation with a CNS and cardiac safety profile comparable to placebo. No patients withdrew from the study as a result of dry mouth and discontinuation related to constipation was rare (0.6% placebo versus 0.9% darifenacin).

A review of the pooled darifenacin data from the three phase III, multicentre, double blind clinical trials in patients with OAB has been carried out [103]. After a 4-week washout/run-in period, 1,059 adults (85% female) with symptoms of OAB (urge incontinence, urgency and frequency) for at least 6 months were randomized to once-daily oral treatment with darifenacin: 7.5 mg ($n = 337$) or 15 mg ($n = 334$) or matching placebo ($n = 388$) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, -8.8 [-68.4%]; 15 mg, -10.6 [-76.8%]). Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg 0.6% of patients; darifenacin 15 mg 2.1%; placebo 0.3%). The incidence of CNS and cardiovascular adverse events were comparable to placebo.

One of the most noticeable clinical effects of antimuscarinics is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin, on the 'warning time' associated with urinary urgency. This

was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks' washout, 2 weeks' medication-free run-in and a 2-week treatment phase [104]. Subjects with urinary urgency for >6 months prior to enrolment and episodes of urgency >4 times daily during run-in were randomized (1:1) to darifenacin controlled-release tablets 30 mg q.d., or matching placebo. Warning time was defined as the time from the first sensation of urgency to voluntary micturition or incontinence and was recorded via an electronic event recorder at baseline (visit 3) and study end (visit 4) during a 6-hour clinic-based monitoring period, with the subject instructed to delay micturition for as long as possible. During each monitoring period, up to three urge-void cycles were recorded.

Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant increase in mean warning time with a median increase of 4.3 minutes compared with placebo. Overall, 47% of darifenacin-treated subjects compared with 20% receiving placebo achieved a $\geq 30\%$ increase in mean warning time.

There were methodological problems associated with this study; it utilized a dose of 30 mg, (higher than the dose likely to be recommended for clinical use), the treatment period was short, was conducted in a clinical-centred environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. However, this pilot study is the first study to evaluate changes in warning time, which is potentially important to individuals with symptoms associated with OAB. The observations suggest that darifenacin increases warning time compared with placebo, allowing subjects more time to reach a toilet and potentially avoiding the embarrassing experience of incontinence. It is likely that studies with future studies with other antimuscarinic agents will demonstrate similar findings.

The effect of darifenacin on cognitive function was evaluated in elderly volunteers who did not present with clinical dementia [310]. This double-blind, 3-period crossover study, randomised 129 volunteers (aged ≥ 65 years, with no/mild cognitive impairment) to receive three of five tablets: darifenacin controlled-release 3.75 mg, 7.5 mg or 15 mg q.d.; darifenacin immediate-release 5 mg t.i.d., or matching placebo. Each 14-day treatment period was separated by 7

days' washout. Cognitive function tests and alertness, calmness and contentment evaluations were completed at baseline and at treatment end. For the primary endpoints, memory scanning sensitivity, speed of choice reaction time and word recognition sensitivity, there were no statistically significant differences for darifenacin versus placebo. Darifenacin treatment was not associated with changes in alertness, contentment or calmness that are likely to be clinically relevant. Darifenacin was well tolerated, the most common adverse events being mild-to-moderate dry mouth and constipation. It was concluded from this study that in elderly volunteers, darifenacin did not impair cognitive function. This was suggested to be related to its M₃ receptor selectivity, with negligible M₁ receptor antagonism.

Darifenacin has a well-documented effect in OAB/DO, and the adverse event profile seems acceptable.

f) Solifenacin (YM-905)

Solifenacin (YM905) is a tertiary amine, well absorbed from the gastrointestinal tract (absolute bioavailability 90%). It undergoes significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) C_{max} and AUC_{0-inf} were increased by only approximately 40% and 56%, respectively [105]. The mean terminal half-life is approximately 50 hours [106, 107].

Two large-scale phase 2 trials with parallel designs were performed on men and women treated with solifenacin [108, 109]. The first dose-ranging study evaluated solifenacin 2.5 mg, 5 mg, 10 mg, and 20 mg and tolterodine (2 mg b.i.d.) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO [108]. Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Inclusion criteria for this and subsequent phase 3 studies of patients with OAB included ≥8 micturitions per 24 hours and either one episode of incontinence or one episode of urgency daily as recorded in 3-day micturition diaries. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg, 10 mg, and 20 mg, but not in patients receiving placebo or tolterodine. This effect was rapid with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, the 5 mg, 10 mg, and 20 mg dosing

groups were associated with statistically significant increases in volume voided relative to placebo and numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations due to adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. As the 5 mg and 10 mg doses caused lower rates of dry mouth than tolterodine, and superior efficacy outcomes relative to placebo, these dosing strengths were selected for further evaluation in large-scale phase 3 studies.

The second dose-ranging study of solifenacin 2.5 mg to 20 mg was carried out in the US [109]. This trial included 261 evaluable men and women receiving solifenacin or placebo for 4 weeks followed by a 2-week follow-up period. Micturition frequency was statistically significantly reduced relative to placebo in patients receiving 10 mg and 20 mg solifenacin. Number of micturitions per 24 hours showed reductions by day 7 and continued to decrease through day 28; day 7 was the earliest time point tested in solifenacin trials and these findings demonstrate efficacy as early as one week. The 5 mg, 10 mg, and 20 mg dosing groups experienced statistically significant increases in volume voided and the 10 mg solifenacin dose was associated with statistically significant reductions in episodes of incontinence.

Four pivotal phase 3 studies were conducted to evaluate the efficacy, safety, and tolerability of solifenacin in adult patients with OAB. The primary efficacy variable in all studies was change from baseline to end point in micturitions/24 hours and secondary efficacy variables included change in mean number of daily urgency and incontinence episodes. Mean volume voided per micturition served as an additional secondary efficacy outcome and provided an objective measure of bladder function. Efficacy was assessed by patient diary recordings collected at four assessment points during the 12-week trial. Two studies utilized the King's Health Questionnaire to evaluate QoL. Safety was evaluated on the basis of adverse events, clinical laboratory values, vital signs, physical examinations, and ECGs.

In the first of the double-blind multinational trials, a total of 1077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg bid), or placebo [110].

It should be noted that this study was powered only to compare active treatments to placebo. Compared with placebo (-8%), mean micturitions/24 h were

significantly reduced with solifenacin 10 mg (-20%), solifenacin 5 mg (-17%), and tolterodine (-15%). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg bid.

A second multinational trial reported efficacy outcomes in 857 patients randomized to placebo, 5 mg solifenacin, and 10 mg solifenacin [111]. Primary efficacy analyses showed a statistically significant reduction in micturition frequency following treatment at both doses of solifenacin succinate compared with placebo. Secondary efficacy variables, including urgency, volume voided per micturition, and incontinence episodes per 24 hours also demonstrated the superiority of solifenacin over placebo. Percent reduction in urgency episodes per 24 hours was 51% and 52% with solifenacin (5 mg and 10 mg, respectively) and 33% with placebo. Percent increase in volume voided per micturition was 25.4% (5 mg) and 29.7% (10 mg) with solifenacin compared with 11% for placebo. Percent decreases in episodes of urge incontinence were 62.7% (5 mg) and 57.1% (10 mg) for the solifenacin groups and 42.5% for the placebo group. Finally, all incontinence episodes were reduced by 60.7% (5 mg) and 51.9% (10 mg) with solifenacin compared with a 27.9% change with placebo. Most adverse events reported were mild. The proportion of patients who did not complete the study due to adverse events was low and comparable among treatment groups (ie, 3.3% in the placebo group, 2.3% and 3.9% in the 5-mg and 10-mg solifenacin groups, respectively). Incidences of dry mouth were 2.3%, 7.7%, and 23.1% with placebo and solifenacin 5 mg and 10 mg, respectively. There were no clinically significant effects on ECG parameters, laboratory values, vital signs, physical examination, or postvoid residual volume. Solifenacin treatment was well tolerated and produced statistically significant reductions in QoL domains including incontinence, sleep/energy, role limitations and emotions.

Two additional double-blind pivotal trials with parallel study designs and similar baseline demographics were carried out in the US and results have been pooled for ease of reporting [112]. Data collected from micturition diaries were analyzed for 1208 patients (604 placebo, 604 solifenacin). Reductions in the number of micturitions per 24 hours, the primary efficacy end point, was seen in the solifenacin group compared with the placebo group. Similar benefit was observed with solifenacin compared with placebo in three of the five secondary end points, inclu-

ding a decrease in the number of incontinence and number of urgency episodes per 24 hours, as well as an increase in the volume voided per micturition (46.8 mL vs 7.7 mL, respectively). Among patients who were incontinent at baseline, a significantly greater number of patients in the solifenacin group vs the placebo group became continent by the end of the study (53% vs 31%, respectively).

Patients from the two phase 3 multinational trials described above were invited to enroll in a year long open-label extension trial of solifenacin 5 mg and 10 mg. Preliminary results from this extension trial indicate that solifenacin efficacy and tolerability continues to improve with long-term treatment.

Solifenacin has a well-documented effect in OAB/DO, and the adverse event profile seems acceptable.

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 C^{2+} channels, as well as via mobilization of intracellular Ca^{2+} [1, 113]. 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 DO. However, there have been few clinical studies of the effects of calcium antagonists in patients with DO. Naglie et al. [114] evaluated the efficacy of nimodipine for geriatric urge incontinence in a randomized, double-blind, placebo controlled crossover trial. Thirty mg nimodipine was given twice daily for 3 weeks in older persons with DO and chronic urge incontinence. A total of 86 participants with a mean age of 73.4 years were randomized. The primary outcome was the number of incontinent episodes, as measured by the self-completion of a 5-day voiding record. Secondary outcomes included the impact of urinary incontinence on quality of life measured with a modified incontinence impact questionnaire and symptoms, as measured by the AUA symptom score. In the 76 (88.4%) participants completing the study, there was no significant difference in the number of incontinent episodes with nimodipine versus placebo. Scores on the incontinence impact questionnaire and the AUA symptom score were not significantly different with nimodipine versus placebo, and the authors concluded that treatment of geriatric urge incontinence with 30 mg nimodipine twice daily was unsuccessful.

Available information does not suggest that systemic therapy with calcium antagonists is an effective way to treat DO.

b) Potassium channel openers

Opening of K⁺ channels and subsequent efflux of K⁺ will produce hyperpolarization of various smooth muscles, including the detrusor [113, 115]. This leads to a decrease in Ca²⁺ influx by reducing the opening probability of Ca²⁺ 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 [113, 115], 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 [116, 117]. However, new drugs with K_{ATP} channel opening properties have been described, which may be useful for the treatment of bladder overactivity [113]. K⁺ channel opening is a theoretically attractive way of treating DO, since it would make it possible to eliminate undesired bladder contractions without affecting normal micturition. However, at present there is no evidence from RCTs to suggest that K⁺ channel openers represent a treatment alternative.

3. DRUGS WITH “MIXED” ACTION

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 anti-muscarinic 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 Ca²⁺ 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 pointes) in some patients [118, 119].

a) Oxybutynin

Oxybutynin is a tertiary amine that is well absorbed, and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite, N-desethyloxybutynin (DEO) has pharmacological properties similar to the parent compound [120], but occurs in much higher concentrations after oral administration [121]. It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander et al. [122]. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation [121, 123].

Oxybutynin has several pharmacological effects, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an anti-muscarinic 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 anti-muscarinic agent [124]. 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 [120, 125]. The drug was shown to have a slightly higher affinity for muscarinic M₁ and M₃ receptors than for M₂ receptors [126, 127], but the clinical significance of this is unclear.

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and the newer anti-muscarinic agents are all compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other anti-muscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR and the advantage of the newer formulations lies in improved dosing schedules and side-effect profile [93, 94, 128]. An extended release (OXY-ER) once daily oral formulation gained approval by the US Food and Drug Administration (FDA) in 1999. OXY-ER uses

a patented, push-pull, osmotic delivery system to deliver oxybutynin at a fixed rate over 24 hours and offers dosage flexibility between 5 and 30 mg/day. An oxybutynin transdermal delivery system (OXY-TDS) was approved by the FDA in 2003. This OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability. Again, however, the data support these newer formulations of oxybutynin as effective in the treatment of OAB with significant reductions in urge incontinence, but only a small number of patients reach total dryness. For this reason, in addition to side effects and cost, very few patients continue to remain on the medications for a full year.

Immediate-release oxybutynin (Oxy-IR). Several controlled studies have shown that OXY-IR is effective in controlling DO, including neurogenic DO [5, 129, 130]. 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 [53] (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 an adverse effect 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 [131]. In nursing home residents (n=75), Ouslander et al. [132] 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 [133].

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit [134, 135].

The therapeutic effect of immediate release oxybutynin on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting [136, 137]. The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence [138]; 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 [131].

Extended release oxybutynin (Oxy-ER). This formulation was developed to decrease metabolite formation of DEO with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 hours distally into the large intestine where absorption is not influenced by the cytochrome P-450 enzyme system. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed during the first-pass metabolism through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [139]. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or tolterodine IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [140].

The effects of OXY-ER have been well documented [141]. In the OBJECT study [93], the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose of tolterodine IR totaling 4 mg in a day 2. OXY-ER was statistically more effective than the tolterodine IR in weekly urge incontinence episodes, total incontinence, and frequency and both medications were equally well tolerated. The basic study was repeated as the OPERA study [194] with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and tolterodine ER (4 mg) and the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urge incontinence, however, tolterodine ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than tolterodine ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should no longer be compared with ER entities of the other.

Greater reductions in urge and total incontinence have been reported in patients treated in dose-escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were

compared with OXY-IR. In the 1999 study [142], 105 patients with urge or mixed incontinence were randomized to receive 5-30 mg OXY-ER once daily or 5 mg of OXY-IR 1-4 times/day. Dose titrations began at 5 mg and the dose was increased every 4-7 days until one of three endpoints was achieved. These were 1) the patient reported no urge incontinence during the final two days of the dosing period; 2) the maximum tolerable dose was reached; the maximum allowable dose (30 mg for OXY-ER or 20 mg for OXY-IR) was reached. The mean percentage reduction in weekly urge and total incontinence episodes was statistically similar between OXY-ER and OXY-IR but dry mouth was reported statistically more often with OXY-IR. In the 2000 study [143], 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg daily up to 20 mg daily. As in the 1999 study, OXY-ER again achieved a >80% reduction in urge and total incontinence episodes and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naïve patients included, as all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naïve population [144].

Transdermal oxybutynin (OXY-TDS). Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A recent study [145] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (66% for OXY-TDS and 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study [128] the 3.9-mg daily dose patch significantly reduced the number of weekly incontinence episodes while reducing average daily urinary frequency confirmed by an increased average voided volume. Furthermore, dry mouth rate was similar to placebo (7% vs 8.3%). In a third study [146] OXY-TDS was compared not only to placebo but to TOL-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOL-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14% and erythema in 8.3% with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a ran-

domized, 2-way crossover study [139]. Multiple blood and saliva samples were collected and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared to OXY-ER which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER.

Other administration forms. Rectal administration [147] was reported to have fewer adverse effects than the conventional tablets. Administered intravenously, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults [148], although adverse effects may occur [149, 150].

Oxybutynin has a well-documented efficacy in the treatment of OAB/DO, and is, together with tolterodine, first line treatment for patients with this disorder.

b) Dicyclomine

Dicyclomine has attributed to it both a direct relaxant effect on smooth muscle and an antimuscarinic action [151]. Favorable results in DO have been demonstrated in several studies [5]. Even if published experiences of the effect of dicyclomine on DO are favourable, the drug is not widely used, and controlled clinical trials documenting its efficacy and side effects are scarce.

c) Propiverine

Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have recently been reviewed [152]. The drug is rapidly absorbed (t_{max} 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Propiverine is an inducer on hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man [153]. Several active metabolites are formed [154, 155]. Most probable these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified. The half-life of the mother compound is about 11-14 h.

Propiverine has been shown to have combined antimuscarinic and calcium antagonistic actions [156, 157]. The importance of the calcium antagonistic component for the drug's clinical effects has not been established.

Propiverine has been shown to have beneficial

effects in patients with DO in several investigations. Thüroff et al [53] 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 neurogenic DO, controlled clinical trials have demonstrated propiverine's superiority over placebo [158]. Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate and placebo [159], and propiverine, oxybutynin and placebo [160, 161], have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin.

Madersbacher et al [161] 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 [162] 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). The incidence of adverse events was very low (2% dryness of the mouth under propiverine – 2 out of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes.

Propiverine has a documented beneficial effect in the treatment of DO, and seems to have an acceptable side effect profile.

d) Flavoxate

Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% [60]. The drug is extensively metabolized and plasma half-life was found to be 3.5 h [163]. Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity [164, 165]. 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 anti-muscarinic effect was found [166]. Uckert et al [76], on the other hand, found that in strips of human bladder, the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable. It has been suggested that pertussis toxin-sensitive G-proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, since intracerebroventricularly or intrathecally administered flavoxate abolished isovolumetric rhythmic bladder contractions in anesthetized rats [167].

The clinical effects of flavoxate in patients with DO and frequency, urge and incontinence have been studied in both open and controlled investigations, but with varying rates of success [168]. Stanton [169] 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. [170] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects 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 [171-173]. 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

Even if it is well known that α -AR antagonists can ameliorate lower urinary tract symptoms in men with BPH [174], 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 [175] 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 (BPO). He found that tamsulosin produced 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 DO [5, 176]; however, the success has been moderate.

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 [177].

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 [1]. 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) [178, 179]. Both normal and neurogenic human detrusors were shown to express β_1 -, β_2 -, and β_3 -AR mRNAs, and selective β_3 -AR agonists effectively relaxed both types of detrusor muscle [180-182]. Thus, it seems that the atypical β -AR of the human bladder may be the β_3 -AR.

On the other hand, early receptor binding studies using subtype selective ligands, suggested that the β -ARs of the human detrusor are primarily of β_2 subtype [1], and favourable effects on DO were reported in open studies with selective β_2 -AR agonists such as terbutaline [183]. 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 DO [184]. Other investigators, however, have not been able to show that β -ARs agonists represent an effective therapeutic principle in elderly patients with DO [185], or in young patients with myelodysplasia and DO [186]. Whether or not this is of importance in humans and whether β_3 -AR stimulation will be an effective way of treating the OAB/DO has yet to be shown in controlled clinical trials.

6. ANTIDEPRESSANTS

Several antidepressants have been reported to have beneficial effects in patients with DO [187, 188]. However, imipramine is the only drug that has been widely used clinically to treat this disorder.

Imipramine has complex pharmacological effects, including marked systemic anticholinergic actions [189] and blockade of the reuptake of serotonin and noradrenaline [190], but its mode of action in DO has not been established [191]. Even if it is generally considered that imipramine is a useful drug in the treatment of DO, no good quality RCTs that can document this have been retrieved.

It has been known for a long time that imipramine can have favourable effects in the treatment of nocturnal enuresis in children with a success rate of 10-70 % in controlled trials [191, 192]. 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 [193, 194]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [189].

The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have been performed during the last decade [191]. No good quality RCTs have documented that the drug is effective in the treatment DO. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

7. PROSTAGLANDIN SYNTHESIS INHIBITORS

Human bladder mucosa has the ability to synthesize eicosanoids [195], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [196, 197]. Even if prostaglandins cause contraction of human bladder muscle [1], it is still unclear whether prostaglandins contribute to the pathogenesis of unstable detrusor contractions. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Cardozo et al. [198] performed a double-blind controlled study of 30 women with DO 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 DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache and gastrointestinal symptoms. Palmer [199] studied the effects of flurbiprofen 50 mg x 4 versus placebo in a double-blind, cross-over trial in 37 patients with idiopathic DO (27% of the patients did not complete the trial). Active treatment significantly increased maximum contractile pressure, decreased the number of voids and decreased the number of urgent voids compared to baseline. Indomethacin 50 to 100 mg daily was reported to give symptomatic

relief in patients with DO, compared with bromocriptine in a randomized, single-blind, cross-over study [200]. The incidence of side effects was high, occurring in 19 of 32 patients. However, no patient had to stop treatment because of side effects.

The few controlled clinical trials on the effects of prostaglandin synthesis inhibitors in the treatment of DO, 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 [201]. It is now widely used as a treatment for primary nocturnal enuresis [202, 203]. 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 [204-207]. 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 [208]. Several, controlled, double-blind investigations have shown intranasal administration of desmopressin to be effective in the treatment of nocturnal enuresis in children [202, 203]. 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 efficacy in primary nocturnal enuresis in children and adolescents has been documented in randomized, double blind, placebo controlled studies [209, 210].

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 [211]. Also in patients with multiple sclerosis, desmopressin was shown in controlled studies to reduce nocturia, and micturition frequency [212-215]. Furthermore, desmopressin was shown to be successful in treating nocturnal enuresis in spina bifida patients with diurnal incontinence [216].

Also oral desmopressin has proved to be effective in the treatment of nocturia. In a randomized double

blind study, Mattiasson et al [217] investigated the efficacy and safety of oral desmopressin in the treatment of nocturia in men. A 3-week dose-titration phase established the optimum desmopressin dose (0.1, 0.2 or 0.4 mg), and after a 1-week 'washout' period, patients who responded in the dose-titration period were randomized to receive the optimal dose of desmopressin or placebo in a double-blind design for 3 weeks. In all, 151 patients entered the double-blind period (86 treated with desmopressin, 65 with placebo). In the desmopressin group 28 (34%) patients and in the placebo group two (3%) patients had significantly fewer than half the number of nocturnal voids relative to baseline; the mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7, respectively, reflecting a mean decrease of 43% and 12%. The mean duration of the first sleep period increased by 59% (from 2.7 to 4.5 h) in the desmopressin group, compared with an increase of 21% (from 2.5 to 2.9 h) in the placebo group. The mean nocturnal diuresis decreased by 36% (from 1.5 to 0.9 ml/min) in the desmopressin group and by 6% (from 1.7 to 1.5 ml/min) in the placebo group. The mean ratio of night/24-h urine volume decreased by 23% and 1%, and the mean ratio of night/day urine volume decreased by 27% and increased by 3% for the desmopressin and placebo groups, respectively. In the double-blind treatment period, similar numbers of patients had adverse events; 15 (17%) patients in the desmopressin and 16 (25%) patients in the placebo group. Most adverse events were mild. Serum sodium levels were <130 mmol/L in 10 (4%) patients and this occurred during dose-titration. The authors concluded that orally administered desmopressin is an effective and well-tolerated treatment for nocturia in men.

Lose et al [218] found similar results in women. In double-blind phase of their study, 144 patients were randomly assigned to groups (desmopressin, n=72; placebo, n=72). For desmopressin, 33 (46%) patients had a 50% or greater reduction in nocturnal voids against baseline levels compared with 5 (7%) patients receiving placebo. The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis, and ratios of nocturnal per 24 hours and nocturnal per daytime urine volumes changed significantly in favor of desmopressin versus placebo. In the dose-titration phase headache (22%), nausea (8%), and hyponatremia (6%) were reported.

Robinson et al [219] introduced antidiuresis as a new concept in managing female daytime urinary incon-

tinence. In a multicentre, multinational, randomized, double blind, placebo-controlled, cross over exploratory study of women (aged 18-80 years) complaining of severe daytime urinary incontinence, 60 received study medication (safety population) and 57 completed the study. The primary efficacy endpoint was the number of periods with no leakage for 4 h after dosing. There was a higher mean incidence of periods with no leakage in the first 4 h on desmopressin, at 62 (35)%, than on placebo, at 48 (40)%, and during the first 8 h, at 55 (37)% vs 40 (41)%. There was also a higher frequency of dry days on desmopressin than on placebo; 36% of patients had no leakage on virtually all treatment days (6 or 7) for 4 h after dosing. The time from dosing to first incontinence episode was longer on desmopressin, at 6.3 (2.5) h, vs 5.2 (3.3) h, whilst the volume leaked per incontinence episode was lower on desmopressin than placebo. The total volume voided was consistently lower on desmopressin, at 1180 (58) ml vs 1375 (57) ml, over the 24-h period after administration. There were no serious or severe adverse events reported, and it was concluded that desmopressin is an effective and safe treatment in women with daytime urinary incontinence.

Even if side effects are uncommon during desmopressin treatment, there is a risk of water retention and hyponatremia [220-222]. In elderly patients, it was recommended that serum sodium should be measured before and after a few days of treatment [223].

Desmopressin is a well-documented therapeutic alternative in paediatric nocturnal enuresis, and is effective also in adults with nocturia with polyuric origin. Whether or not it will be an alternative for managing female daytime incontinence requires further documentation,

9. OTHER DRUGS

a) *Baclofen*

Baclofen is considered to depress monosynaptic and polysynaptic motoneurons and interneurons in the spinal cord by acting as a GABA agonist, and has been used in voiding disorders, including DO secondary to lesions of the spinal cord [5]. The drug may also be an alternative in the treatment of idiopathic DO [224]. However, published experience with the drug is limited. Intrathecal baclofen may be useful in patients with spasticity and bladder dysfunction, and increase bladder capacity [225].

b) *Capsaicin and resiniferatoxin (vanilloids)*

By means of capsaicin (CAP), a subpopulation of pri-

mary afferent neurons innervating the bladder and urethra, the "capsaicin-sensitive nerves", has been identified. It is believed that capsaicin exerts its effects by acting on specific, "vanilloid" receptors, on these nerves [226]. Capsaicin exerts a biphasic effect: initial excitation is followed by a long-lasting blockade, which renders sensitive primary afferents (C-fibers) resistant to activation by natural stimuli. In sufficiently high concentrations, capsaicin is believed to cause "desensitization" initially by releasing and emptying the stores of neuropeptides, and then by blocking further release [227]. Resiniferatoxin (RTX) is an analogue of CAP, approximately 1,000 times more potent for desensitization than CAP [228], but only a few hundred times more potent for excitation [229]. Possibly, both CAP and RTX can have effects on A δ -fibers. It is also possible that CAP at high concentrations (mM) has additional, non-specific effects [230].

The rationale for intravesical instillations of vanilloids is based on the involvement of C-fibers in the pathophysiology of conditions such as bladder hypersensitivity and neurogenic DO. In the healthy human bladder C-fibers carry the response to noxious stimuli, but they are not implicated in the normal voiding reflex. After spinal cord injury major neuroplasticity appears within bladder afferents in several mammalian species, including man. C-fiber bladder afferents proliferate within the suburothelium and become sensitive to bladder distention. Those changes lead to the emergence of a new C-fiber mediated voiding reflex, which is strongly involved in spinal neurogenic DO. Improvement of this condition by defunctionalization of C-fiber bladder afferents with intravesical vanilloids has been widely demonstrated in humans and animals.

Capsaicin. Cystometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans was originally presented by Maggi et al. [231], who instilled capsaicin (0.1-10 μ M) intravesically in five patients with hypersensitivity disorders with attenuation of their symptoms a few days after administration. Intravesical capsaicin, given in considerably higher concentrations (1-2 mM) than those administered by Maggi et al. [231], has since been used with success in neurological disorders such as multiple sclerosis, or traumatic chronic spinal lesions [5, 232, 233]. 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 [234]. No

pre-malignant or malignant changes in the bladder have been found in biopsies of patients who had repeated capsaicin instillations for up to 5 years [235].

Resiniferatoxin (RTX). The beneficial effect of RTX has been demonstrated in several studies [5, 233, 236-239].

de Seze et al [233] compared the efficacy and tolerability of nonalcohol capsaicin (1 mM) vs RTX (100 nM) in 10% alcohol in a randomized, double blind, parallel groups study in 39 spinal cord injured adult patients with neurogenic DO (hyperreflexia). Efficacy (voiding chart and cystomanometry) and tolerability were evaluated during a 3-month followup. On day 30 clinical and urodynamical improvement was found in 78% and 83% of patients with capsaicin vs 80% and 60% with RTX, respectively, without a significant difference between the 2 treated groups. The benefit remained in two-thirds of the 2 groups on day 90. There were no significant differences in regard to the incidence, nature or duration of side effects in capsaicin vs RTX treated patients. The data suggested that the capsaicin and RTX are equally efficient for relieving the clinical and urodynamic symptoms of neurogenic DO, and that glucidic capsaicin is as well tolerated as ethanolic RTX.

Available information (including data from RCTs) suggests that both capsaicin and RTX may have useful effects in the treatment of neurogenic DO. There may be beneficial effects also in non-neurogenic DO in selected cases refractory to antimuscarinic treatment, but further RCT based documentation is desired. RTX is an interesting alternative to capsaicin, but the drug is currently not in clinical development owing to formulation problems.

c) *Botulinum toxin (BTX)*

Seven immunologically distinct antigenic subtypes of botulinum toxin have been identified: A, B, C1, D, E, F and G. Types A and B are in clinical use in urology, but most studies have been performed with botulinum toxin A type. There are three commercially-available products: type A (Botox®, Allergan, Irvine CA: BTX-A₁; Dysport®, Ipsen, Berkshire, UK: BTX-A₁; type B (Myobloc™ Neurobloc™, Dublin/Princeton, NJ: BTX-B₁). It is important not to use these products interchangeably, as they have very different dosing and side effect profiles.

On a weight basis, botulinum toxin is the most potent naturally occurring substance known. The toxin blocks the release of acetylcholine and other trans-

mitters from presynaptic nerve endings interacting with the protein complex necessary for docking vesicles [240-242]. This results in decreased muscle contractility and muscle atrophy at the injection site. The produced chemical denervation is a reversible process, and axons are regenerated in about 3 to 6 months. The botulinum toxin molecule cannot cross the blood-brain barrier and therefore has no CNS effects.

There are many open-label and a few double-blind studies and reports describing positive outcomes after treatment with BTX in many urologic conditions including: detrusor striated sphincter dyssynergia (DSD), neurogenic DO (detrusor hyperreflexia) pelvic floor spasticity, and possibly BPH and interstitial cystitis [242-244]. However, toxin injections may also be effective in refractory idiopathic DO [245, 246].

Preliminary studies look very promising with BTX-A. It seems too early to tell whether the same results will be seen with BTX-B. The safety of these products appears satisfactory. A good response rate appears to occur within one week and last from 6 to 9 months before reinjection is necessary. It remains to be seen whether this treatment will be cost-effective for all of the diseases currently being studied.

IX. DRUGS USED FOR TREATMENT OF STRESS INCONTINENCE

Many factors seem to be involved in the pathogenesis of stress urinary incontinence (SUI): urethral support, vesical neck function, and function of the muscles of the the urethra and pelvic floor [247]. Such anatomical factors cannot be treated pharmacologically. However women with SUI have lower resting urethral pressures than age-matched continent women [248, 249], and since it seems likely that there is a reduced urethral closure pressure in most women with SUI, it seems logical to increase urethral pressure to improve the condition.

Factors, which may contribute to urethral closure, include tone of urethral smooth and striated muscle and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacological evidence that a substantial part of urethral tone is mediated through stimulation of α -ARs in the urethral smooth muscle by released noradrenaline [1].

A contributing factor to SUI, mainly in elderly women with lack of estrogen, may be lack of mucosal function. The pharmacological treatment of SUI (Table 3) aims at increasing intraurethral closure forces by increasing tone in the urethral smooth and striated muscles. Several drugs may contribute to such an increase [61, 250], but limited efficacy or side effects have often limited their clinical use.

Table 3. Drugs used in the treatment of stress incontinence. Assessments according to the Oxford system (modified)

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

1. α -ADRENOCEPTOR AGONISTS

Several drugs with agonistic effects on α -ARs have been used in the treatment of SUI. However, ephedrine and norephedrine (phenylpropanol amine; PPA) seem to have been the most widely used [5]. The original Agency for Healthcare Policy and Research Guideline [251] reported 8 randomized controlled trials with PPA, 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) were listed as 0% to 14%, percent reduction in continence as 19% to 60%, and percent side effects and percent dropouts as 5% to 33%, and 0% to 4.3% respectively. A recent Cochrane Review [252] evaluated randomized or quasi-randomized controlled trials, which included an adrenergic agonist in at least one arm. There were 11 trials, which utilized PPA, two which utilized midodrine, and 2 which utilized clenbuterol. There was “weak evidence” to suggest that use of an adrenergic agent was better than placebo treatment.

Ephedrine and PPA lack selectivity for urethral α -ARs and can increase blood pressure and cause sleep disturbances, headache, tremor and palpitations [5].

Kernan et al. [253] reported the risk of hemorrhagic stroke to be 16 times higher in women less than 50 years of age who had been taking PPA as an appetite suppressant (statistically significant) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (not statistically significant). There was no increased risk in men. PPA has been removed from the market in the United States.

Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some [254] had suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003, the Food and Drug Administration of the U.S. decreed such a ban, a move which has survived legal appeal.

Midodrine and methoxamine stimulates α_1 -ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate and the clinical usefulness seems to be limited by adverse effects [252, 255, 256].

Attempts have been made to develop agonists with selectivity for the human urethra. Musselman et al. [257] reported on a phase 2 randomized crossover study with Ro 115-1240, a peripheral active selective $\alpha_{1A/1L}$ adrenoceptor partial agonist [258], in 37 women with mild to moderate SUI. A moderate, positive effect was demonstrated, but also side effects curtailing further development of the drug.

2. 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 [259-260], there are no RCTs supporting such an action. In the Gleason et al [259] study, the beneficial effects become manifest only after 4 to 10 weeks of treatment, a difficult to explain phenomenon. Donker and Van der Sluis [261] reported that β -blockade did not change UPP in normal women. Although suggested as an alternative to α -AR agonists in patients with SUI and hypertension these agents have major potential cardiac and pulmonary side effects of their own, related to their therapeutic β -AR blockage effects.

3. 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. Gilja et al [262] 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. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement.

Lin et al [263] 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.

4. CLENBUTEROL

β -AR stimulation is generally conceded to decrease urethral pressure [1], but β_2 -AR agonists have been reported to increase the contractility of some fast contracting striated muscle fibers and suppress that of slow contracting fibers of others [264]. Some β -AR agonists also stimulate skeletal muscle hypertrophy – in fast twitch more so than slow twitch fibers [265]. Clenbuterol has been reported to potentiate the field stimulation induced contraction in rabbit isolated periurethral muscle preparations, an action which is suppressed by propranolol and greater than that produced by isoproterenol [266]. These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yaminishi et al [267] reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs, abolished by β -AR blockade.

Yasuda et al. [268] described the results of a double blind placebo controlled trial with this agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad usage per day, and overall global assessment. Pad weight decreased from 11.7 ± 17.9 g to 6.0 ± 12.3 g for drug and from 18.3 ± 29.0 g to 12.6 ± 24.7 g for placebo, raising questions about the comparability of the 2 groups. The “significant” increase in MUCP was from 46.0 ± 18.2 cmH₂O to 49.3 ± 19.1 cmH₂O, versus a change of -1.5 cm H₂O in the placebo group. 56/77 patients in the clenbuterol group reported some degree of improvement ver-

sus 48/88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko et al [269] 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 [270] 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.

5. DULOXETINE

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition (**Figure 11**) in the cat acetic acid model of irritated bladder function [271-271]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [274]. The sphincteric effects were reversed by α_1 adrenergic (prazosin) and 5HT₂ serotonergic (LY 53857) antagonism, while the bladder effects were blocked by non-selective serotonergic antagonism (methiothepin), implying that both effects were mediated by temporal prolongation of the actions of serotonin and norepinephrine in the synaptic cleft [274]. Duloxetine lipophilic, well absorbed and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 h [275].

There are several RCTs documenting the effects of duloxetine in SUI [276-278]. Dmochowski et al [276] enrolled a total of 683 North American women 22 to 84 years old a double-blind, placebo controlled study. The case definition included a predominant symptom of SUI with a weekly incontinence episode frequency (IEF) of 7 or greater, the absence of predominant symptoms of urge incontinence, normal diurnal and nocturnal frequency, a bladder capacity of 400 ml or greater, and a positive cough stress test and stress pad test. After a 2-week placebo lead-in

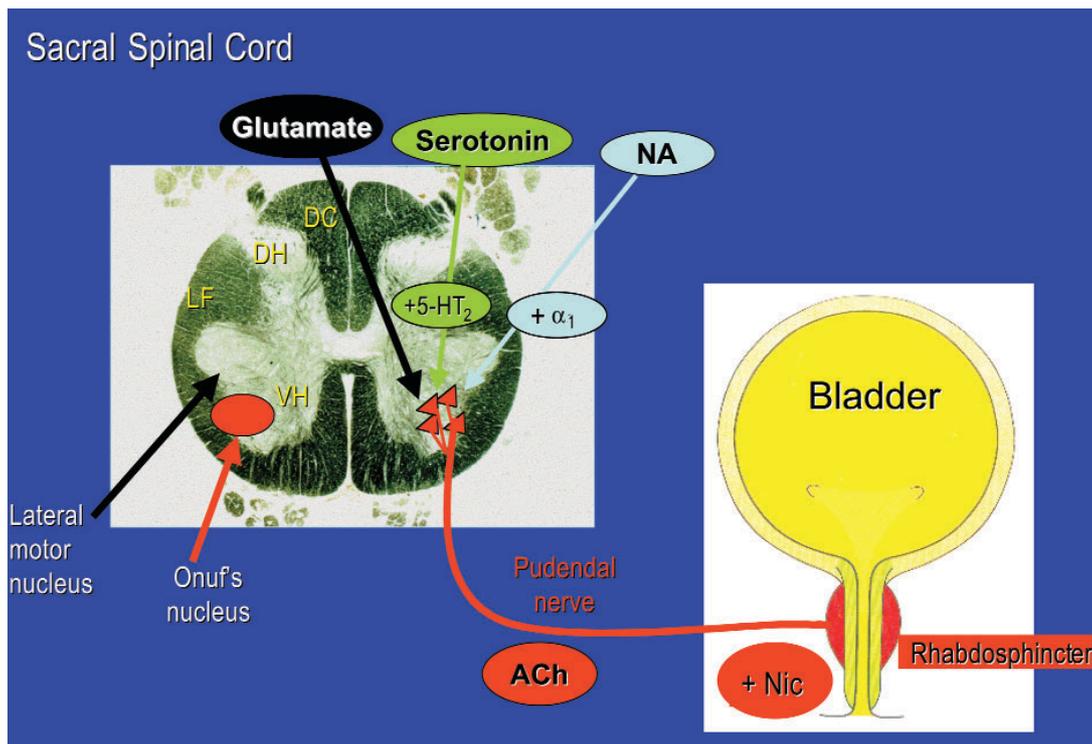


Figure 11. Mode of action of duloxetine. The striated urethral sphincter is innervated by the pudendal nerve, which contains the axons of motor neurons whose cell bodies are located in Onuf's nucleus. Glutamate exerts a tonic excitatory effects on these motor neurons, and this effect is enhanced by noradrenaline (NA) and serotonin, acting on α_1 -adrenoceptors and 5-HT₂-receptors, respectively. By inhibition of the reuptake of noradrenaline and serotonin, duloxetine increases the contractile activity in the striated sphincter (nicotinic receptors: + Nic).
 DC = dorsal commissure; DH = dorsal horn; VH = ventral horn; LF = lateral funiculus; ACh = acetylcholine
 (Adapted from Zinner et al., 2004)

period subjects were randomly assigned to receive placebo (339) or 80 mg duloxetine daily (344) as 40 mg twice daily for 12 weeks. Primary outcome variables included IEF and an incontinence quality of life questionnaire. Mean baseline IEF was 18 weekly and 436 subjects (64%) had a baseline IEF of 14 or greater. There was a significant decrease in IEF with duloxetine compared with placebo (50% vs 27%) with comparably significant improvements in quality of life (11.0 vs 6.8). Of subjects on duloxetine 51% had a 50% to 100% decrease in IEF compared with 34% of those on placebo ($p < 0.001$). These improvements with duloxetine were associated with a significant increases in the voiding interval compared with placebo (20 vs 2 minutes) and they were observed across the spectrum of incontinence severity. The discontinuation rate for adverse events was 4% for placebo and 24% for duloxetine ($p < 0.001$) with nausea the most common reason for discontinuation (6.4%). Nausea, which was also the most common side effect, tended to be mild to moderate and transient, usually resolving after 1 week to 1 month. Of the 78 women who experienced treatment

emergent nausea while taking duloxetine 58 (74%) completed the trial. The authors concluded that duloxetine 40 mg twice daily improved incontinence and quality of life.

Similar results were reported by Millard et al. [277] studying the effects of duloxetine 40 mg. b.i.d. vs. placebo in 458 women in 4 continents outside North America, and by van Kerrebroeck et al. [278] investigating 494 European and Canadian women.

The effectiveness of duloxetine for treatment of SUI is well documented. Adverse effects occur but seem tolerable [279].

X. DRUGS USED FOR TREATMENT OF OVERFLOW INCONTINENCE

According to the definition of the ICS (1997), overflow incontinence is "leakage of urine at greater than normal bladder capacity. It is associated with incomplete bladder emptying due to either impaired detrusor contractility or bladder outlet obstruction". Two

types of overflow incontinence are recognized, one as a result of mechanical obstruction, and the other secondary to functional disorders.

Occasionally both types can coexist. The clinical presentation of overflow incontinence may vary depending on the age of the patient and the cause of the incontinence. In children, overflow incontinence can be secondary to congenital obstructive disorders (e.g., urethral valves) or to neurogenic vesical dysfunction (myelomeningocele, Hinman syndrome). In adults, overflow incontinence may be associated with outflow obstruction secondary to 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.

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

Drug	Level of evidence	Grade of recommendation
Alpha-Adreceptor antagonists		
Alfuzosin	4	C
Doxazosin	4	C
Prazosin	4	C
Terazosin	4	C
Tamsulosin	4	C
*(Phenoxybenzamine)	4	NR
Muscarinic receptor antagonists		
Bethanechol	4	D
Carbachol	4	D
Cholinesterase inhibitors		
Distigmine	4	D
Other drugs		
Baclofen	4	C
Benzodiazepines	4	C
Dantrolene	4	C

NR = NOT RECOMMENDED

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 [4, 280]. 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 [4, 61].

The "autonomous" contractions in patients with parasympathetic decentralisation are probably mediated by α -AR mediated bladder activity, since they can be inhibited by α -AR antagonists [281]. The α -AR antagonist that has been most widely used is probably phenoxybenzamine [282-284]. However, uncertainties about the carcinogenic effects of this drug, and its side effects, have focused interest on selective α_1 -AR antagonists such as prazosin [285]. Other means of decreasing outflow resistance in these patients, particularly if associated with spasticity are baclofen, benzodiazepines (e.g., diazepam) and dantrolene sodium [4].

XI. 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. 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.

2. 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 [286]. 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 [287] 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 [288] 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 [289]. 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 [290] 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 [291] 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.

The above conclusions still seem valid. Thus, reviews of recent literature, agree on that “estrogen therapy has little effect in the management of urodynamic stress incontinence...” [292, 293].

3. ESTROGENS FOR URGE INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS

Estrogen has been used to treat postmenopausal urgency and urge incontinence for many years, but there have been few controlled trials performed to confirm that it is of benefit [286]. A double blind

multi-center study of 64 postmenopausal women with the “urge syndrome” failed to show efficacy [294]. 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. Another recent RCT from the same group, using 25 mg estradiol implants, confirmed the previous findings [295], and furthermore found a high complication rate in the estriol treated patients (vaginal bleeding). Grady et al [296] determined whether postmenopausal hormone therapy improves the severity of urinary incontinence in a randomized, blinded trial among 2763 postmenopausal women younger than 80 years with coronary disease and intact uteri. The report included 1525 participants who reported at least one episode of incontinence per week at baseline. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet daily (n = 768) or placebo (n = 757) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved (decrease of at least two episodes per week), unchanged (change of at most one episode per week), or worsened (increase of at least two episodes per week). The results showed that incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to hormones, while 27% of the placebo group worsened compared with 39% of the hormone group (P=0.001). This difference was evident by 4 months of treatment and was observed for both urge and stress incontinence. The number of incontinent episodes per week increased an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group (P <0.001). The authors concluded that daily oral estrogen plus progestin therapy was associated with worsening urinary incontinence in older postmenopausal women with weekly incontinence, and did not recommend this therapy for the treatment of incontinence. It cannot be excluded that the progestagen component may influence the effects found in 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. This apparently contrasts to the conclusions of a recent Cochrane review [297] that “Oestrogen treatment can improve or cure incontinence and the evidence suggests that this is more likely to occur with urge incontinence”.. A recent systematic review of the effects of estrogens for symptoms suggestive of overactive bladder also concluded that estrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration [298].

It seems reasonable to assume that estrogen therapy may be of benefit for the irritative symptoms of urinary urgency, frequency, and urge incontinence, and that this is due to reversal of urogenital atrophy rather than to a direct action on the lower urinary tract [293].

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ADDENDUM 1

Clinical Research Criteria

The Committee has included a section on clinical research criteria to encompass general considerations relating to design of clinical trials and appropriate assessments of efficacy of pharmacotherapy for incontinence.

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 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 consequence 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

Ethical Issues Regarding the use of Placebos in Clinical Trials

Placebo – the Lie that Heals Brody, [299]

Although the use of placebo, or inactive drug, in controlled clinical trials began half a century ago, there are still discussions regarding both mechanisms and ethical issues. The placebo (PBO) effect baffles patients, confounds clinicians and frustrates drug developers. Issues of placebo (PBO) are important to both patients and industry developing new therapies. The PBO response has made the development of new drugs for the treatment of incontinence difficult since the efficacy of the active ingredient should, and must, statistically exceed that of the inactive therapy. The biological/psychological mechanisms that underlie the effect have been poorly understood. There is some evidence that patients in fact know whether they are taking the active or PBO compound. Recent directives, e.g., The Declaration of Helsinki [300], raise ethical issues regarding the use of placebo in clinical studies. Finally, do patients who refuse to enter a randomized placebo controlled clinical trial represent the same treated population?

It is well established that patients in all drug trials have significant response rates on placebo. Responses to placebo range between 15% and 40% in controlled randomized trials and sometimes make it difficult for the active-treatment arm to statistically surpass the placebo arm. Why is this? Is this a learned behavior or a mind-body response? The psychological and biological factors involved in the 'placebo' response may be not distinct although recent evidence. Behavior change based on pleasing the provider or learned behavior may be an important message for clinician.

Are all surrogate markers in incontinence trials (or OAB?) modified by provider-patient interaction? Does learning to please the provider as well as the appropriate use of diet and toileting behavior so improve the patients' symptoms without active drug? Studies conducted by DuBeau et al. [301, 302] suggest that patients on the placebo arm of a clinical study may actually know that they are on a placebo. In one urge incontinence study patients on an immediate-release oxybutynin correctly identified (96%) that they were on active drug while 61% correctly identified that they were on placebo. Importantly, subjects who thought there were on active drug had

significantly better percent decrease in urinary incontinence outcomes compared with subjects who thought they had taken placebo (80-83% vs 1.1-7.2%) regardless of their actual randomization [301]. The investigators confirmed these findings in a second study were 58% of the patients identified they were on active drug (tolterodine) and 37% correctly identified that they were on placebo [302].

Patients are better at deducing what therapy they are on and when they believe they are on the real drug, they appear to do better clinically. Should this surprise us? It would be a rare patient that did not recognize the symptoms of an antimuscarinic drug. Does the population of patients who decline to be enrolled in a randomized placebo controlled clinical trial provide any further information?

There is some evidence that the sensory experience is shaped by one's attitudes and beliefs, especially our ability to modulate pain perception. Placebo analgesia is a phenomenon in which the mere belief that one is receiving an effective analgesic treatment can reduce pain [303]. Recent work in pain responses suggests that the placebo itself activates the neural system. These neuroimaging studies have provided evidence of placebo-induced changes in brain activity in regions associated with sensory, affective, and cognitive pain processing. Clearly much is to be learned from future imaging studies. In addition, identifying changes that occur at particular times—in anticipation of pain, early or late during pain processing—may shed light on how cognitive systems mediating expectancy interact with pain and opioid systems. Recent studies using positron emission tomography have shown that the placebo effect in Parkinson's disease, pain, and depression is related to the activation of the limbic circuitry. The observation that placebo administration induces the release of dopamine in the ventral striatum of patients with Parkinson's disease suggests a link between the placebo effect and reward mechanisms [304-305].

The important question remains whether the use of placebos in any clinical trials is ethical? The following concepts should be addressed in any study, including clinical trials for bladder disease:

- The disease being treated clearly can be identified by a reliable and valid biomarker

- The biomarkers or endpoints clearly delineate a response
- Lack of appropriate treatment would hurt the patient
- There is available and appropriate therapy that can be compared to the new product.

The Declaration of Helsinki (or the Declaration) addresses and describes the ethical principles regarding placebo in Part C item 29. This International document describes ethical principles for clinical investigation. <http://www.wma.net/e/policy/b3.htm>

Part C. Additional principles for medical research combined with medical care: regarding research subjects.

Item 29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

This item has been a highly discussed one with both international medical associations and regulatory bodies. The footnote to the Declaration from the World Medical Association (WMA) states:

Footnote to Article 29: The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial **and that in general this methodology should only be used in the absence of existing proven therapy.**

However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

The statement that extreme care must be taken in making use of a placebo-controlled trial and this methodology should only be used in the absence of

existing proven therapy” would suggest that the use of PBO in many studies may not be appropriate. Every antimutagenic study to date has used placebo controls rather than comparison to proven therapies. Should this practice be continued when there are active comparators?

Regulatory agencies, e.g. the United States (U.S.), Canada, and the European Union (EU) have made many statements regarding the use of placebo in clinical trials aimed at the drug approval process.

U.S. Food and Drug Administration (FDA - <http://www.fda.gov>)

Publications from authors [306-308] representing FDA would suggest that the above phrase in the Declaration was not meant to discourage placebo-controlled trials, but was rather to reinforce the idea that the physician-patient relationship must be respected. The informed consent becomes more important document in trials when there is an existing available therapy. The authors suggest that the use of informed consent allows trials to be ethically conducted even when effective therapy exists, “as long as patients will not be harmed by participation and are fully informed about their alternatives. “The Agency believes that the use of placebo-controlled trials is ethical in clinical studies.”

These publications do not consider the impact of a skewed patient population - a population reflecting only patients willing and able to enter a placebo-controlled study when an active therapy is available. Nor does it consider the ability of patients to identify whether they are on active or PBO compound Where there are active comparators should it be mandatory to include these in clinical trials with a new product?

Canada – Health Canada (<http://www.hc-sc.gc.ca/>)

Canada has provided an Executive Summary -Draft Report of the National Placebo Working Committee “Research involving human subjects is essential in demonstrating the safety and efficacy of new compounds, drugs and devices. The regulatory process for evaluation of therapeutic products, including the approval of clinical trials with or without the use of placebos, falls within the jurisdiction of Health Canada, under the authority of the Food and Drugs Act and Regulations. The requirements for conducting clinical trials in Canada can be found in Part C, Division of the Food and Drug Regulations (Drugs for Clinical Trials Involving Human Subjects). The

involvement of human subjects, industry, health care institutions, academic centers and research-granting agencies are all key actors in the framework for therapeutic products.

They state in the document that the research governance and standards for the review of clinical trials in Canada can follow one of two approaches. One approach is the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans published in 1998 as a joint policy initiative by the Medical Research Council of Canada (now Canadian Institutes of Health Research, CIHR), the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Natural Sciences and Engineering Research Council of Canada (NSERC). The other approach is to follow Canada's Clinical Trial Regulations and international guidelines, such as those produced by the International Conference on Harmonization.

European Union (EU)

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The harmonized tripartite guideline was finalized, having reached Step 4 in July 2000.

This addresses the choice of control groups in clinical trials needed for an approval of a dossier with respect to efficacy and safety. At present, there are major differences in practice and attitudes toward the need for placebo controlled trials (or other trials in which a difference between treatments is shown) and the acceptability of active control equivalence trials as evidence of efficacy and safety. This difference applies both to determinations of intrinsic efficacy and to the need for comparison with other drugs.

In summary, many patients in incontinence drug clearly know whether they are on an active or inactive drug and respond better when they know they are on an active compound. We fail to fool most of the patients most of the time. There are active comparators available in most cases of incontinence therapy (or OAB therapy). The mind-body relationship plays an enormous role in clinical response. There are clear situations in which the decision on placebo control is controversial and must be taken into consideration, e.g., "efficacy of the investigational drug is sufficient to make the possible risk acceptable; the

results of a short term treatment are less known than a long term one; documented evidence is limited without knowledge about long term effects; and active treatment is too expensive" [309]. It is not clear that a placebo controlled randomized clinical trial represents the entire population at risk, since there may be only a subset of patients willing to enter a clinical trial when an active comparator is available.