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Pharmacological Treatment of Urinary Incontinence

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CONTENTS

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A. INTRODUCTION

The function of the lower urinary tract (LUT) is to store and periodically release urine, and is dependent on the activity of smooth and striated muscles in the bladder, urethra, 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 [Andersson, 1993; de Groat and Yoshimura, 2001; Andersson and Wein, 2004]. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of voiding/emptying. Failure to store urine may lead to various forms of incontinence (mainly urgency and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence. A disturbed filling/storage function can, at least theoretically, be improved by agents decreasing detrusor activity, increasing bladder capacity, and/or increasing outlet resistance [Wein, 2007].

Many drugs have been tried, but the results are often disappointing, partly due to poor treatment efficacy and/or side effects. The development of pharmacologic treatment of the different forms of urinary incontinence has been slow, but several promising targets and drug principles have been identified [Andersson et al., 2002; 2005; Andersson, 2007; Colli et al., 2007].

In this report, we update the recommendations from the 2004 International Consensus meeting [Andersson et al., 2005]. 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. Our clinical drug recommendations are based on evaluations made using a modification of the Oxford system (**Table 1**). The terminology used is that recommended by the International Continence Society (ICS) [Abrams et al., 2002].

Table 1. ICI assessments 2008: Oxford guidelines (modified)

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

I. PUBLICATION SEARCHES

The review undertook a comprehensive search of all major literature databases and the abstract books from several major conferences: American Urological Association, ICS, European Association of Urology, International Urogynaecological Association, International Consultation of Incontinence and Societe Internationale d’Urologie. There were no restrictions on the inclusion of publications by language; publications in languages other than English were translated into English.

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 four to six years, voiding is initiated voluntarily by the cerebral cortex [de Groat et al., 1999]. Studies in humans and animals have identified areas in the brainstem and diencephalon that are specifically implicated in micturition control, including Barrington's nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum [Griffiths, 2004., Fowler et al., 2008]. 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 [Griffiths, 2004; Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Griffiths et al., 2007; Hruz et al., 2008; Mehnert et al., 2008; Tadic et al., 2008].

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 2-4**). These nerves are parts of reflex pathways, which either keep the bladder in a relaxed state, enabling urine storage at low intravesical pressure, or which initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Contraction of the detrusor smooth muscle and relaxation of the outflow region result from activation of *parasympathetic* neurones located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2-S4 [de Groat et al., 1993]. The postganglionic neurones in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine (ACh) acting on muscarinic receptors. However, an atropine-resistant component has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by release of nitric oxide [Andersson and Persson, 1993], although other transmitters might be involved [Bridgewater and Brading, 1993; Hashimoto et al., 1993; Werkström et al., 1995].

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 [Lincoln and Burnstock, 1993].

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

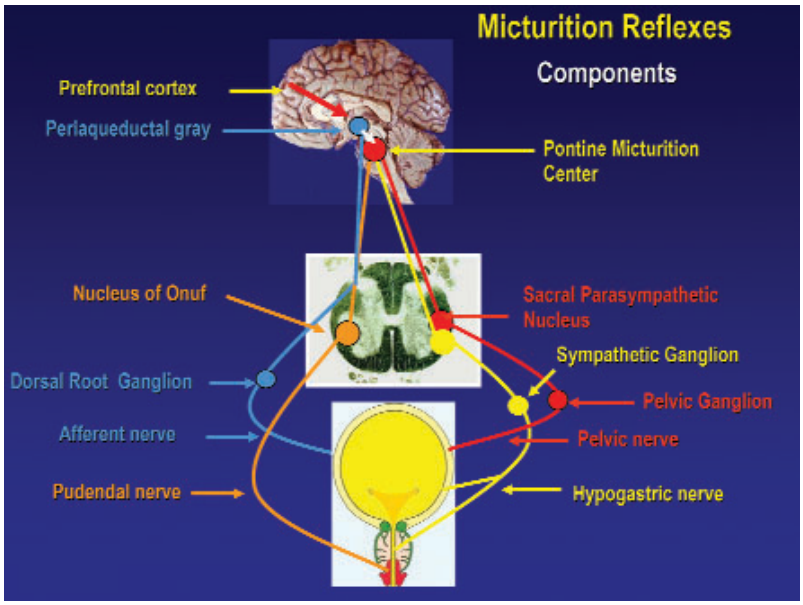

Figure 1 : Components of the micturition reflex.

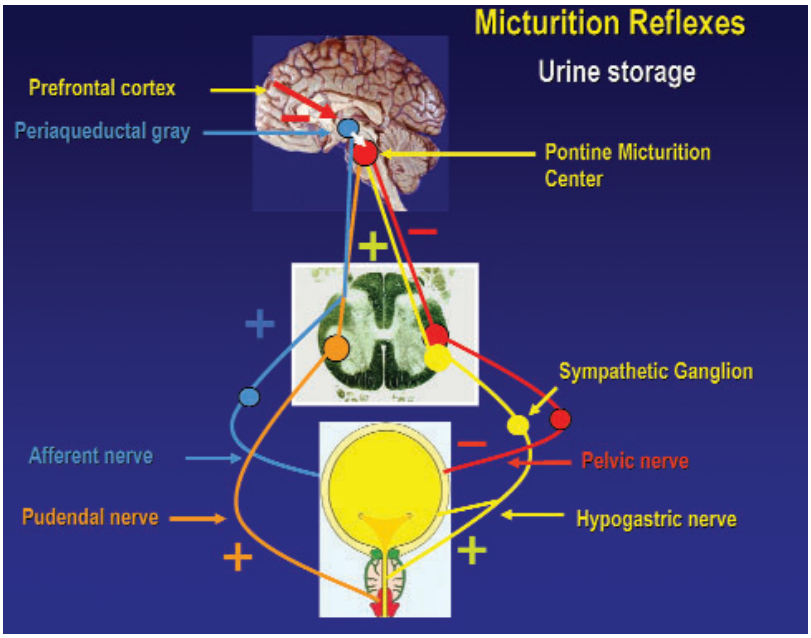

Figure 2 : Activity in the micturition reflex during storage. The pontine micturition center is inhibited by impulses from the prefrontal cortex, afferent impulses unable to initiate micturition. Activities in the hypogastric and pudendal nerves keep the bladder relaxed and the outflow region contracted.

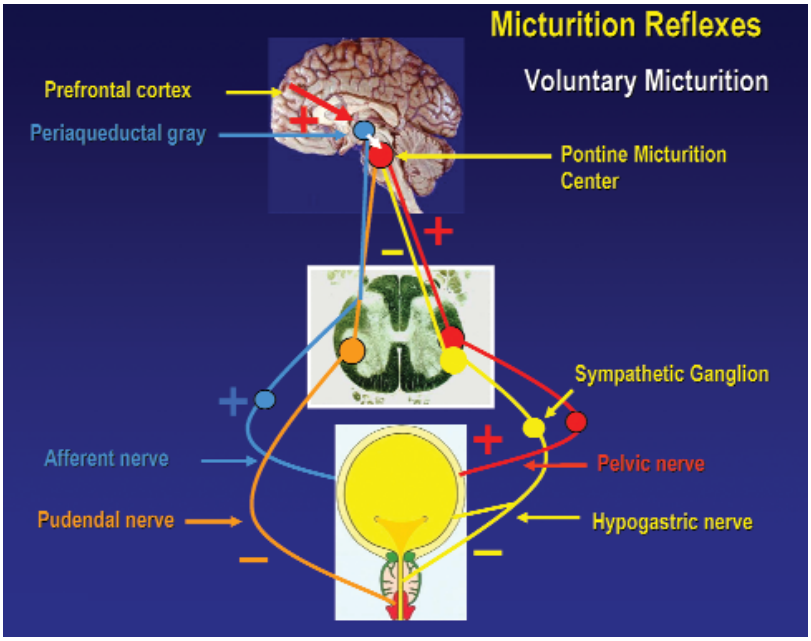

Figure 3 : Activity in the micturition reflex during voluntary voiding. The inhibitory impulses from the prefrontal cortex pontine micturition center are removed and afferent impulses are able to initiate micturition. Activities in the hypogastric and pudendal nerves are inhibited, the outflow region is relaxed, and the bladder is contracted by the activity in the pelvic nerve.

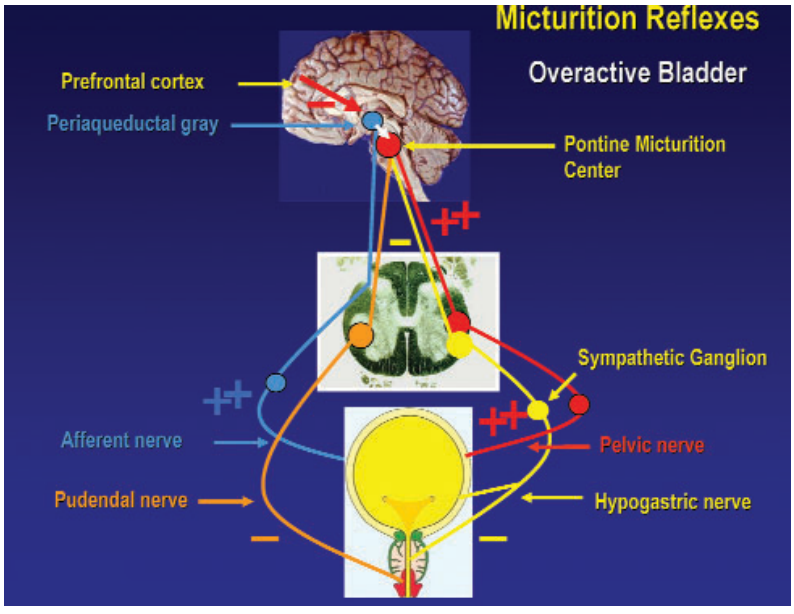

Figure 4 : Detrusor overactivity. Despite the inhibitory impulses from the prefrontal to the cortex pontine micturition center the enhanced (?) afferent impulses are able to initiate micturition.

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).

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

IV. PATHOGENESIS OF BLADDER CONTROL DISORDERS

As pointed out previously, bladder control disorders can be divided into two general categories: disorders of filling/storage and disorders of voiding [Wein, 2007].

Storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence. Failure to store also occurs if the bladder is overactive, as in the overactive bladder (OAB) syndrome. The prevalence varies with the criteria used for diagnosis, but according to Irwin et al. (2006), using the ICS definition of 2002 [Abrams et al., 2002], the overall prevalence of OAB, based on computer assisted telephone interviews (the EPIC study) was 11.8%; rates were similar in men and women and increased with age [Irwin et al., 2006]. A similar study based on a cross Canada telephone survey found the prevalence of OAB to be 13 % in men and 14.7% in women [Herschorn et al., 2008]. OAB (symptomatic diagnosis) is often assumed to be caused by detrusor overactivity (DO; urodynamic diagnosis), even if this does not always seem to be the case [Hyman et al., 2001; Digesu et al., 2003; Hashim and Abrams, 2004; Aschkenazi et al., 2007].

DO/OAB 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 consequent upon damage to the central nervous system (CNS) inhibitory pathways (**Figure 5**), as can be seen in various neurological disorders, such as multiple sclerosis, cerebrovascular disease, Parkinson's disease, brain tumors, and spinal cord injury [Ouslander, 2004]. Urinary retention and overflow incontinence can be observed in patients with urethral outlet obstruction (e.g. prostate enlargement), decreased detrusor contractility, or both), 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 or bladder smooth muscle directly [Wein, 2007].

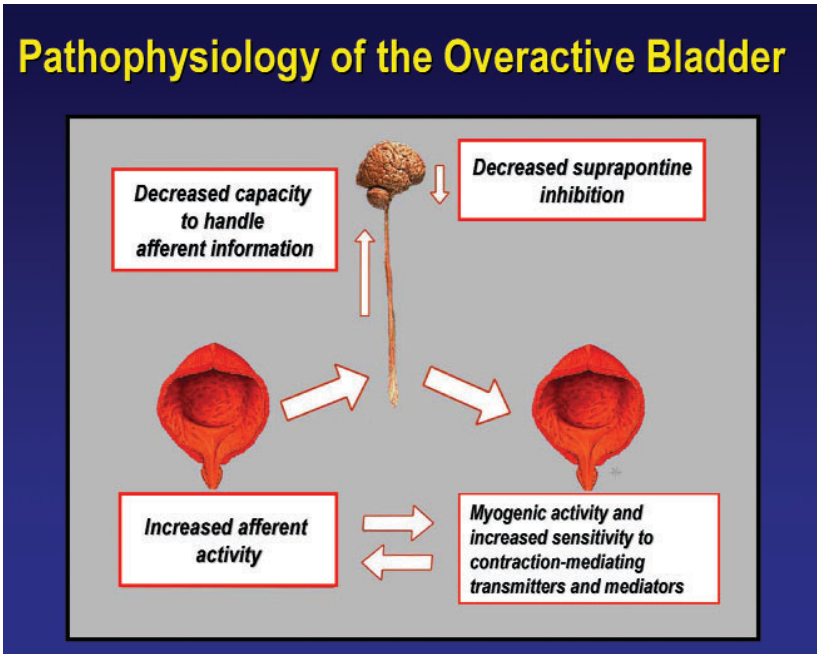

Figure 5 : The diverse pathophysiology of detrusor overactivity. a) increased afferent activity generated within the detrusor muscle and/or the urothelium may initiate the micturition reflex. b) the central nervous system may be unable to control afferent information from the bladder. c) activation of the pontine micturition center may occur more or less independent of afferent information.

V. BLADDER CONTRACTION

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle. Atropine resistance, i.e. contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species, but seems to be of little importance in normal human bladder muscle [Andersson, 1993; Bayliss et al., 1999]. However, atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions have been reported in normal human detrusor and may be caused mainly by adenosine triphosphate (ATP) [Andersson, 1993; Bayliss et al., 1999, Andersson and Wein, 2004; Kennedy et al., 2007]. ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G-protein-coupled receptor family (P2Y). Seven P2X subtypes and eight P2Y subtypes have been identified. In several species (rabbit, cat, rat, and human), various studies suggested that multiple purinergic excitatory receptors are present in the bladder [de Groat and Yoshimura, 2001]. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that $P2X_1$ receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder. Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells [de Groat and Yoshimura, 2001]. $P2X_3$ receptors, which have been identified in small-diameter afferent neurons in dorsal root ganglia, have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves. In $P2X_3$ knockout mice, afferent activity induced by bladder distension was significantly reduced [Cockayne et al., 2000; Ford et al., 2006; Ruggieri et al., 2006]. These data indicate that purinergic receptors are involved in mechanosensory signaling in the nonprimate mammalian 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 [Sjögren et al., 1982], interstitial cystitis [Palea et al., 1993], neurogenic bladders [Wammack et al., 1995], and in the aging bladder [Yoshida et al., 2001]. The importance of the NANC component to detrusor contraction in vivo, normally, and in different micturition disorders, remains to be established.

VI. MUSCARINIC RECEPTORS

The neurotransmitter ACh acts on two classes of receptors, the nicotinic and the muscarinic receptors. While the former play a role in the signal transduction between neurones or between neurones and skeletal muscle (e.g. in the distal urethra), the signal transduction between parasympathetic nerves and smooth muscle of the detrusor involves muscarinic receptors [Abrams and Andersson, 2007]. Importantly, the endogenous muscarinic receptor agonist ACh is not necessarily derived only from parasympathetic nerves in the urinary bladder, but can also be formed and released non-neuronally by the urothelium [Bschleiper et al., 2007; Mansfield et al., 2005; Zarghooni et al., 2007]. Five subtypes of muscarinic receptors have been cloned in humans and other mammalian species, which are designated $M_{1\text{-}5}$ [Caulfield and Birdsall 1998]. Based upon structural criteria and shared preferred signal transduction pathways, the subtypes can be grouped into M_1, M_3 and M_5 on the one hand and the subtypes M_2 and M_4 on the other. The former prototypically couple via pertussis toxin-insensitive G_q proteins to stimulation of a phospholipase C followed by elevation of intracellular calcium and activation of a protein kinase C, whereas the latter prototypically couple via pertussis toxin-sensitive G_i proteins to inhibition of adenylyl cyclase and modulation of several ion channels [Caulfield and Birdsall 1998]. While sensitive molecular techniques such as reverse transcriptase polymerase chain reaction can detect mRNA for all five subtypes in the mammalian bladder [Abrams et al., 2006: Hegde, 2006], studies at the protein level, e.g. based upon radioligand binding, have typically detected only M_2 and M_3 receptors, with the former dominating quantitatively [Abrams et al., 2006: Hegde, 2006]. Functional studies have implicated an involvement of M_1 and M_4 receptors (alongside with M_2 receptors) in the prejunctional regulation of neurotransmitter release in the mammalian bladder, with M_1 receptors enhancing and M_2 and M_4 receptors inhibiting ACh release [Braverman et al., 1998; D`Agostini et al., 1997]. However, most muscarinic receptors in the urinary bladder are located on smooth muscle and urothelial cells.

Apparently, most muscarinic receptors in the bladder are found on the smooth muscle cells of the detrusor. While the detrusor expresses far more M_2 than M_3 receptors, it appears that detrusor contraction under physiological conditions is largely if not exclusively mediated by the M_3 receptor [Hegde et al., 1997; Chess-Williams et al., 2001; Fetscher et al., 2002; Kories et al., 2003; Schneider et al., 2004a, b]. Studies in knock-out mice confirm this conclusion [Matsui et al., 200; 2002; Stengel et al., 2002; Ehlert et al., 2007]. Under physiological conditions M_2 receptor-selective stimulation causes little contraction [Schneider et al., 2005a], but rather appears to act mainly by inhibiting ß-adrenoceptor-mediated detrusor relaxation [Hegde et al., 1997; Ehlert et al., 2007; Matsui et al., 2003]. It has been proposed that M_2 receptors can also directly elicit bladder contraction under pathological conditions [Braverman et al., 1998; 2002; 2003; 2006; Pontari et al., 2003] , but such observations have not

been confirmed by other investigators using distinct methodological approaches [Schneider et al., 2005a; b].

Based upon the prototypical signalling pathway of M_3 receptors [Cauldfield and Birdsall, 1998] and the presence of phospholipase C stimulation by muscarinic agonists in the bladder [Kories et al., 2003; Schneider et al., 2005a] it had originally been believed that muscarinic receptor-mediated contraction is largely mediated by an activation of phospholipase C [Ouslander, 2004]. While some earlier data had supported this concept, it now appears clear that, at least in rat, mice and humans, muscarinic receptor-mediated bladder contraction occurs largely independent of phospholipase C [Schneider et al., 2004; Wegener et al., 2004; Frazier et al., 2007]. Rather, alternative signalling pathways such as opening of L-type calcium channels and activation of a rho-kinase (**Figure 6**) appear to contribute to muscarinic receptor-mediated bladder contraction in a major way [Frazier et al., 2008].

More recently, muscarinic receptors have also been identified in the urothelium [Chess-Williams, 2002; Kumar et al., 2005]. Similarly to the findings in bladder smooth muscle, the muscarinic receptors in the urothelium mainly belong to the M_2 and M_3 subtype, with the former dominating quantitatively [Mansfield et al., 2005; Bschleiper et al., 2007]. At present the functional role of muscarinic receptors in the urothelium has largely been studied indirectly, i.e. by investigating the effects of urothelium removal or of administration of pharmacological inhibitors. These data indicate that muscarinic stimulation of the urothelium causes release of an as yet unidentified factor which inhibits detrusor contraction [Hawthorn et al., 2000; Wuest et al., 2005; Sadananda et al., 2008]. Some data indicate that muscarinic receptors in the urothelium may partly act by releasing nitric oxide (NO) [Andersson et al., 2008a]. Thus, it appears that muscarinic receptors in the urothelium also contribute to the regulation of overall bladder function but their specific roles in health and disease have not been fully established [Andersson et al., 2008b].

Based upon the involvement of muscarinic receptors in physiological *voiding* contractions of the bladder, numerous studies have explored whether an overactivity of the muscarinic system may play a causative role in bladder dysfunction. This could involve, e.g., an enhanced expression of such receptors and/or an increased functional responsiveness. In vitro, an increased sensitivity to muscarinic receptor stimulation was found in both idiopathic and neurogenic overactive human detrusors (Stevens et al. 2006). However, according to Michel and Barendrecht [2008] the overall balance of available studies suggests that the muscarinic receptor system is not hyperactive under conditions of DO and, if anything, can be even hypoactive [Michel and Barendrecht, 2008]. This does not exclude a contribution to DO of ACh and muscarinic receptor stimulation during *bladder filling* (see below). It appears that the contribution of muscarinic mechanisms to the overall regulation of bladder contractility decreases in favour of non-cholinergic mechanisms under pathological conditions [Yoshida et al., 2001; 2008; Rapp et al 2005]. These observations may help to explain the moderate efficacy of muscarinic receptor antagonists relative to placebo in controlled clinical studies [Herbison et al., 2003; Chapple et al., 2005; 2008; Novara et al., 2008; Shamliyan et al., 2008].

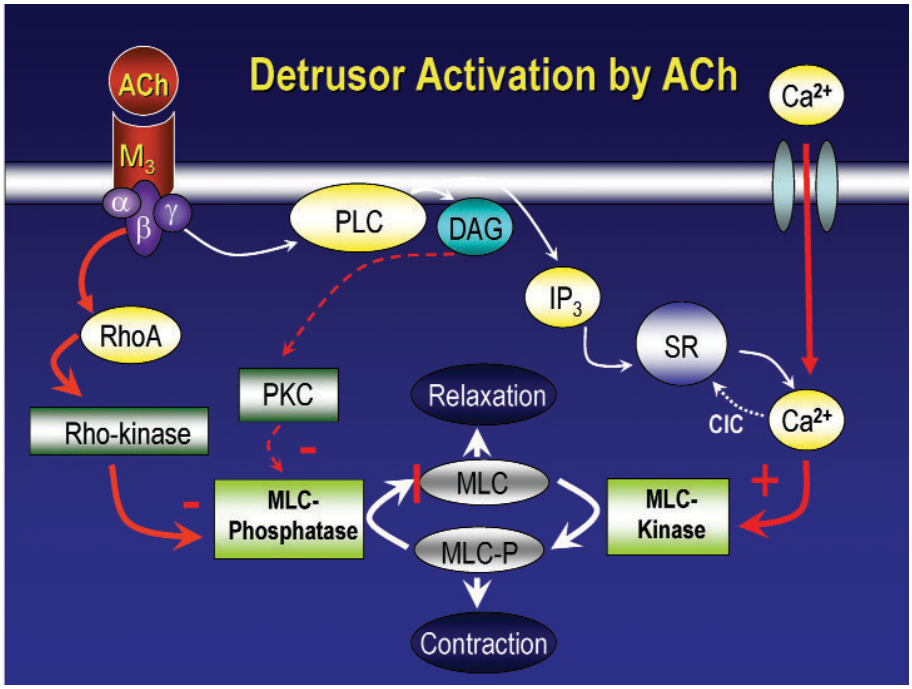

Figure 6 : Muscarinic M_3 receptor-mediated detrusor activation. Calcium influx and activation of the Rho-kinase system are the main pathways mediating activation of the contractile system.

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

It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence, and an abundance of drugs has been used for treatment (**Table 2**). 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.

I. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS

Mechanism of action. Antimuscarinics block, more or less selectively, muscarinic receptors [Abrams and Andersson, 2007]. The common view is that in OAB/DO, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by ACh, released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity, and during this phase, there is normally no parasympathetic input to the lower urinary tract [Andersson, 2004]. Furthermore, antimuscarinics are usually competitive antagonists. This implies that when there is a massive release of ACh, as during micturition, the effects of the drugs should be decreased, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinics can produce urinary retention in humans, but in the dose range used for beneficial effects in OAB/DO, there is little evidence for a significant reduction of the voiding contraction [Finney et al., 2006; **Figure 7**]. However, there is good experimental evidence that the drugs act during the storage phase by decreasing the activity in afferent nerves (both C- and Aδ -fibres) from the bladder [De Laet et al., 2006; Ijima et al., 2007].

As mentioned previously, 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 [Andersson, 2002; Birder and de Groat, 2007], but whether the muscarinic receptors on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues [2004; 2006; 2008] found that there is basal ACh release in human bladder. This release was resistant to tetrodotoxin and much diminished when the urothelium was removed; thus, the released ACh was probably of non-neuronal origin and, at least partly, generated by the urothelium. There is also indirect clinical evidence for release of ACh during bladder filling. Smith and co-workers [1974] found that in patients with recent spinal-cord injury, inhibition of ACh breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch and colleagues [2001] inhibited ACh breakdown with edrophonium in a series of patients with disturbed voiding or urinary incontinence. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly decreased detrusor compliance in 78% of the patients with the symptom pattern of overactive bladder, but in no patients without specific complaints suggesting DO. Thus, during the storage phase, ACh and ATP may be released from both neuronal and non-neuronal sources (eg, the urothelium) and directly or indirectly

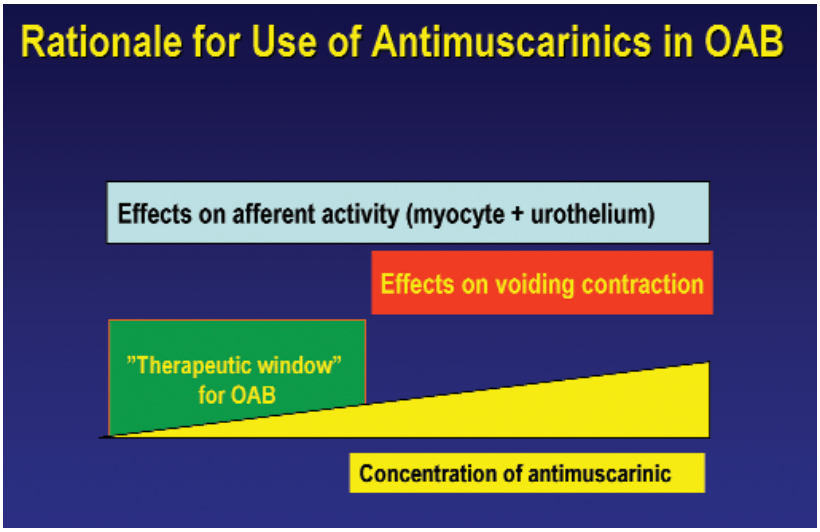

Figure 7 : Rationale for use of antimuscarinics for treatment of OAB/DO. Blockade of muscarinic receptors at both detrusor and non-detrusor sites may prevent OAB symptoms and DO without depressing the contraction during voiding

Table 2. Drugs used in the treatment of OAB/ DO. Assessments according to the Oxford system (modified)

	Level of evidence	Grade of recommendation
Antimuscarinic drugs		
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Fesoterodine	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs acting on membrane channels		
Calcium antagonists	2	D
K-Channel openers	2	D
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
Alpha-AR antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Beta-AR antagonists		
Terbutaline (beta 2)	3	C
Salbutamol (beta 2)	3	C
YM-178 (beta 3)	2	B
PDE-5 Inhibitors+		
(Sildenafil, Taladafil, Vardenafil)	2	B
COX-inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)***	2	A
Botulinum toxin (idiopathic)***	3	B
Capsaicin (neurogenic)**	2	C
Resiniferatoxin (neurogenic)**	2	C
Other drugs		
Baclofen*	3	C
Hormones		
Estrogen	2	C
Desmopressin#	1	A

+(male LUTS/OAB); * intrathecal; ** intravesical; *** bladder wall; #nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!

(by increasing detrusor smooth muscle tone, **Figures 8, 9 and 10**) excite afferent nerves in the suburothelium and within the detrusor. These mechanisms may be important in the pathophysiology of OAB/DO and represent possible targets for antimuscarinic drugs.

Pharmacologic properties. Generally, antimuscarinics can be divided into tertiary and quaternary amines [Guay, 2003, Abrams and Andersson, 2007]. 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, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl-tolterodine), oxybutynin, propiverine, solifenacin, and tolterodine, are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the CNS, dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood brain barrier, but in some cases, such as trospium, darifenacin, and fesoterodine, that is compensated by active transport out of the CNS by the product of the MDR1 gene (P-glykoprotein, see **Table 3**). Quaternary ammonium compounds, like propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects [Guay 2003]. They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, tachycardia, and dryness of mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites [Guay 2003]. 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 urgency and urgency incontinence [Andersson, 2004]. However, currently used drugs lack selectivity for the bladder, and effects on other organ systems (**Figure 11**) may result in side effects, which limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow angle glaucoma.

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

Several antimuscarinic drugs are and have been used for treatment of OAB/DO. For some of them, documentation of effects is not based on randomized controlled trials (RCTs) satisfying currently required criteria, and some drugs can be considered as obsolete (e.g., emepronium). Information on these drugs has not been included, but can be found elsewhere [Andersson, 1988; Andersson et al., 1999].

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned. Herbison et al. [2003] stated in a widely discussed article: “Anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo.

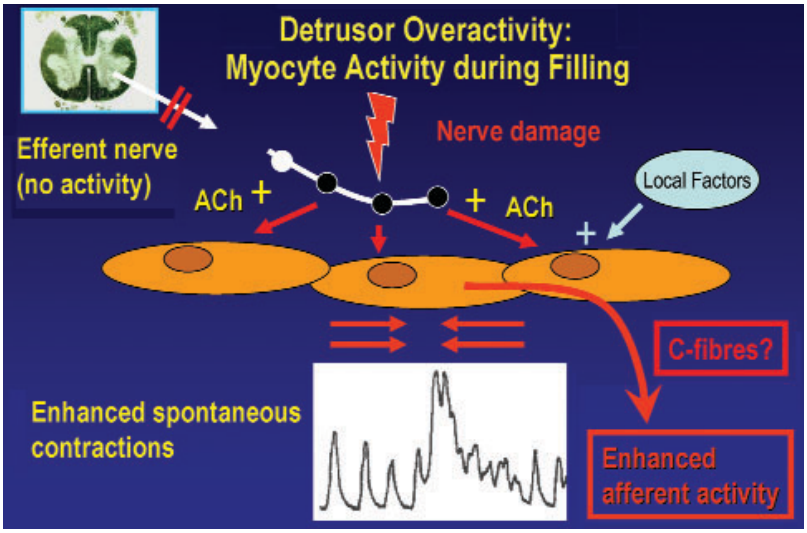

Figure 8 : The hypothetical role of acetylcholine (ACh) in the generation of DO) and OAB. During bladder filling, there is no activity in the parasympathetic outflow from the bladder. However, the myocytes have a spontaneous (myogenic) contractile activity that generates afferent nerve activity (C-fibres and Ad-fibres). In DO bladders, there are areas of “patchy denervation” and ACh in low concentrations is “leaking” from the nerves. This enhances the sponta-neous activity and the basal afferent nerve activity (“afferent noise”). This means that the Ad-fibre activity, generated by bladder distension, can initiate the micturition reflex at low degrees of bladder filling. Antimuscarinics in therapeutically recommended doses can inhibit the effects of these low concentrations of acetylcholine, but not of the high concentrations necessary for the generating the voiding contraction (requiring efferent nerve activity). Structural changes in the bladder (e.g., secondary to outflow obstruction) can generate local factors, such as prostaglandins and endothelins, which also can contribute to enhancement of the spontaneous activity.

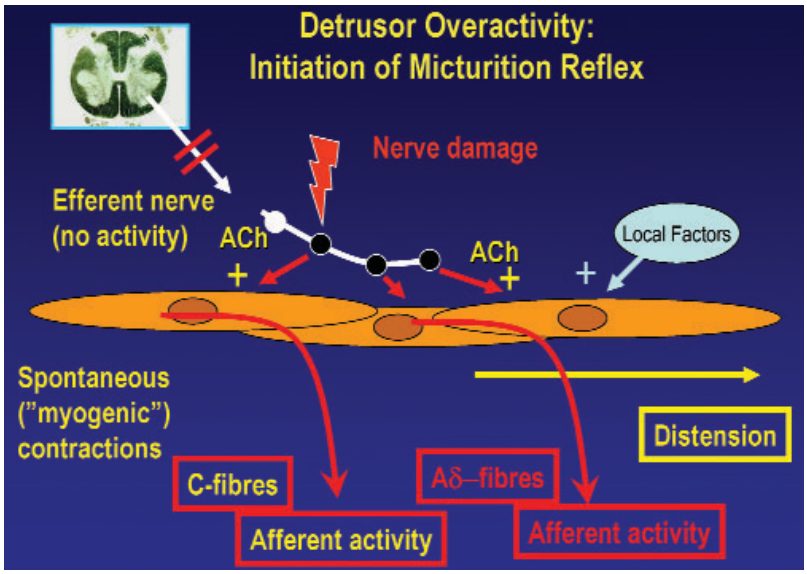

Figure 9 : The hypothetical role of acetylcholine (ACh) in the generation of DO) and OAB. During bladder filling, there is no activity in the parasympathetic outflow from the bladder. However, the myocytes have a spontaneous (myogenic) contractile activity that generates afferent nerve activity (C-fibres and Ad-fibres). In DO bladders, there are areas of "patchy denervation" and ACh in low concentrations is "leaking" from the nerves. This enhances the spontaneous activity and the basal afferent nerve activity ("afferent noise"). This means that the Ad-fibre activity, generated by bladder distension, can initiate the micturition reflex at low degrees of bladder filling. Antimuscarinics in therapeutically recommended doses can inhibit the effects of these low concentrations of acetylcholine, but not of the high concentrations necessary for the generating the voiding contraction (requiring efferent nerve activity). Structural changes in the bladder (e.g., secondary to outflow obstruction) can generate local factors, such as prostaglandins and endothelins, which also can contribute to enhancement of the spontaneous activity.

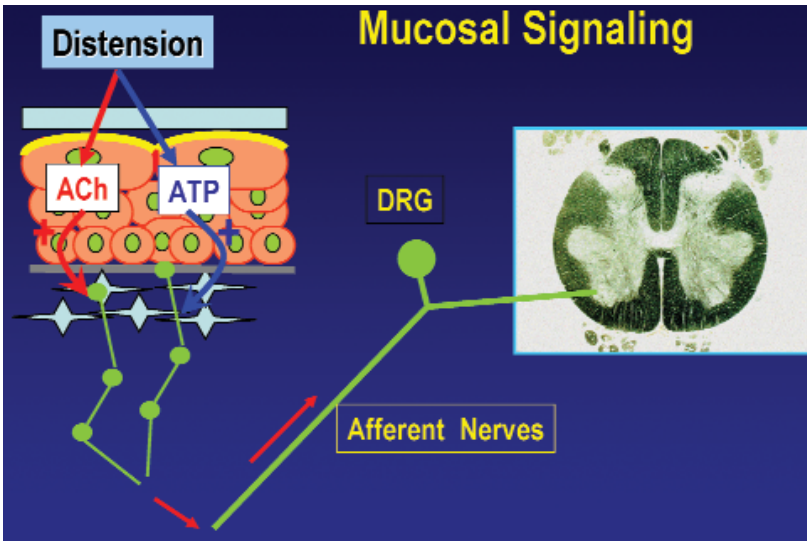

Figure 10 : Distension of the bladder and shape-change of the urothelium (U) will generate and release different signaling molecules, including ATP and acetylcholine (ACh), which either directly or by action via the interstitial cells (IC) will initiate activity in the suburothelial afferent nerves. Antimuscarinics may inhibit this ACh-induced activation. GC = glycocalix layer; DRG = dorsal root ganglion.

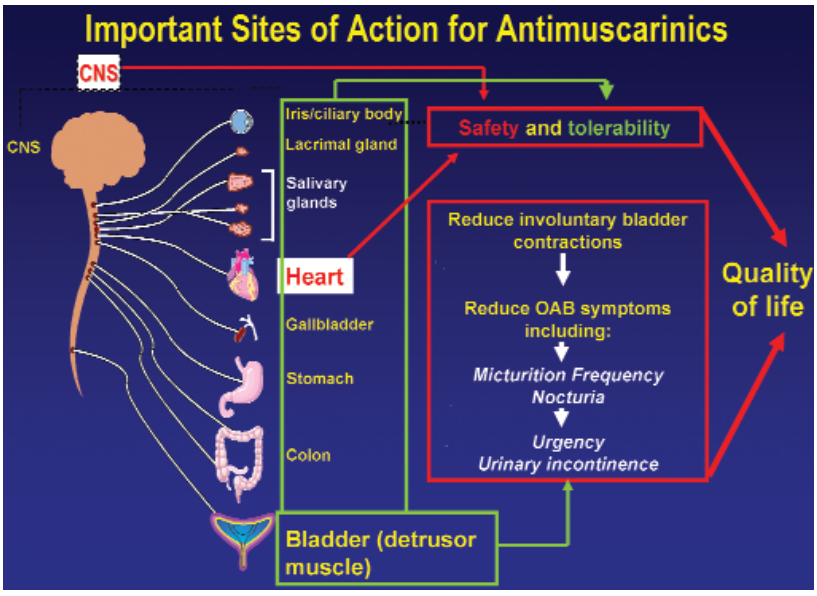

Figure 11 : Important sites of action of antimuscarinics.

The benefits are, however, of limited clinical significance" Large meta-analyses of studies performed with the currently most widely used drugs [Chapple et al., 2005; 2008; Novara et al., 2008], clearly show that antimuscarinics are of significant clinical benefit. Novara et al. [2008] reviewed 50 RCTs and 3 pooled analyses, which they considered of good methodological quality. They concluded that still more clinical studies are needed to decide which of the drugs should be used as first-, second-, or third-line treatment. Reviewing information from more than 12,000 references (**Figure 12**), Chapple et al. [2008], based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that since the profiles of each drug (see below) and dosage differ, these factors should be considered in making treatment choices.

The consequence of this is that none of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine or trospium) is ideal as a first-line treatment for ***all*** OAB/DO patients. Optimal treatment should be individualized, implying that the patient´s co-morbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration [Chapple et al., 2008].

Below data on the different antimuscarinics are presented. The amount of information for the individual drugs varies, and so does the degree of details from the different studies presented. However, the information has been chosen to give a reasonable efficacy and adverse effect profile of each individual drug.

1. ATROPINE SULFATE

Atropine (dl-hyoscyamine) is rarely used for treatment of OAB/DO because of its systemic side effects, which preclude its use as an oral tratment. 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 [Ekström et al., 1992; Glickman et al., 1995; Deaney et al., 1998; Enskat et al., 2001; Fader et al 2007]. It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with neurogenic DO [Fader et al., 2007].

The pharmacologically active antimuscarinic component of atropine is l-hyoscyamine. Although still used, few clinical studies are available to evaluate the antimuscarinic activity of l-hyoscyamine sulfate [Muskat et al., 1996]. For assessment, see Table 2.

2. PROPANTHELINE BROMIDE

Propantheline 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 halflife (less than 2 h) [Beermann et al., 1972]. 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 detrusor overactivity contractions [Blaivas et al., 1980] in an open study obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline 15 mg four times daily. The range of dosages varied from 7.5 to 60 mg four times daily. In contrast, Thüroff et al. [1991] comparing the effects of oxybutynin 5 mg three times daily, propantheline 15 mg three times daily, and placebo, in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency and incontinence related to DO (154 patients), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic DO), and with dose titration, Holmes et al. [1991] found no differences in efficacy between oxybutynin and propantheline. Controlled randomized trials (n=6) reviewed by Thüroff et al [1998], 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 (Table 2). No new studies on the use of this drug for treatment of OAB/DO seem to have been performed during the last decade.

3. TROSPIUM CHLORIDE

Trospium is a quaternary ammonium compound with a biological availability less than 10% [Fusgen and Hauri, 2000; Doroshyenko et al., 2005]. The drug has a plasma half-life of approximately 20 h, and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model [Kim et al., 2006]. Whether or not it contributes to the clinical efficacy of the drug remains to be established.

Trospium is not metabolized by the cytochrome P450 enzyme system [Beckmann-Knopp et al., 1999; Doroshyenko et al., 2005]. It is expected to cross the blood-brain to a limited extent and seems to have no negative cognitive effects [Fusgen and Hauri, 2000; Todorova et al., 2001; Widemann et al., 2002].

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 [Uckert et al., 2000].

Several RCTs have documented positive effects of trospium both in neurogenic [Stöhrer, et al., 1991;

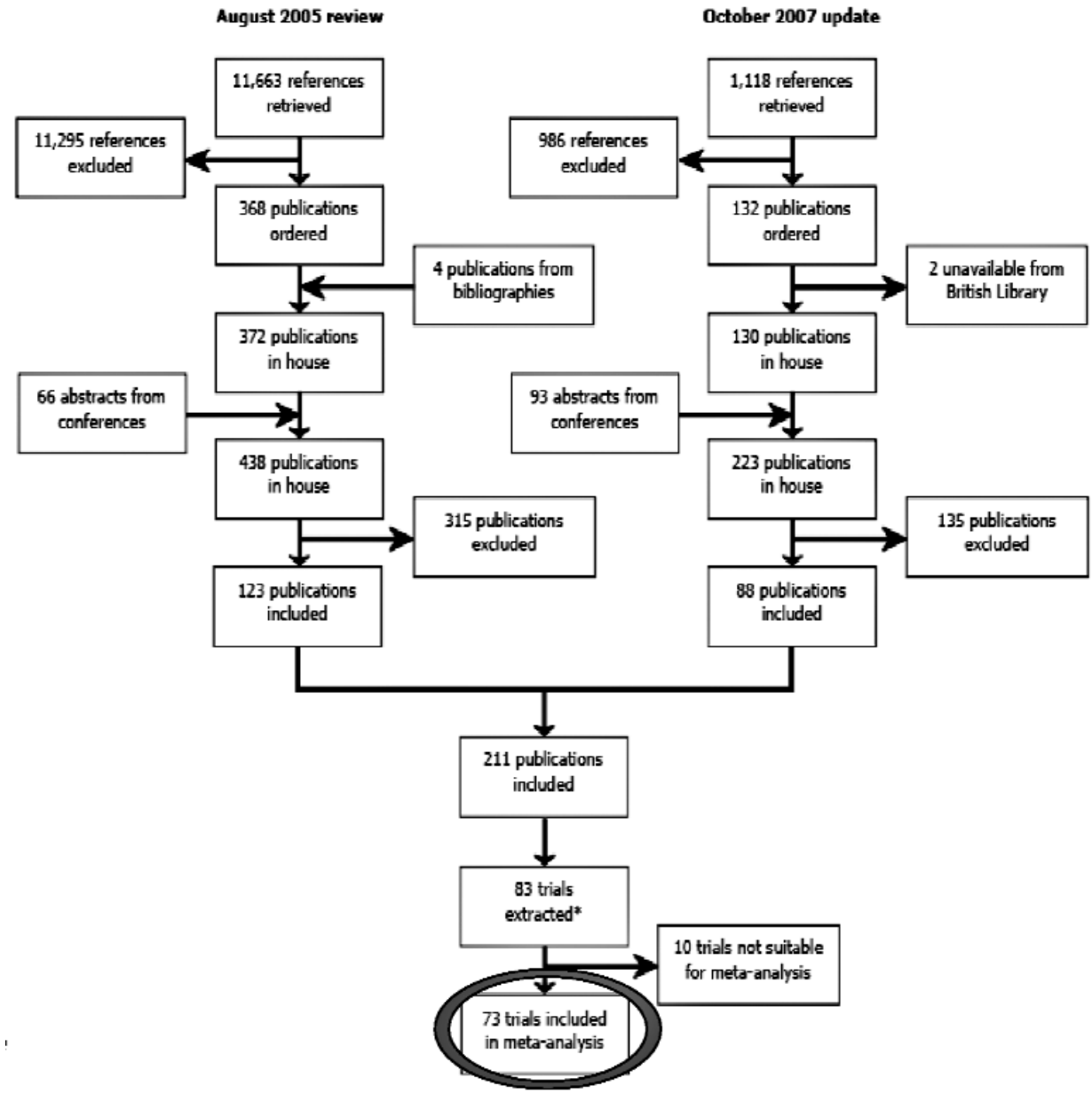

Figure 12 : Trials included in metanalysis. From Chapple et al. , Eur Urol 2005; 48: 5-26 and Chapple et al., Eur Urol. 2008 Sep;54(3):543-62.

Table 3. Some physico-chemical properties of antimuscarinics (Kay et al., AUA presentation, 2009)

	5-HMT	Fesoterodine[1]	Tolterodine	Trospium[2]	Solifenacin[2]	Darifenacin[2]	Oxybutynin[2]
logD, Octanol-Water Ratio	0.74	1.42	1.83	-1.22	1.69	2.7	> 3.3
Permeability x10^6 (cm/s)	6.49	35.5	23.4	0.57	31.5	28.5	30.3
Brain-Blood Ratio[3]	0.04-0.07		0.1-0.3[2]	NA	NA	NA	NA
PgP Substrate	Yes	Yes	NA	Yes	No	Yes	NA

[1] Fesoterodine is not detectable in blood after oral administration in humans due to rapid and extensive hydrolysis to 5-HMT by non-specific esterases.
[2] Literature data, except PBEC permeability
[3] Drug-related radioactivity
NA : Not Available

Madersbacher et al., 1995; Menarini et al., 2006] and non-neurogenic DO [Allousi et al., 1998; Cardozo et al., 2000; Junemann et al., 2000; Halaska et al., 2003; Zinner et al., 2004a; Rudy et al., 2006; Staskin et al., 2007; Dmochowski et al., 2008]. In a placebo-controlled, double blind study on patients with neurogenic DO [Stöhrer et al, 1991], the drug was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equieffective; however, trospium seemed to have fewer side effects [Madersbacher et al., 1995].

The effect of trospium in urgency incontinence has been documented in several RCTs. Allousi et al. [1998] compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3 weeks duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum bladder capacity. Cardozo et al. [2000] investigated 208 patients with DO, who were treated with trospium 20 mg twice daily for two weeks. Also in this study, significant increases were found in mean volume at first unstable contraction (from 233 to 299 ml; placebo 254 to 255 ml) and in maximum bladder capacity (from 329 to 356 ml; placebo 345 to 335 ml) in the trospium treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Jünemann et al. [2000] compared trospium 20 mg twice daily with tolterodine 2 mg twice daily in a placebo-controlled double-blind study on 232 patients with urodynamically proven DO, urgency incontinence without demonstrable DO, or mixed incontinence. Trospium reduced the frequency of micturition, which was the primary endpoint, more than tolterodine and placebo, and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7 and 9%, respectively).

Halaska et al. [2003] studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urgency syndrome. The trial comprised a total of 358 patients with urgency syndrome or urgency incontinence. After 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. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgency episodes in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 ml after 26 weeks and 115 ml after 52 weeks (P=0.001). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 65% of the patients treated with trospium and 77% of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the mouth. An overall assessment for each of the drugs revealed a comparable efficacy level and a better benefit-risk ratio for trospium than for oxybutynin due to better tolerability.

Zinner et al. [2004] treated 523 patients with symptoms associated with OAB and urgency 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 urgency incontinent episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urgency severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire. By week 12, trospium significantly decreased average frequency of toilet voids per 24 hours (-2.37;placebo -1,29) and urgency incontinent episodes (-59%;placebo -44%). It significantly increased average volume per void (32 ml; placebo: 7.7) ml, and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (-0.43; placebo: 0.17) - and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%) and headache (6.5%; placebo 4.6%).

In a large US multicenter trial with the same design, and including 658 patients with OAB, Rudy et al. [2006] confirmed the data by Zinner et al [2004], both with respect to efficacy and adverse effects.

An extended release formulation of trospium allowing once daily dosing, has been introduced and and its effects tested in controlled trials [Staskin et al., 2008; Dmochowski et al., 2008]. These RCTs demonstrated similar efficacy as found with previous formulations. The most frequent side effects were dry mouth (12.9%; placebo 4.6) and constipation (7.5%; placebo 1.8) [Dmochowski et al., 2008].

Intravesical application of trospium may be an interesting alternative. Frölich et al. [1998] performed a randomised, single-blind, placebo-controlled, mono-centre clinical trial in 84 patients with urgency or urgency incontinence. Compared to placebo, intra-

vesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium does not seem to be absorbed [Walter et al., 1999], thus offering an opportunity for treatment with minimal systemic antimuscuscarinic effects.

Trospium has a well-documented effect in OAB/DO, and tolerability and safety seems acceptable (Table 2).

4. TOLTERODINE TARTRATE

Tolterodine is a tertiary amine, rapidly absorbed and extensive metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacological profile as the mother compound [Nilvebrant et al., 1997], and significantly contributes to the therapeutic effect of tolterodine [Brynne et al., 1997; Brynne et al., 1998]. Both tolterodine and 5-HMT have plasma half-lifes of 2-3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for <1-2.4 % of the dose; 5 – 14% of 5-HMT is eliminated in the urine [Brynne et al., 1997]. Whether or not the total antimuscarinic activity of unchanged tolterodine and 5-HMT excreted in urine is sufficient to exert any effect on the mucosal signaling mechanisms has not been established. However, the preliminary studies by Kim et al. [2005] and Chuang et al., [2008], do not support such an effect.

The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT, implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [Hills et al., 1998, Clemett et al., 2001; Salvatore et al., 2008]. However, tolterodine may disturb sleep in subjects unable to form the even less lipophilic 5-HMT due to a low activity of CYP 2D6 [Diefenbach et al., 2008].

Tolterodine has no selectivity for muscarinic receptor subtypes, but is claimed to have functional selectivity for the bladder over the salivary glands [Stahl et al., 1995; Nilvebrant et al. 1997b]. 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 hour after administration of the drug [Stahl et al., 1995]. However, 5 hours 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 (TOLT-IR; 1 or 2 mg; twice daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability [Van Kerrebroeck et al. 2001].

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 [Hills et al., 1998; Clemett et al., 2001; Salvatore et al., 2008]. Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment), and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness.

The OBJECT trial compared oxybutynin ER (OXY-ER) 10 mg once daily with TOLT-IR 2 mg twice daily [Appell et al., 2001] in a 12-week randomized, double blind, parallel-group study including 378 patients with OAB. Participants had between 7 and 50 episodes of urgency incontinence per week and 10 or more voids in 24 hours. The outcome measures were the number of episodes of urgency incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, OXY-ER was found to be significantly more effective than TOLT-IR in each of the main outcome measures adjusted for baseline (see also below: oxybutynin chloride). Dry mouth, the most common adverse event, was reported by 28% and 33% of participants taking OXY-ER and TOLT-IR, respectively. Rates of central nervous system and other adverse events were low and similar in both groups. The authors concluded that OXY-ER was more effective than TOLT-IR and that the rates of dry mouth and other adverse events were similar in both treatment groups.

In the OPERA study [Diokno et al., 2003], OXY-ER at 10 mg/d or TOLT-ER at 4 mg/d were given for 12 weeks to women with 21 to 60 urgency incontinence episodes per week and an average of 10 or more voids per 24 hours. Episodes of incontinence episodes (primary end point), total (urgency and non urgency) incontinence, and micturition were recorded in seven 24-hour urinary diaries at baseline and at weeks 2, 4, 8 and 12 and compared. Adverse events were also evaluated. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER (n=391) or TOLT-ER (n=399). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0% of women taking OXY-ER reported no episodes of urinary incontinence compared with 16.8% of women taking TOLT-ER. Dry mouth, usually mild, was more common with OXY-ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable; including adverse events involving the central nervous system.

In the ACET (Antimuscarinic Clinical Effectiveness Trial) [Sussman and Garely, 2002] study, which consisted of two trials, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOLT-ER (study one) and to 5 mg or 10 mg of OXY-ER (study two). A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial in the TOLT-ER 4 mg group (12%) than either the OXY-ER 5 mg (19%) or OXY-ER 10 mg groups (21%). More patients in the OXY-ER 10 mg group than the TOLT-ER 4 mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOLT-ER 4 mg group perceived an improved bladder condition, compared with 60% in the TOLT-ER 2 mg group, 59% in the OXY-ER 5 mg group and 60% in the OXY-ER 10 mg group. Dry mouth was dose-dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; p=0.05). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) than of OXY-ER (10 mg) is weakened by the the open label design of the study.

Zinner et al. [2002] evaluated the efficacy, safety, and tolerability of TOLT-ER in older (> or =65) and younger (<65) OAB patients, in a 12-week RCT including 1015 patients with urgency incontinence and urinary frequency. Patients were randomized to treatment with TOLT-ER 4 mg once daily (n = 507) or placebo (n = 508) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments, safety, and tolerability endpoints were evaluated, relative to placebo. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment arms, irrespective of age (<65: ER 22.7%, placebo 8.1%; > or =65: ER 24.3%, placebo 7.2%). A few patients (< 2%) experienced severe dry mouth. No central nervous system (cognitive functions were not specifically studied), visual, cardiac (per electrocardiogram), or laboratory safety concerns were noted in this study. Withdrawal rates due to adverse events on TOLT-ER 4 mg once daily were comparable in the two age cohorts (<65: 5.5%; > or =65: 5.1%).

The central symptom in the OAB syndrome is urgency. Freeman et al. [2003] presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OAB. Patients with urinary frequency (eight or more micturitions per 24 hours) and urgency incontinence (five or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily (n=398) or placebo (n=374) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44% reported improved urgency symptoms (compared with 32% for placebo), and 62% reported improved bladder symptoms (placebo, 48%). The proportion of patients unable to hold urine upon experiencing urgency was decreased by 58% with TOLT-ER, compared with 32% with placebo (P<.001).

In the IMprovement in Patients: Assessing symptomatic Control with Tolterodine ER (IMPACT) study [Elinoff et al., 2005], the efficacy of TOLT-ER for patients' most bothersome OAB symptom was investigated in an open label, primary care setting. Patients with OAB symptoms for ≥3 months received TOLT-ER (4 mg once daily) for 12 weeks. By week 12, there were significant reductions in patients' most bothersome symptom: incontinence, urgency episodes, nocturnal and daytime frequency. The most common adverse events were dry mouth (10%) and constipation (4%), and it was concluded that in primary care practice, bothersome OAB symptoms can be effectively and safely treated with TOLT-ER, even in patients with comorbid conditions.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs [Dmochowski et al., 2007a; 2007; Barucha et al., 2008; Choo et al., 2008; Coyne et al., 2008; Rogers et al., 2008; Rovner et al., 2008a; see further: Novara et al, 2008, Chapple et al., 2008]. Importantly, the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo was performed. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500 ms absolute QTc or 60ms change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval [Malhotra et al., 2007].

Olshansky et al. [2008] compared in a randomized, placebo-controled, double blind, crossover study, the effects on heart rate of TOLT-ER 4mg/day with those of darifenacin 15 mg/day and placebo in 162 healthy volunteers. They found that tolterodine, but not darifenacin and placebo, significantly increased mean heart rate per 24 hours. The proportion of subjects with an increase > 5 beats/min was significantly greater in those receiving TOLT-ER (1 out of 4) than with darifenacin (1 out of 10).

In a prospective, open study, Song et al. [2006] compared the effects of bladder training and/or tolterodine as first line treatment in female patients with OAB. One hundred and thirty-nine female patients with OAB were randomized to treatment with bladder training (BT), tolterodine (2 mg twice daily) or both for 12 weeks. All treatments were efficacious, however,

combination therapy was the most effective. Mattiasson et al. [2003] 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%; $p<0.001$), while the median percentage increase in volume voided per void was 31% with tolterodine + BT and 20% with tolterodine alone ($p<0.001$). There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine + BT (-87%). It was concluded that the effectiveness of tolterodine 2mg twice daily can be augmented by a simplified BT regimen. However, Millard et al. [2004] 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.

The beneficial effect of TOLT-ER in men with benign prostatic enlargement (BPE) and LUTS, including OAB, has been well documented. Both as monotherapy, but in particularly in combination with α-adenoceptor (AR) antagonist, TOLT-ER was found effective [Kaplan et al., 2006; Höfner et al., 2007; Kaplan et al., 2008a; 2008b; Rovner et al., 2008; Roehrborn et al., 2008]. This effect was obtained irrespective of prostate size, and was not associated with increased incidence of acute urinary retention (AUR) [Roehrborn et al., 2008].

Thus both the IR and ER forms of tolterodine have a well-documented effect in OAB/DO (Table 2), and are well tolerated.

5. DARIFENACIN HYDROBROMIDE

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 latter saturating within the therapeutic range [Skerjanec 2006]. UK-148,993, UK-73,689, and UK-88862 are the three main circulating darifenacin metabolites of which only UK-148,993 is said to have significant anti-muscarinic activity. However, available information suggests that various metabolites of darifenacin contribute little to its clinical effects [Michel and Hegde, 2006]. 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 [Kerbusch et al., 2003].

Darifenacin is a relatively selective muscarinic M_3 receptor antagonist. In vitro, it is selective for human cloned muscarinic M3 receptors relative to M1, M_2, M_4 or M_5 receptors. Theoretically, drugs with selectivity for the M_3 receptor can be expected to have clinical efficacy in OAB/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes [Andersson, 2002]. However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg per day. The clinical effectiveness of the drug has been documented in several RCTs [Haab et al., 2004; Cardozo and Dixon 2005; Steers et al., 2005; Chapple et al., 2005; Foote et al., 2005; Hill et al., 2006; Haab et al., 2006; Zinner et al., 2006, Chapple et al., 2007; Abrams et al., 2008, Chancellor et al., 2008; Dwyer et al., 2008; for reviews, see Guay, 2005; Zinner, 2007; Novara et al., 2008; Chapple et al., 2008]. Haab et al. [2004] reported a multicentre, double-blind, placebo-controlled, parallel-group study which enrolled 561 patients (19–88 years; 85% female) with OAB symptoms for more than 6 months, and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were 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 (median) improvements in micturition frequency (7.5 mg: -1.6; 15 mg: -1.7; placebo -0.8, frequency of urgency per day (-2.0; -2.0; -0.9), and number of incontinence episodes leading to a change in clothing or pads (-4.0; -4.7; -2.0). There was no significant reduction in nocturnal awakenings due to 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).

In a dose titration study on 395 OAB patients, darifenacin, allowing individualized dosing (7.5 or 15 mg), was found to be effective and well-tolerated [Steers et al., 2005]. A 2-year open label extension study of these investigations [i.e., Haab et al., 2004; Steers et al., 2005], confirmed a favorable efficacy, tolerability and safety profile [Haab et al., 2006].

A review of the pooled darifenacin data from the three phase III, multicentre, double blind clinical trials in patients with OAB was reported by Chapple et al. [2005] After a 4-week washout/run-in period, 1,059 adults (85% female) with symptoms of OAB (urgency incontinence, urgency and frequency) for at least six months were randomized to once-daily oral treatment with darifenacin: 7.5 mg (n = 337) or 15 mg (n = 334) or matching placebo (n = 388) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, –8.8 [–68.4%; placebo -54%, P<004]; 15 mg, –10.6 [–76.8%; placebo 58%, p<0.001]. Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg 0.6% of patients; darifenacin 15 mg 2.1%; placebo 0.3%). The incidence of CNS and cardiovascular adverse events were comparable to placebo. The results were confirmed in other RCTs, including also a pooled analysis of three phase III studies in older patients (≥65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability and safety profile [Foote et al., 2005, Zinner et al., 2005; Hill et al. 2006].

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 [Cardozo and Dixon, 2005]. 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 urgency-void cycles were recorded. Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant ($p<0.004$) increase in mean warning time with a median increase of 4.3 minutes compared with placebo (darifenacin group from 4.4 to 1.8 minutes; placebo from 7.0 to -1.0 minutes). Overall, 47% of darifenacin-treated subjects compared with 20% receiving placebo achieved a ≥30% increase in mean warning time. There were methodological problems associated with this study; it utilized a dose of 30 mg (higher than the dose recommended for clinical use), the treatment period was short, it was conducted in a clinical-centred environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. In another warning time study [Zinner et al., 2006] on 445 OAB patients, darifenacin treatment (15 mg) resulted in numerical increases in warning time, however, these were not significant compared to placebo.

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements on health related quality of life (HRQoL) in patients with OAB [Abrams et al., 2008], and such improvements were sustained as shown in a two-year extension study [Dwyer et al., 2008]. It was shown that neither the positive effects on micturition variables, nor on HRQoL produced by darifenacin (7.5 and 15 mg) were further enhanced by a behavioural modification programme including timed voiding, dietary modifications and Kegel exercises [Chancellor et al., 2008].

Several studies have been devoted to study possible effect on cognition by darifenacin. Neither in healthy volunteers (19-44 years) and healthy subjects (≥60 years), nor in volunteers 65 years or older, could any effect of darifenacin (3.75-15mg daily) be demonstrated, compared to placebo [Kay and Wesnes, 2005; Lipton et al., Kay et al., 2006; Kay and Ebinger 2008].

To study whether darifenacin had any effect on QT/QTc intervals [Serra et al., 2005] performed a 7-day, randomized, parallel-group study (n = 188) in healthy volunteers receiving once-daily darifenacin at steady-state therapeutic (15 mg) and supratherapeutic (75 mg) doses, alongside controls receiving placebo or moxifloxacin (positive control, 400 mg) once daily. No significant increase in QTcF interval could be demonstrated compared with placebo. Mean changes from baseline at pharmacokinetic T_{max} versus placebo were –0.4 and –2.2 milliseconds in the darifenacin 15mg and 75 mg groups, respectively, compared with

+11.6 milliseconds in the moxifloxacin group (P < .01). The conclusion was that darifenacin does not prolong the QT/QTc interval.

Darifenacin 15 mg per day given to healthy volunteers did not change heart rate significantly compared to placebo [Olshansky et al., 2008].

Darifenacin has a well-documented beneficial effect in OAB/DO (Table 2), and tolerability and safety seems acceptable.

6. SOLIFENACIN SUCCINATE

Solifenacin succinate (YM905) is a tertiary amine and well absorbed from the gastrointestinal tract (absolute bioavailability 90%). The mean terminal half-life is 45-68 hours [Kuipers et al., 2002; Smulders et al., 2002; 2004]. It undergoes hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) C_{max} and $AUC_{0\text{-}inf}$ were increased by only approximately 40% and 56%, respectively [Swart et al., 2006]. Solifenacin has a modest selectivity for M3 over M2 (and M1) receptors [Abrams and Andersson, 2007].

Two large-scale phase 2 trials with parallel designs, comprising men and women, were performed [Chapple et al., 2004a, Smith et al., 2002]. The first dose-ranging study evaluated solifenacin 2.5 mg, 5 mg, 10 mg, and 20 mg and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO [Chapple et al., 2004a]. 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 at least 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 (-2.21), 10 mg (-2.47), and 20 mg (-2.75), but not in patients receiving placebo (-1.03) or tolterodine (-1.79). This effect was rapid with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, there was 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 United States (USA) [Smith et al., 2002]. 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. The 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. Efficacy was demonstrated at this time. The 5 mg, 10 mg, and 20 mg dosing groups experienced significant increases in volume voided; the 10 mg solifenacin dose was associated with significant reductions in episodes of incontinence.

In one of the early RCTs, a total of 1077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg twice daily), or placebo [Chapple et al., 2004b]. It should be noted that this study was powered only to compare active treatments to placebo. Compared with placebo (-8%), mean micturitions/24 h were significantly reduced with solifenacin 10 mg (20%), solifenacin 5 mg (17%), and tolterodine (15%). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg twice daily.

Cardozo et al. [2004] randomized 911 patients to 12-week once daily treatment with solifenacin 5 mg, solifenacin 10 mg or placebo. The primary efficacy variable was change from baseline to study end point in mean number of micturitions per 24 hours. Secondary efficacy variables included changes from baseline in mean number of urgency, nocturia and incontinence episodes per 24 hours, and mean volume voided per micturition. Compared with changes obtained with placebo (-1.6), the number of micturitions per 24 hours was statistically significantly decreased with solifenacin 5 mg (-2.37) and 10 mg (-2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg: -1.63, 61%; 10 mg: -1.57, 52%), but not with placebo (-1.25, 28%). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin (based on a 3-day micturition diary, placebo responses not given). Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg versus placebo. Episodes of urgency and mean volume voided per micturition were statistically significantly reduced with solifenacin 5 mg and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs 2.3% with placebo). A 40-week follow up of these studies [i.e., Chapple et al., 2004b and Cardozo et al., 2004] demonstrated that the favourable profile, both in terms of efficacy and tolerability was maintained over the study period [Haab et al., 2005].

The STAR trial [Chapple et al., 2005; 2007] was a prospective, double blind, double-dummy, two-arm, parallel-group, 12-week study conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and TOLT-ER 4 mg once daily in OAB patients. The primary effect variable was micturition frequency. After 4 weeks of treatment patients had the option to request a dose increase, but were dummied throughout as approved product labelling only allowed an increase for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was "non-inferior" to tolterodine concerning the primary effect variable, micturition freqency. However, solifenacin showed significant greater efficacy to tolterodine in decreasing urgency episodes (-2.85 vs -2.42), incontinence (-1.60 vs -.83), urgency incontinence (-1.42 vs -0.83), and pad usage (-1.72 vs -1.19). More solifenacin treated patients became continent by study endpoint (59 vs 49%) and reported improvements in perception of bladder condition (1.51 vs -1.33) assessments. However, this was accompanied by an adverse event incidence which was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild + moderate + severe) were the most common (solifenacin 30% and 6.4%, tolterodine 23% and 2.5%). The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low (5.9 and 7.3%) in both groups.

A number of studies and reviews have further documented the effects of solifenacin [Cardozo et al., 2006; Chapple et al., 2006; 2007; Maniscalco et al., 2006, see also Chapple et al., 2008; Novara et al., 2008]. In a pooled analysis of four RCTs, Abrams and Swift (2005) demonstrated positive effects on urgency, frequency and nocturia symptoms in OAB dry patients. In an analysis of four phase III clinical trials, Brubaker and FitzGerald [2007] confirmed a significant effect of solifenacin 5 and 10 mg on nocturia in patients with OAB (reductions of nocturia episodes with 5 mg: -0.6, $p<0.025$; with 10 mg: -0.6, $p<0.001$vs placebo: -0,4) but without nocturnal polyuria.

Kelleher et al. [2006] and Staskin and Te [2006] presented data showing efficacy in patients with mixed incontinence. A pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly ($\geq$ 65 years) patients, and also showed a high level of persistence in a 40 week extension trial [Wagg et al., 2005]. Improvement of QoL by solifenacin treatment has been documented in several studies [Kelleher et al., 2005; Garely et al., 2006].

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

Michel et al. [2008] studied cardiovascular safety and overall tolerability of solifenacin in routine clinical use in a 12-week, open-label, post-marketing surveillance study. They concluded that "in real-life conditions, i.e. with inclusion of large numbers of patients with cardiovascular co-morbidities and taking comedications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure".

Solifenacin has a well-documented beneficial effect in OAB/DO (Table 2), and the adverse event profile seems acceptable.

7. FESOTERODINE FUMARATE

Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases [Michel, 2008]. This compound, which is is chemically identical to the 5-hydroxy metabolite of tolterodine, is a non-subtype selective muscarinic receptor antagonist [Ney et al., 2008]. All of the effects of fesoterodine in man are thought to be mediated via 5-HMT, since the parent compound remains undetectable upon oral dosing. 5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism. Since the renal clearance of 5-HMT is about 250 mL/min, with >15% of the administered fesoterodine dose excreted as unchanged 5-HM, this raises the possibility that 5-HMT also could work from the luminal side of the bladder [Michel, 2008].

Fesoterodine is indicated for use at doses of 4 and 8 mg once daily. In clinical studies both doses of fesoterodine were consistently superior to placebo in improving the symptoms of OAB [Chapple et al., 2007; Nitti et al., 2007], with 8 mg/day having significantly greater effects than 4 mg/day [Khullar et al., 2008]. Analysis of pooled data on QoL, using King´s Health Questionnaire and ICI Questionnaire-short Form, showed that both doses of the drug caused a significant improvement of QoL. Compared to TOLT-ER (4 mg), fesoterodine (8 mg) had statistically significant advantages for improving incontinence episodes, severe urgency with incontinence, mean voided volumes and number of continent days a week [Chapple et al., 2008; Khullar et al., 2008]. Adverse events were characteristic for an antimuscarinic, dry mouth being the most frequently reported – it was

was rated as mild to moderate in most cases. In one phase III study it was seen in 7%, 16% and 36% of patients receiving placebo, 4 and 8 mg/d fesoterodine, respectively [Nitti et al., 2007], whereas in the another phase III study it was 7.1%, 21.7% and 33.8% in the same groups (16.9% for 4 mg/day TOLT-ER) [Chapple et al., 2007].

Kelleher et al. [2008] evaluated the effect of fesoterodine on HRQoL in patients with OAB syndrome. Pooled data from two randomized placebo-controlled phase III studies were analysed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolterodine extended release (tolterodine-ER) 4 mg. By the end of treatment, all active-treatment groups had significantly improved HRQoL compared with those on placebo.

A study on possible effects on QT-intervals has been performed [Michel, 2008]. This included parallel groups of 64-68 subjects each who were treated for 3 days with 4 mg/d fesoterodine, the highly supratherapeutic dose of 28 mg/d fesoterodine, the active control moxifloxacin 400 mg/day or placebo. Both the standard dose of 4 mg/day and the highly supratherapeutic dose of 28 mg/d did not provide any evidence of QT-prolongation (e.g., QT_C for 28 mg/day from 404.5 ± 16.7 to 400.1 ± 14.0 ms, delta: -5.0 ± 7.9 ms).

Fesoterodine has a well-documented beneficial effect in OAB (Table 2), and the adverse event profile seems acceptable.

II. DRUGS ACTING ON MEMBRANE CHANNELS

1. CALCIUM ANTAGONISTS

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and thereby contribute to the regulation of smooth muscle tone. Two major groups of calcium channels include the voltage-gated [Caterall et al., 2003] and the store-operated channels (Leung et al., 2008). While both can contribute to the maintenance of smooth tone in general, store-operated calcium channels apparently contribute only to a limited if any extent to the regulation of bladder smooth muscle tone [Schneider et al., 2004 a; b]. On the other hand, various types of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle tone including including Q-type [Frew and Lundy, 1995] and L-type channels [Wuest et al., 2007]. The latter appears to be of particular importance as inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in vitro with tissue from multiple mammalian species, including humans [Frazier et al., 2008]. However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species [Wuest et al., 2007]. In confirmation of the role of L-type calcium channels, it has been shown that knock-out mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility [Wegener et al., 2004].

While these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical instillation of the calcium channel inhibitor verapamil, the muscarinic receptor antagonists oxybutynin and trospium and placebo to patients with urgency or urgency incontinence. While the two muscarinic receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function [Fröhlich et al., 1998]. In a clinical study of limited size the calcium channel inhibitor nimodipine (30 mg per day) did not significantly improve the number of incontinence episodes as compared to placebo [Naglie et al., 2002]. Larger studies with clinical endpoints related to effects of calcium channel inhibitors have not been reported in incontinent patients (based upon a Medline search using the MeSH terms “calcium channel blockers” and “urinary incontinence”). Moreover, it should be noted that despite a long-standing and wide-spread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro and the lack of clinical data are not fully clear, but it may relate to pharmacokinetic properties of the currently used drugs which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction (Table 2).

2. POTASSIUM CHANNEL OPENERS

In a similar fashion to calcium channels, potassium channels also contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. Numerous types of potassium channels exist [Gutman et al., 2003]. With regard to bladder function, ATP-dependent (K_{ATP}) and big calcium-activated (BK_{Ca}) channels have been studied most intensively. The BK_{Ca} channels also appear to be important physiologically as their activation can cause hyperpolarization of bladder smooth muscle cells and by this mechanism they can contribute to the relaxation of bladder smooth muscle by, e.g., β-adrenoceptor agonists [Frazier et al., 2008]. Openers of both K_{ATP} [Howe et al., 1995; Hu et al., 1997; Martin et al., 1997] and BK_{Ca} channels [Hu et al.,

1997; Sheldon et al., 1997] have been shown to induce bladder smooth muscle relaxation in various mammalian species, but the density of some types of potassium channels may differ markedly between species. Some potassium channel openers have also been shown to suppress non-voiding detrusor contractions in vivo in animal models of DO [Howe et al., 1995; Martin et al., 1997; Tanaka et al., 2003] and this also includes activators of the KCNQ type of potassium channels [Streng et al., 2004]. Although potassium channel openers are believed to mainly act directly on smooth muscle cells [Gopalakrishnan and Shieh, 2004], they may also at least in part affect bladder function by modulating the activity of afferent neurones [Tanaka et al., 2003].

While the above data demonstrate the potential of potassium channel openers to inhibit non-voiding detrusor contractions, these channels are expressed not only in bladder, but also e.g. in vascular smooth muscle. Therefore, potassium channel openers may also affect cardiovascular function, and in effective doses may considerably lower blood pressure [Howe et al., 1995; Shieh et al., 2007]. While some compounds of this class have a certain degree of selectivity for the bladder as compared to the cardiovascular system, it remains unclear whether the degree of selectivity offers a sufficiently large therapeutic window for clinical use. This consideration has led to a considerable hesitancy to study potassium channel openers in OAB patients. Nevertheless, one randomized, placebo-controlled clinical study on the K_{ATP} opener ZD0947 has been reported [Chapple et al., 2006]. While ZD0947 at the chosen dose did not lower blood pressure or cause adverse events typical for a vasodilating drug, it also failed to achieve superiority relative to placebo for the treatment of OAB symptoms. Therefore, despite promising preclinical efficacy data, potassium channel openers at present are not a therapeutic option and may never become one due to a lack of selectivity for bladder over cardiovascular tissues (Table 2).

III. DRUGS WITH "MIXED" ACTION

Some drugs used to block DO have been shown to have more than one mechanism of action. They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined "direct" action on bladder muscle. For several of these drugs, the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage operated Ca^{2+} channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action. Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsade de pointes) in some patients [Connolly et al., 1991; Stewart et al., 1992].

1. OXYBUTYNIN CHLORIDE

Oxybutynin is a tertiary amine that is well absorbed, and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite, N-desethyloxybutynin (DEO) has pharmacological properties similar to the parent compound [Waldeck et al., 1997], but occurs in much higher concentrations after oral administration [Hughes et al., 1992]. 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. [1988]. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation [Hughes et al., 1992; Douchamps et al, 1988].

Oxybutynin has several pharmacological effects *in vitro*, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent [Kachur et al., 1988]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions [Waldeck et al., 1997; Nilvebrant et al., 1988]. The drug was shown to have slightly higher affinity for muscarinic M1 and M_3 receptors than for M_2 receptors [Nilvebrant et al., 1986; Norhona-Blob et al., 1991], but the clinical significance of this is unclear.

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other 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 [Appell et al., 2001; Diokno et al., 2003; Dmochowski et al., 2002]. An extended release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability.

Available formulations of oybutynin were overviewed by McCrery and Appell [2006].

a) Immediate-release oxybutynin (OXY-IR)

Several controlled studies have have shown that OXY-IR is effective in controlling DO, including neurogenic DO [Yarker et al., 1995; Andersson and Chapple, 2001]. The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff et al. [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 per 24 h was 33% (data on placebo not presented). The overall "subjective improvement" rate was reported as 74 % (range 61% - 100%). The mean percent of patients reporting an adverse effect was 70 (range 17% - 93%). Oxybutynin, 7.5 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, were reported by only 8% of the patients [Amaranco et al., 1998]. In nursing home residents (n=75), Ouslander et al. [1995] found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double blind, cross-over trial. On the other hand, in another controlled trial in elderly subjects (n=57), oxybutynin with bladder training was found to be superior to bladder training alone [Szonyi et al., 1995].

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit [Szoller et al., 1996; Kim et al., 1996].

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting [Baigrie et al., 1988; Jonville et al., 1992]. The effects on the electro-cardiogram of oxybutynin were studied in elderly patients with urinary incontinence [Hussain et al., 1998]; no changes were found. It cannot be excluded that the commonly recommended dose 5 mg 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 [Amarenco et al., 1998].

b) Extended release oxybutynin (OXY-ER)

This formulation was developed to decrease liver metabolite formation of desethyloxybutynin (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 primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [Appell et al., 2003]. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [Chancellor et al., 2001].

The effects of OXY-ER have been well documented [Siddiqui et al., 2004]. In the OBJECT study [Appell et al., 2001], the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6% to 6.1%; TOLT-IR 24.1% to 7.8%), total incontinence (OXY-ER from 28.6% to 7.1%; TOLT-IR 27.0% to 9.3%), and frequency (OXY-ER from 91.8% to 67.1%; TOLT-IR 91.6% to 71.5%) and both medications were equally well tolerated. The basic study was repeated as the OPERA study [Diokno et al., 2003] with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg) and the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urgency incontinence, however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should not be compared with ER entities of the other.

Greater reductions in urgency and total incontinence have been reported in patients treated in dose-escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with OXY-IR. In the 1999 study [Anderson et al., 1999], 105 patients with urgency or mixed incontinence were randomized to receive 5-30 mg OXY-ER once daily or 5 mg of OXY-IR 1-4 times/day. Dose titrations began at 5 mg and the dose was increased every 4-7 days until one of three endpoints was achieved. These were 1) the patient reported no urgency incontinence during the final 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 urgency and total incontinence episodes was statistically similar between OXY-ER and OXY-IR but dry mouth was reported statistically more often with OXY-IR. In the 2000 study [Versi et al., 2000], 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg daily up to 20 mg daily. As in the 1999 study,

OXY-ER again achieved a >80% reduction in urgency and total incontinence episodes and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naïve patients included, as all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naïve population [Gleason et al., 1999].

In an RCT comparing different daily doses of oxybutynin (5, 10 and 15 mg), Corcos et al. [2006] found a significant dose-response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg oxybutynin/day.

c) Transdermal oxybutynin (OXY-TDS)

Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study [Davila et al., 2001] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study [Dmochowski et al., 2002] the 3.9-mg daily dose patch significantly (vs placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from 5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 ml; placebo from 175 to 182 ml). Furthermore, dry mouth rate was similar to placebo (7% vs 8.3%). In a third study [Dmochowski et al., 2003] OXY-TDS was compared not only to placebo but to TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14% and erythema in 8.3% with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a randomized, 2-way crossover study [Appell et al., 2003]. Multiple blood and saliva samples were collected and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared to OXY-ER which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER.

Dmochowski et al. [2005] analyzing the combined results of two RCTs concluded that transdermal oxybutynin was shown to be efficacious and well tolerated. The most common systemic side effect was dry mouth (7.0 % vs placebo 5.3%). Application site erythema occurred in 7% and pruritus in 16.1 %. Also Cartwright and Cardozo [2006], reviewing published and presented data concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower that with oral antimuscarinics – however, this benefit was offset by the rate of local skin reaction. Sahai et al. [2008] in a recent review largely confirmed these conclusions.

d) Other administration forms

Rectal administration [Collas and Malone-Lee, 1997] was reported to have fewer adverse effects than the conventional tablets.

Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults [Lose and Norgaard, 2001; Fader et al., 2007; George et al., 2007; Guerra et al., 2008], although adverse effects may occur [Kasabian et al., 1994; Palmer et al., 1997].

e) Effects on cognition

Several studies have documented the possibility that oxybutynin may have negative effects on cognitive functions, particularly in the elderly population but also in children [see, e.g., Kay et al., 2006; Klausner al Steers, 2007; Kay and Ebinger, 2008]. This factor should be taken into consideration when prescribing the drug.

Oxybutynin has a well-documented efficacy in the treatment of OAB/DO (Table 2). Despite the adverse effect profile, it is still an established therapeutic option.

2. PROPIVERINE HYDROCHLORIDE

Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Murz [2001]. The drug is rapidly absorbed (t_{max} 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man [Walter et al., 2003]. Several active metabolites are formed which quantitatively and qualitatively differ from the mother compound [Haustein et al., 1988; Muller et al., 1993; Wuest et al., 2006; Zhu et al., 2008; Sugiyama et al., 2008]. Most probable these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified (Michel and Hegde, 2006). The half-life of propiverine itself is about 11-14 h. An extended release preparation was shown to be effective [Junemann et al., 2006; May et al., 2008].

Propiverine has combined antimuscarinic and calcium antagonistic actions [Haruno, 1992; Tokuno et al., 1993]. The importance of the calcium antagonistic component for the drug´s clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes.

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff et al [1998] collected 9 randomized studies on a total of 230 patients, and found a 17% reduction in micturitions per 24 hours, 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 [Stöhrer et al., 1999]. Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate and placebo [Wehnert et al., 1989], and propiverine, oxybutynin and placebo [Wehnert et al., 1992; Madersbacher et al., 1999], have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared [Stöhrer et al., 2007]. The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin.

Also in children and adolescents with neurogenic DO, propiverine was found to be effective [Schulte-Baukloh et al., 2006; Grigoleit et al., 2006], with a low incidence rate of adverse events: <1.5% [Grigoleit et al., 2006].

Madersbacher et al. [1999] compared the tolerability and efficacy of propiverine (15 mg three times daily) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin. Dorschner et al. [2000] 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, urgency incontinence or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine – 2 out of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes.

In a randomised, double-blind, multicentre clinical trial, patients with idiopathic DO were treated with 15 mg propiverine twice daily or 2 mg TOLT-IR twice daily over a period of 28 days [Junemann et al., 2005]. The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary endpoint. Secondary endpoints were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, post void residual urine, and quality of life. It was found that the mean maximum cystometric capacity increased significantly ($p < 0.01$) in both groups. The volume at first urgency and the frequency/volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the quality of life improved comparably in both groups.

Abrams et al. [2006] compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring (AUM) parameters, safety, and tolerability in OAB patients. Patients (n=77) received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. They found that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. Oxybutynin had a higher rate of dry mouth, and propiverine had a more pronounced effect on gastrointestinal, cardio-vascular, and visual function.

A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5–10 yr was performed by Marschall-Kehrel et al. [2008]. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy parameter; secondary endpoints included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well-tolerated: 23% of side-effects were reported for propiverine and 20% for placebo.

Yamaguchi et al. [2008] performed a multicentre, 12-week, double-blind phase III trial in Japanese men and women with OAB (1593 patients were randomized and 1584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at endpoint in number of voids/24 hours, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence and quality of life (QoL) were examined. It was found that at endpoint, there were greater reductions in mean (SD) voids/24 hours with all drug regimens than with placebo. All active treatments

improved the volume voided and QoL vs placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided vs propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg.

Propiverine has a documented beneficial effect in the treatment of OAB/DO (Table 2), and seems to have an acceptable side effect profile.

3. FLAVOXATE HYDROCHLORIDE

Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% [Guay, 2003].The drug is extensively metabolized and plasma half-life was found to be 3.5 h [Sheu et al., 2001]. Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity [Cazzulani et al., 1988; Caine et al., 1991]. The 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 phosphodiesterases, and to have local anesthetic properties; no antimuscarinic effect was found [Guarneri et al., 1994]. Uckert et al. [2000], 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 rhytmic bladder contractions in anesthetized rats [Oka et al., 1996].

The clinical effects of flavoxate in patients with DO and frequency, urgency and incontinence have been studied in both open and controlled investigations, but with varying rates of success [Ruffman, 1988]. Stanton [1973] compared emepronium bromide and flavoxate in a double-blind, cross-over study of patients with detrusor overactivity and reported improvement rates of 83% and 66% after flavoxate or emepronium bromide, respectively, both administered as 200 mg 3 times daily. In another double-blind, cross-over study comparing flavoxate 1200 mg/day with that of oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency, and utilising both clinical and urodynamic criteria, Milani et al. [1993] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects of flavoxate with those of placebo, have not been able to show any beneficial effect of flavoxate at dosages up to 400 mg three times daily [Briggs et al., 1980; Chapple et al., 1990; Dahm et al., 1995]. In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared to other therapeutic alternatives, is not well documented (Table 2).

No RCTs seem to have been performed with flavoxate during the last decade.

IV. α-ADRENOCEPTOR (AR) ANTAGONISTS

Even if it is well known that α-AR antagonists can ameliorate lower urinary tract symptoms in men with BPE [Andersson et al., 2002], there are no controlled clinical trials showing that they are an effective alternative in the treatment of OAB/DO in this patient category. In an open label study, Arnold [2001] evaluated the clinical and pressure-flow effects of tamsulosin 0.4 mg once daily in patients with lower urinary tract symptoms (LUTS) caused by benign prostatic obstruction (BPO). He found that tamsulosin produced a significant decrease in detrusor pressure, increase in flow rate and a symptomatic improvement. In a study where tamsulosin was given alone, or together with tolterodine, to patients with male LUTS, monotherapy with the drug was not effective [Kaplan et al., 2006]. An RCT, comprising 364 women with OAB, revealed no effect of tamsulosin vs placebo [Robinson et al., 2007]. On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were successfully treated with an α_1-AR antagonist [Kessler et al., 2006, Low et al., 2008].

α_1-AR antagonists have been used to treat patients with neurogenic DO [Abrams et al., 2003]; however, the success has been moderate. Thus, there is no convincing evidence that α_1-AR antagonists are effective in patients with storage symptoms. Although α_1-AR antagonists may be effective in selected cases, convincing effects documented in RCTs are lacking (Table 2). In women, these drugs may produce stress incontinence [Dwyer and Teele, 1992].

V. β-ADRENOCEPTOR AGONISTS

In isolated human bladder, non-subtype selective β-AR agonists like isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in man [Andersson, 1993]. However, the β-ARs of the human bladder were shown to have functional characteristics typical of neither β_1-, nor β_2- ARs, since they could be blocked by propranolol, but not by practolol or metoprolol (β_1) or butoxamine (β_2) [Nergard et al., 1977; Larsen, 1979]. 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 [Andersson 1993], and favourable effects on DO were reported in open studies with selective

β_2-AR agonists such as terbutaline [Lindholm and Lose, 1986]. In a double-blind investigation clenbuterol 0.01 mg 3 times daily was shown to have a good therapeutic effect in 15 of 20 women with DO [Gruneberger, 1984]. Other investigators, however, have not been able to show that β-ARs agonists represent an effective therapeutic principle in elderly patients with DO [Castleden and Morgan, 1980], or in young patients with myelodysplasia and DO [Naglo et al, 1981].

However, three subtypes (β_1, β_2, and β_3) have been identified in the detrusor of most species, including humans [Andersson and Arner, 2004; Michel and Vrydag, 2006]. Also the human urothelium contains all three receptor subtypes [Otsuka et al., 2008]. Studies, using real-time RT-PCR, have revealed a predominant expression of β_3-AR mRNA in human detrusor muscle [Nomiya and Yamaguchi, 2003; Michel and Vrydag, 2006] and the functional evidence for an important role in both normal and neurogenic bladders is convincing [Fujumura et al., 1999; Igawa et al., 1999; Takeda et al., 1999; Morita et al., 2000; Igawa et al., 2001; Biers et al., 2006; Michel and Vrydag, 2006; Badawi et al., 2007; Leon et al., 2008]. The human detrusor also contains β_2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in this structure [Andersson and Arner 2004; Michel and Vrydag, 2006].

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species, is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder K+ channels, particularly BK_{Ca} channels, may be more important in β-AR mediated relaxation than cAMP [Hudman et al., 2000; Frazier et al., 2005; Uchida et al., 2005; Frazier et al., 2008].

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated [Murakami et al., 2007; Otsuka et al., 2008]. Murakami et al. [2007] found that the relaxation responses of the detrusor were not influenced by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka et al. [2008]. However, to what extent a urothelial signaling pathway contributes *in vitro* and *in vivo* to the relaxant effects of β-AR agonists in general, and β_3-AR agonists specifically, remains to be elucidated.

The in vivo effects of β_3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β_3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [Fujimura et al., 1999; Woods et al., 2001; Takeda et al., 2002; Kaidoh et al., 2002]. For example, Hicks et al. [2007] studied the effects of the selective β_3-AR agonist, GW427353, in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid evoked bladder hyperactivity, without affecting voiding.

A number of β_3-AR selective agonists are currently being evaluated as potential treatment for OAB in humans including GW427353 (solabegron) and YM178 [Colli et al., 2007]. Takaku et al. [2007] found that the selective β_3 -AR agonist, YM187, mediated muscle relaxation of human bladder strips. Chapple et al. [2008] reported the results of a controlled clinical trial with this drug in patients with OAB. Tolterodine and placebo served as controls. The primary efficacy analysis showed a statistically significant reduction in mean micturition frequency, compared to placebo (-2.19 vs -1.18). With respect to secondary variables YM178 (100 mg) was significantly superior to placebo concerning mean volume voided per micturition (26 vs 11 ml), mean number of incontinence episodes (-2.17 vs -1.01), and urgency episodes per 24 hour (-2.30 vs -1.03). The drug was well tolerated, and the most commonly reported side effects were headache and gastrointestinal adverse effects. The results of this proof of concept study showed that the principle of β_3-AR agonism may be useful for treatment of patients with OAB (Table 2). However, to show that this class of drugs offers a viable therapeutic alternative or complement to current treatment of LUTS/OAB requires further well designed RCTs.

VI. PHOSPHODIESTERASE (PDE) INHIBITORS

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [Andersson 1999; Andersson and Arner, 2004]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [Andersson and Arner, 2004]. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach [Andersson et al., 2007]. There are presently 11 families of PDEs, some of which preferentially hydrolyse either cAMP or cGMP [Andersson et al. 2007].

As a basis for PDE inhibitor treatment of LUTS, Uckert et al. [2001] investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. *In vitro*, human detrusor muscle responded poorly to sodium nitroprusside, and to agents acting via the cGMP system [Truss et al., 2001]. However, significant relaxation of human

detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone. Significant dose-dependent relaxations were also induced by human cAMP analogs [Truss et al., 2001]. With these studies as a background, Truss et al. [2000] presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders, and not responding to standard antimuscarinic therapy. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine showed statistically significant results only for one parameter [Truss et al., 2001]. Studies with other PDE 1 inhibitors than vinpocetin (which may not be an optimal drug for elucidation the principle) do not seem to have been performed.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the *in vitro* contractile response of guinea pig [Longhurst et al., 1997] and rat [Nishiguchi et al., 2006; Kaiho et al., 2008] bladder strips, and also suppressed rhythmic bladder contractions of the isolated guinea pig bladder [Gillespie, 2004]. Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose -limiting effect [Giembycz, 2005]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

Nitric oxide (NO) has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [Andersson and Wein, 2004]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita et al. [1994] examined the effects of isoproterenol, prostaglandin E_1 and E_2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström et al. [2006] characterized the distribution of PDE 5, cGMP and PKG1 in female pig and human urethra, and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations.

The distribution of PDEs in the male urethral structures does not seem to have been studied.

The observation that patients treated for erectile dysfunction with PDE 5 inhibitors had an improvement of their LUTS, has sparked a new interest in using these drugs also for treatment of LUTS and OAB. After the report in an open study [Sairam et al., 2002] that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS, this observation has been confirmed in several well designed and conducted RCTs [McVary et al., 2007a;b, Stief et al., 2008].

McVary et al. [2007a] evaluated the effects of sildenafil (50-100 mg daily for 12 weeks) on erectile dysfunction and LUTS in men men 45 years or older who scored 25 or less on the erectile function domain of the International Index of Erectile Function (IIEF) and 12 or greater on the International Prostate Symptom Score (IPSS). In 189 men receiving sildenafil significant improvements were observed in IPPS (-6.32 vs -1.93, $p<0.0001$), Benign Prostatic Hyperplasia Impact Index (-2.0 vs -0.9, $p<0.0001$), mean IPSS quality of life score (-0.97 vs -0.29, $p<0.0001$) and total Self-Esteem and Relationship questionnaire scores (24.6 vs 4.3, $p<0.0001$). Interestingly, there was no difference in urinary flow between the groups ($p=0.08$). Significantly more sildenafil vs placebo treated patients were satisfied with treatment (71.2 vs 41.7, $p<0.0001$). Sildenafil was well tolerated.

In an RCT, treatment with tadalafil once daily, in addition to improving erectile function in men with LUTS, was demonstrated to produce a clinically meaningful and statistically significant symptomatic improvement of LUTS [McVary et al., 2007b]. In another RCT, vardenafil given twice daily for eight weeks to men with ED and LUTS, was shown to significantly improve LUTS, erectile function, and quality of life Stief et al. [2008].

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In none of the trials referred to such an effect was found. However, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstital cells, and suburothelial afferent nerves).

PDE-5 inhibitors have a documented effect in men with LUTS/OAB (Table 2). The place of PDE-5 inhibitors in the treatment of OAB/DO remains to be established. Specifically, there seems to be no published information the effects of these drugs in women with OAB/DO.

VII. ANTIDEPRESSANTS

1. IMIPRAMINE

Several antidepressants have been reported to have beneficial effects in patients with DO [Martin and Schiff, 1984, Lose et al., 1989]. However, imipramine is the only drug that has been widely used clinically to treat this disorder.

Imipramine has complex pharmacological effects, including marked systemic antimuscarinic actions [Baldessarini, 1985] and blockade of the reuptake of serotonin and noradrenaline [Maggi et al., 1989], but its mode of action in DO has not been established [Hunsballe and Djurhuus, 2001]. 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 [Hunsballe and Djurhuus, 2001; Glazener et al., 2003]. It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine [Bigger et al, 1977; Giradina et al., 1979]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [Baldessarini, 1985].

The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have have been performed during the last decade [Hunsballe and Djurhuus, 2001]. No good quality RCTs have documented that the drug is effective in the treatment DO (Table 2). However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

2. DULOXETINE

Duloxetine is a combined noradrenaline and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Thor et al., 1995; Katofiasc et al, 2002]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [Fraser et al., 2003]. The effects of duloxetine were studied in a placebo-controlled study comprising 306 women (aged 21-84 years) with OAB, randomly treated with placebo (153) or duloxetine (80-mg/day for 4 weeks, which was increased to 120-mg/day for eight weeks [Steers et al., 2008]. The primary efficacy analysis compared the treatment effects on mean change from baseline to endpoint in the mean number of voiding episodes per 24 hours. Patients randomized to duloxetine had significant improvements over those randomized to placebo for decreases in voiding and incontinence episodes (-1.81 vs -0.62), for increases in the daytime voiding intervals (29 vs 7 minutes), and for improvements in I-QoL scores at both doses of the drug. Urodynamic studies showed no significant increases in maximum cystometric capacity or in the volume threshold for DO. The most common treatment-emergent adverse events with duloxetine (nausea, 31%, placebo, 4.6; dry mouth, 16%, placebo, 1.3; dizziness, 14%, placebo 0.7; constipation, 14%, placebo, 3.3; insomnia, 13%, placebo1.3; and fatigue, 11%, placebo 2.0) were the same as those reported by women with SUI (see below) and were significantly more common with duloxetine than placebo. Also in females with mixed incontinence, improvement of the OAB component has been demonstrated [Bent et al., 2008; Schagen van Leeuwen et al., 2008]. For assessment, see Table 2.

VIII. CYCLOOXYGENASE (COX) INHIBITORS

Human bladder mucosa has the ability to synthesize eicosanoids [Jeremy et al., 1987], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [Downie and Karmazyn, 1984; Leslie et al., 1984]. Even if prostaglandins cause contraction of human detrusor [Andersson, 1993], it is still unclear whether prostaglandins contribute to the pathogenesis of DO. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Cardozo et al. [1980] performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg three 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 [1983] 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

[Cardozo and Stanton, 1980]. 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 (Table 2).

No new RCTs on the effects of COX inhibitors in OAB/DO patients seem to have been published during the last decade.

IX. TOXINS

The persisting interest around intravesical pharmacological therapy for neurogenic DO (NDO) stems from the fact that it circumvents systemic administration of active compounds. This offers two potential advantages. First, intravesical therapy is an easy way to provide high concentrations of pharmacological agents in the bladder tissue without causing unsuitable levels in other organs. Second, drugs effective on the bladder, but inappropriate for systemic administration, can be safely used. This is the case of botulinum toxin (BONT) and vanilloids. Attractive as it may be, intravesical pharmacological therapy should still be considered as a second line treatment in patients refractory to conventional oral antimuscarinic therapy or who do not tolerate its systemic side effects. For assessments, see Table 2.

1. BOTULINUM TOXIN

a) Mechanism of action of BONT

Botulinum toxin (BONT) is a neurotoxin produced by *Clostridium botulinum*. Of the seven subtypes of BONT, sub-type A (BONT-A) is the most relevant clinically. Most of the intravesical experience reported on BONT-A deals with Botox®. However, BONT-A toxin is also available under the trade names of Dyspor®, and Xeomin,. Bladder experience with the latter was, however, never reported. Available information indicates that Botox® is roughly three times more potent than Dyspor® [Cruz and Silva, 2004; Nitti et al, 2006]. However this relation has never been clearly defined. Therefore at a bladder setting these equivalents should be approached with caution [for clinical reviews, see Nitti et al., 2006; Patel et al., 2006; Cruz and Dinis, 2007; Karsenty et al, 2008]. In addition to sub-type A, recent reports have investigated the detrusor injection of BONT sub-type B (Neurobloc®, Miobloc®). For further details see section 9.1.9.

BONT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 [Dong et al., 2006] through its heavy chain and is internalized by the nerve terminal. Upon cleavage, the light chain is released in the cytosol, where it impedes binding of neurotransmitter-containing synaptic vesicles to the plasma membrane. This is achieved through the N-ethylmaleimide-sensitive factor attachment protein (SNARE) complex made up of synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein -VAMP) and syntaxin. BONT-A cleaves SNAP 25 rendering the SNARE complex inactive [Humeau et al., 2000; Chancellor et al., 2008]. Subtype B, acts preferentially through the inactivation of VAMP [Humeau et al., 2000].

BONT-A application was extensively evaluated in striated muscle. Paralysis occurs by prevention of ACh release from cholinergic motor nerve endings [Humeau et al, 2000]. Accumulation of neurotransmitter containing synaptic vesicles is followed by terminal axonal degeneration. Muscular paralysis recovers within two to four months time. During this time axons are developing lateral sprouts and eventually regenerate completely [de Paiva et al., 1999]. As parasympathetic cholinergic nerves are also fundamental for detrusor contraction the blockade of ACh release was immediately put forward as the rationale for the neurotoxin effect when injected in the bladder. However axon sprouting concomitant with clinical remission has not been documented in the detrusor [Haferkamp et al., 2004]. Furthermore fragments of cleaved SNAP 25 are detectable in bladder biopsy specimens of patients treated intravesically with BONT-A long after they become undetectable in striated muscle [Schulte-Baukloh et al., 2007]. These facts indicate that additional mechanisms of action are probably operative in the bladder. BONT-A inhibits the spinal cord release of glutamate, Substance P (SP) and CGRP by sensory nerves [Aoki et al., 2005; Purkiss et al., 2000; Meng et al., 2007] as well as the release of neuropeptides at the peripheral extremities [Lucioni et al., 2008; Rapp et al., 2006]. In the bladder, BONT-A has been shown to reduce the suburothelial immunoreactivity for TRPV1 or P2X3 [Apostolidis et al, 2005]. Furthermore BONT-A has been shown to inhibit ATP release from urothelium in animal models of spinal cord injury [Khera et al, 2004; Smith et al., 2008]. Morenilla Palao et al. [2004] have shown co-localization of SNARE proteins and TRPV1 in sensory nerves and that BONT-A impedes TRPV1 trafficking from intracellular vesicles to the plasma membrane during inflammation.

BONT-A may decrease the levels of neurotrophic agents in the bladder tissue. Neurogenic DO (NDO) patients produce more Nerve Growth Factor (NGF) in the bladder than control individuals [Giannantoni et al, 2006; Liu et al, 2008] and a significant decrease can be detected after intravesical the application of

the toxin. As NGF is paramount for sensory nerve growth, maintenance and plasticity, this finding may point toward another mechanism whereby BONT-A acts upon the bladder.

b) BONT-A injection protocol

When the treatment was first described in 1999, BONT-A (Botox®) was diluted in normal saline in order to obtain a concentration of 10 Units/ml [Schurch et al., 2000]. Under visual control through a rigid cystoscope and a flexible 6 Fr injection needle, 30 injections of 1 ml (10 Units (U) of BONT-A toxin) were done in 30 different locations above the trigone to prevent vesico-urethral reflux (**Figure 13**). Additional refinements have been added to this technique along the following years, including the use of a local anaesthetic agent (4% lidocaine) and a flexible cystoscope [Harper et al., 2003]. For Dyspor® the technique was similar, including the number of injection sites. Only the dilutions were different taking in consideration that 500-1000 U were used [Cruz and Silva, 2004].

The effect of BONT-A after increasing the dose per injection site and decreasing the number of injected sites was investigated in one study. Patients were randomized to receive 300 U either in 10 or 30 sites [Karsenty et al., 2005]. The authors reported that 10-site injection was quicker and less painful and that no differences in efficacy between the two procedures could be detected up to 24 weeks. Another variation is the neurotoxin injection in the trigone. The suggested risks of injecting bladder trigone has never been demonstrated, whether Botox® or Dyspor® was used [Karsenty et al., 2007; Mascarenhas et al., 2008; Citeri et al., 2008]. However, this does not mean that trigonal injections bring marked benefits to the treatment. One trial concluded that 100 U of Botox® injected only in the trigone were less effective and durable than when administered in the detrusor [Kuo et al., 2007]. Injection in the sub-urothelial space was also assayed on the suggestion that in this position the BONT-A effect could be more pronounced in sensory than in parasympathetic motor fibers (Kuo et al., 2005). However, in one comparative study injection of 100 U of Botox® in the suburothelial space was less effective than in the detrusor [Kuo et al., 2007]. Another variable of the injection technique is the diluent volume. Most studies used 1.0 mL per injection, although a few used 0.5 mL [Grosse et al., 2005; Schulte-Baukloh et al., 2005), 0.2 mL (Kuo et al., 2004), or even 0.1 mL per injection site [Rapp et al., 2004]. In conclusion, at this point it must be concluded that further controlled studies designed to compare different number and locals of injections sites are necessary.

c) Effect of BONT-A on NDO adult patients

Following the preliminary report of BONT-A (Botox®, 200 or 300U) detrusor application in 21 patients with traumatic spinal cord injury resistant to antimuscarinic drugs [Schurch et al., 2000a; b], a large multicenter non-controlled clinical trial was conducted in Europe enrolling 231 NDO patients, most with spinal cord injury [Reitz et al., 2004]. Botox®, 300 U was injected in 30 points in the detrusor above the trigone. Data were available for 200 patients. In 180 incontinent patients, this study, which still represents the largest trial conducted with BONT-A, brought urinary continence to 132 and a marked improvement to 48 patients. A marked increment of the volume for first detrusor contraction and decline of maximal detrusor pressure were observed during urodynamic evaluations up to 36 weeks after injection. No injection related complications or toxin side effects were reported. Several other non-controlled studies

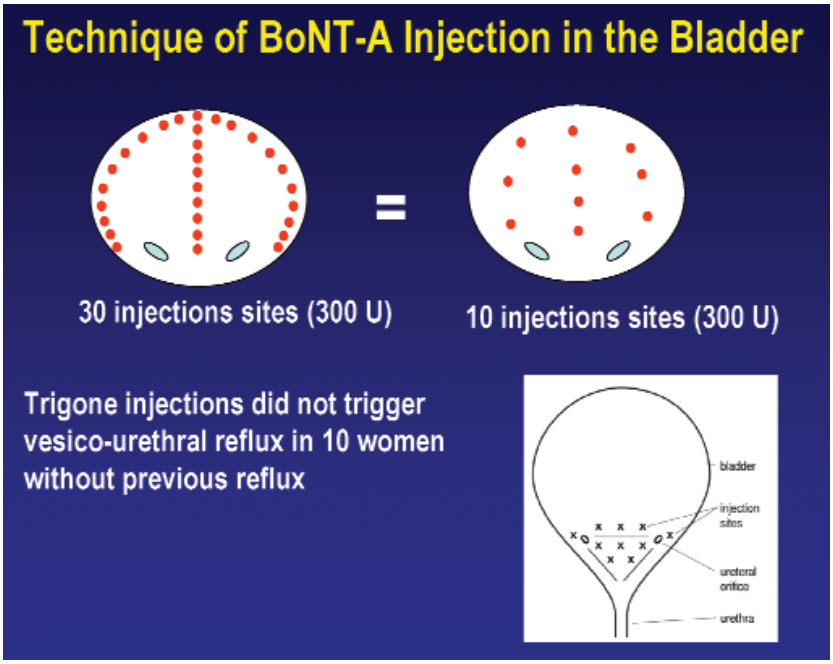

Figure 13 : Techniques for injection of BoNT-A in the bladder.

published subsequently confirmed these observations [see, Patel et al., 2006; Dmochowski et al., 2007; Karsenty et al., 2008 for review].

Botox® and Dyspor® efficacy in NDO was also demonstrated in small double blind placebo controlled trials [Schurch et al., 2005; Ehren et al, 2007]. Fifty-nine NDO patients due to spinal cord injury were randomized to receive Botox®, 200 U, 300 U or placebo. BONT-A treated patients showed a significant reduction in incontinence episodes and amelioration of urodynamic parameters versus placebo that were maintained in the 6 month observation period. Unfortunately the study was not powered to detect differences between 200 and 300 U of BONT-A [Schurch et al., 2005]. In a further subanalysis, a single dose of BONT-A 300 U significantly improved total and subscale I-QoL scores compared with placebo at all time points [Schurch et al., 2007].

Another small single center study randomized a total of 31 NDO patients due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis to intravesical injections of either 500 U of Dyspor® or placebo [Ehren et al, 2007]. Intake of tolterodine and episodes of urinary leakage were registered. Cystometry was performed after 6, 12 and 26 weeks and quality of life was assessed. Patients in the BONT-A arm had a significantly higher cystometric capacity at 6 and 12 weeks. Maximum detrusor pressure and episodes of urinary leakage and tolterodine consumption were significantly lower in the BONT-A than in the placebo group.

In general, the reported duration of BONT-A effect in NDO patients (Botox®, 300U) ranged between 6 and 9 months at the first injection [see, Cruz and Silva, 2004; Dmochowski et al., 2007; Karsenty et a., 2008 for reviews]. The duration of subsequent injections was investigated by three studies along several consecutive injections. Del Popolo et al. [2008] studied the long term effect of BONT-A (Dyspor®) in 199 spinal cord injured patients over a period of 6 years. Initial doses ranged from 500 to 1000 but subsequently the 1000 U dose was abandoned to avoid side effects (see below). The duration of the effect averaged 12 months and was similar for all the three doses. Urodynamic and clinical improvements detected at the first injection were maintained at each re-injection, associated with a highly significant improvement in patient´s satisfaction. Reitz and co-workers [2007] studied intradetrusor BONT-A (Botox®) injections in 20 patients who received at least five intradetrusor injections for long term treatment of NDO. Continence, volume to first detrusor contraction, maximum cystometric capacity, maximum detrusor pressure and compliance at baseline improved significantly after the first injection and at all re-injections. Injection intervals, in average 7 months, tended to lengthen with repeat injections albeit insignificantly. Another study used Botox® 300 U or Dyspor® 750 U in 44 and 22 spinal NDO patients, respectively. Although most of the patients had 2-4 injections, a few had up to 7 consecutive injections. The interval between subsequent injections averaged 9–11 months at all injections. The antimuscarinic use decreased substantially. Significant improvements were found in clinical parameters and in cystometric capacity, whereas compliance improved only after the second treatment. The incidence of DO was significantly reduced. Four patients had transient adverse events after Dyspor® [Grosse et al., 2005].

The onset of BONT-A effect starts within the first 2 weeks after neurotoxin injection [Cruz and Silva, 2004; Dmochowski et al., 2007; Karsenty et al., 2008]. This time course was further evaluated in a small open-label prospective study that specifically investigated the chronology of the BONT-A effects. Urgency, nocturia and frequency were shown to improve as soon as two days after neurotoxin injection in NDO patients [Kalsi et al., 2008].

The majority of the patients included in the BONT-A trials, whether open label or controlled, were spinal cord injured patients [Cruz Silva., 2004; Dmochowski et al., 2007; Karsenty et al., 2008]. The few patients with multiple sclerosis that were included were never analyzed separatedly. Such a gap was filled recently with the study of BONT-A in a MS cohort. Forty-three MS patients suffering from severe urgency and incontinence were treated with 300 U BONT-A (Botox®) [Kalsi et al., 2007]. Highly significant improvements in urgency, incontinence episodes, frequency and nocturia were observed. In addition, bladder capacity, volume to detrusor overactivity and maximal detrusor pressure also improved. The mean duration of the effect was 9.7 months. Similar results were seen with repeat treatments. However, all but one of the treated patients had to perform self-catheterization after treatment. In spite of this drawback, authors concluded that the treatment was likely to have a major impact on future management of multiple sclerosis patients with detrusor overactivity [Kalsi et al., 2007].

d) BONT-A and urinary tract infection (UTI) in adult NDO patients

A consequence of BONT-A treatment only recently noticed is a decrease in the incidence of urinary tract infections in NDO patients. In 30 SCI patients, Gamé et al. [2008] observed that the number of pyelonephritis, orchitis and prostatitis in the six months before BONT-A, 1.75±1.87 per patient, decreased to 0.2±0.41 in the first six months after treatment. In 17 SCI patients that received BONT-A (Botox®) injections for a period of six years, the number of urinary tract infection at the sixth year was 1.8±0.5 per year, significantly lower than at baseline, 6.7±2.1 [Giannantoni et al., 2008]. In a multicentre, cross-sectional retrospective cohort study, data from 214

NDO patients treated in seven German centers were collected. The rate of urinary tract infections in 12 months preceding and in the 12 months following BONT-A (Botox®) treatment was 68% and 28%, respectively [Boy et al., 2008]. The reason for these findings is unclear but may lie in a decreased maximum detrusor pressure resulting in less bladder wall ischemia and vesico-ureteral reflux.

e) BONT-A in NDO children

In children, the dose of BONT-A (Botox®) should be calculated according to body weight. Doses of between 12 U/kg of weight up to a maximum dose of 300 U [Schulte-Baukloh et al., 2002] and four U/Kg [Corcos et al., 2002] have been used for Botox®. The maximum suggested Dysport® dose was 20 U/kg up to a maximum of 400 U [Altaweel et al., 2006, Akbar et al., 2007]. BONT-A has been essentially assayed in children with myelomeningocele [Schulte-Baukloh et al., 2002; Schulte-Baukloh et al., 2003; Corcos et al., 2002; Riccabona et al., 2004; Kajbafzadeh et al., 2006; Altaweel et al., 2006]. Like in adults, the toxin increased bladder capacity and decreased maximal detrusor pressure. In 26 children with a mean age of 6.9 years, 19 of them (73%) became completely dry between clean intermittent catheterizations while 88% reported a global improvement in urine incontinence. Interestingly, of the 15 children who had vesicoureteral reflux before the procedure, 11 (73%) found improvement, which either disappeared or decreased in grade. BONT-A also improved bowel function in 66% of the children with intestinal problems [Kajbafzadeh et al., 2006].

The success rate in terms of continence and cessation of antimuscarinic medication may, however, be substantially inferior to that seen in adults, potentially due to irreversible bladder wall changes associated with longstanding detrusor overactivity [Altaweel et al., 2006]. In a group of 20 children with myelo-meningocele continence was achieved in only 13 children. At a second injection, this number also did not change appreciably [Altaweel et al., 2006].

f) BONT-A in idiopathic DO (IDO) patients

When compared to NDO, information existing on the use of BONT-A in IDO patients refractory to antimuscarinic agents is more scarce and based on small clinical trials. However, the results of BONT-A application in the bladder of NDO patients and the success of recent trials are pushing more and more clinicians to offer the neurotoxin to their patients before its approval for bladder administration.

In the first report, by Radziszewski and Borkowski [2002], 300 UI of Dyspor® were injected in 10-20 bladder sites of 12 IDO patients. Bladder capacity increased significantly, all patients became continent and no side effects were reported, including urinary retention. However subsequent studies reported in general a high incidence of voiding dysfunction. Kuo [2004] reported on 18 IDO patients detrusor injections of BONT-A (Botox®, 200 U). Continence was regained in seven patients (39%) and another seven (39%) reported some degree of clinical improvement. Mean duration of effect was 5.3 months. However, six (33%) patients required clean intermittent catheterization (CIC) at one month to empty their bladders [Kuo et al., 2004]. Popat et al. (2005) also injected 200 U of Botox® in the detrusor and reported at 16 weeks a clear improvement in urgency, urgency incontinence frequency and maximal cystometric capacity. Six patients (19.3%) required prolonged CIC. Sub-urothelial injections were suggested to decrease the incidence of urinary retention, by preferentially targetting suburothelial sensory fibers. However, in 20 patients who received suburothelial BONT-A (Botox®, 200 U) urinary retention occurred in six (30%) [Kuo et al., 2005].

The results of these open label studies were confirmed in two albeit small double-blind, placebo controlled trials in which patients were randomized to intradetrusor injections of 200 U BONT-A (Botox®) or placebo [Sahai et al., 2007; Brubaker et al., 2008]. Sahai et al. [2007] used maximum cystometric capacity as primary outcome measure and changes in overactive bladder symptoms, post-void residual, maximum detrusor pressure during filling cystometry, reflex detrusor volume and QoL questionnaires as secondary outcome measures. Follow-up occurred at four and 12 weeks after injection, at which point the study was unblinded. Further followup in the BONT-A group occurred at 24 weeks. Significant increases in maximum cystometric capacity were observed at four and 12 weeks in patients treated with BONT-A compared to placebo. BONT-A also reduced frequency and urgency incontinence episodes at four and 12 weeks. Urgency was significantly reduced only at four weeks in BONT-A group. Post-void residual increased at four weeks in patients receiving BONT-A, but differences to placebo became insignificant by 12 weeks. Despite significant improvements in quality of life observed among patients treated with BONT-A, 37.5% of them required intermittent self-catheterization to empty the bladder. Brubaker et al. [2008] randomized 28 women to Botox® 200 U and 15 for placebo. Approximately 60% of the women who received BONT-A had a clinical response based on the Patient Global Impression of Improvement. The median duration of their responses was 373 days, significantly longer than the 62 days or less for placebo. Post-void residual urine increased in 43% of the women in the BONT-A group (12 out of 26 women) and urinary tract infection developed in 75% of these women (9 of 12). These numbers exceeded by far the expected ranges and forced the suspension of screening and injection. Median duration of urinary retention after the first injection was approximately

two months but increased to five months at a second injection [Brubaker et al., 2008].

The obvious necessity of reducing micturition dysfunction after BONT-A injections is being investigated through a substantial reduction in the amount of neurotoxin delivered into the detrusor. Schmid et al. [2006] injected 100 U of Botox® in 100 IDO patients refractory to antimuscarinic therapy. BONT-A treatment completely abolished incontinence and urgency sensation in 86% and 82% of patients, respectively, during an average period of six months. Temporary urinary retention occurred in four % of the cases, with additional 15% reporting moderate voiding difficulties. In a recent update of this experience [Schmid et al., 2008] an increase in the duration of BONT-A effect upon repeated injections was observed. Kuo and co-workers [2007] randomly compared detrusor, suburothelial and bladder base injections of 100 U BONT-A (Botox®) in 45 IDO patients refractory to antimuscarinic therapy. Urgency scores improved significantly in all groups. However, duration of clinical improvement was different in the three groups. Percentage of patients with clinical improvement after detrusor, suburothelial and bladder base injections was 67%, 47% and 13% by six months and to 20%, 20% and 6.7% at nine months, respectively. At three months significant increases in cystometric capacity and post-void residual compared to baseline were found in the detrusor and suburothelial but not in the bladder base group. Vesicoureteral reflux was not identified in any patient after BONT-A injection into the trigone.

The definition of an ideal dose of BONT-A for IDO patients as well as the ideal local of injections will require further well designed clinical trials. In addition it is unclear at this time what percentage of IDO patients can stop antimuscarinic medication. For assessment, see Table 2).

A small open-label prospective study specifically investigated the chronology of the BONT-A effects in IDO patients. Urgency, nocturia and frequency improved as soon as four days in IDO patients, therefore slightly later than in NDO cases [Kalsi et al., 2008].

g) Effect of BONT-A on quality of life

Quality of life (QoL) in NDO patients treated with intravesical BONT-A has been addressed in several studies. Kalsi et al. [2006] examined QOL changes in 32 NDO and 16 IDO patients, using the short forms of the Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7). Highly significant decreases in QoL scores at four and 16 weeks for both the NDO and IDO subgroups were observed. Percent improvement in QoL score was similar for both groups of patients. A multicenter, randomized, double blind placebo controlled trial confirmed these data [Schurch et al., 2007]. Fifty-nine NDO patients with urinary incontinence received a single dose of BONT-A (200U or 300 U, Botox®) or placebo. I-QoL scores improved significantly with BONT-A, whether 300U or 200 U were used. A single center, double blind, placebo controlled study was performed by Ehren et al. [2007] to evaluate the effect of a single injection of 500 U of BONT-A (Dysport ®) on quality of life in 31 NDO patients with incontinence. Patients were randomized to intravesical injections of either 500 U of BONT-A or placebo. Patients in the BONT-A group showed improved quality-of-life parameters compared to the placebo group [Ehren et al., 2007]. Unlike the previous studies, in which patients had various neurological conditions, a recent study measured the efficacy and impact on quality of life of BONT-A (300 U of Botox® ®) in 43 patients with multiple sclerosis [Kalsi et al., 2007]. There was a 45% decrease in urinary frequency, 77% decrease in incontinence episodes, 78 % decrease in micturition episodes associated with urgency and a 47 % decrease in nocturia. Although 98% of patients had to perform self-catheterization after treatment, there were sustained improvements in all quality-of-life scores with a mean duration of effect of 9.7 months. Results were maintained with repeat treatments (two injections in 18 and three in two patients) for 11.7 months.

h) Side effects of intradetrusor BONT-A

One of the most frequent side effects reported after intradetrusor BONT-A injection is bladder pain [Karsenty et al., 2008; Del Popolo et al., 2008]. Hematuria may also occur, most of the times mild in nature. The most feared one, paralysis of the striated musculature due to circulatory leakage of the toxin has never been reported. Transient muscle weakness was however reported with Dysport® application in several studies [Wyndaele and Van Dromme, 2002; Akbar et al., 2007; Del Popolo et al., 2008]. Among 199 NDO patients followed during 8 years, five developed hypostenia when injected with 1000 U of Dyspor®. In another study with 44 patients, three adults also treated with 1000 units developed muscular weakness which subsided after 5 to 7 weeks [Akbar et al., 2007]. No such cases were reported with Botox® BONT-A [Karsenty et al., 2008]. The reason for the lack of transient muscle weakness among Botox®-treated patients is unclear but might be related with the larger size of its molecule which limits diffusion into the blood stream. The risk of hyposthenia associated with Dysport® might be avoided by using lower doses of the toxin, no more that 750 units for adults and 20 U/kg for children [Akbar et al., 2007; Del Popolo et al., 2008]. In addition, caution should be used in selecting high risk patients for botulism including children, patients with low pulmonary reserve or patients with myasthenia gravis. Aminoglycosides should be avoided during BONT-A treatment since they might blockade motor plates and therefore enhance BONT-A effect.

Fear of vesicoureteral reflux, which for long precluded trigone injections [Schurch et al., 2000a; Reitz et al., 2004] seems unfounded whether Botox® or Dysport® is used [Karsenty et a., 2007; Mascarenhas et a., 2008; Citeri et a., 2008; Eichel et al., 2008]. However trigonal injections may not enhance BONT-A effects, as observed in a study with IDO patients [Kuo et al., 2007].

In IDO patients the commonest complication is urinary retention. When injecting 200 U of Botox® a 20-30% rate of prolonged urinary retention might be expected which will require prolonged clean intermittent catheterization to ensure bladder emptying [Kuo et al., 2004; Popat et al., 2005|; Kuo et al., 2005; Sahai et al., 2007]. Open-label trials which used lower doses (100 U of Botox®) reported a lower incidence of this complication [Schmid et al., 2006; Kuo et al., 2007].

Although it is a concern frequently raised, at this moment there is no evidence that repeated BONT-A injections cause detrusor atrophy or bladder wall fibrosis. Whether Dysport® or Botox® was used repeated injections in NDO patients in the short to medium term did not decrease bladder compliance, which would presumably be the case if fibrosis were to develop [Del Popolo et al., 2008; Reitz et al., 2007].

Histological inspection of injected bladders did not show inflammatory changes, fibrosis, or dysplasia after repeated treatments and independently of the neurogenic or non-neurogenic origin of the detrusor overactivity [Haferkamp et al., 2004; Compérat et al., 2006; Apostolidis et al., 2008]. Rather the reverse, one study demonstrated that NDO patients treated with BONT-A had less fibrosis than nontreated patients [Compérat et al., 2006]. Curiously, the presence of eosinophilic infiltrate was shown to increase in specimens of patients receiving multiple treatments, a finding that could not be fully explained [Apostolidis et al., 2008].

i) Cost-effectiveness of BONT-A in NDO patients

Economic aspects of BONT-A are a concern due to the price of the drug and the need for repeated cystoscopies, very often performed under general anaesthesia and under close monitoring to detect and treat eventual episodes of autonomic dysreflexia. Nevertheless, In UK, in a cohort of 101 patients with detrusor overactivity, 63 of whom of neurogenic origin, BONT-A treatment was shown to be cost-effective in both NDO and IDO cases [Kalsi et al., 2006].

Costs were based on the resources used by typical patients in UK and in the cost-effectiveness of 200-300 U BONT-A (Botox®) compared with standard care [Kalsi et al., 2006]. In Germany BONT-A (Botox®) treatment halved costs for incontinence aids and for urinary tract infection treatment in 214 NDO patients [Boy et al., 2008].

j) BONT-B

Some humans repeatedly injected with BONT-A may develop resistance to the toxin, possibly due to antibody formation. Although this event seems very rare in the case of bladder injections, a minimum interval of three months between two BONT-A injections is generally recommended to decrease its occurrence. If resistance appears, recent reports [Dykstra et al., 2003; Pistolesi et al,, 2004; Reitz et al., 2004] investigated the replacement of BONT-A serotype by BONT-B. At this moment, empiric doses of BONT-B are being used, as there are no clear potency equivalents for the two serotypes and between BONT-B brands.

In three patients with spinal NDO, bladder injection of 5000 UI [Pistolesi et al., 2004] or 7500 UI [Reitz and Schurch, 2004] of BONT-B (Neurobloc®) restored bladder function for six months [Reitz and Schurch, 2004]. Interestingly, one patient experienced dry mouth and dry eyes that resolved within 20 days. As this side effect was not reported after bladder BONT-A application, it is possible that different toxin serotypes have some different degrees of organ affinity. Dykstra et al. [2003] carried on a dose escalation study with BONT-B (Miobloc®) in 15 female patients with OAB. They used doses of 2500, 3750, 5000, 10,000, and 15,000 U injected at 10 sites. Only one patient failed to respond, and a clear dose-dependent effect was observed, with the longest response seen in those injected with 15,000 U. Two patients, both injected with 15,000 U, experienced dry mouth and general malaise. In another study involving IDO and NDO patients, in which BONT-B (Neurobloc®) 5000 U were used, Hirst and coworkers [2007] observed a limited duration of action, with most of the symptomatic beneficial effects wearing off by 10 weeks in most of the patients. The short duration of action for BONT-B at safe doses may, therefore, limit the clinic usefulness of this serotype.

2. CAPSAICIN AND RESINIFERATOXIN (RTX)

a) Rationale for intravesical vanilloids

The rationale for intravesical vanilloid application in patients with DO was offered by the demonstration that capsaicin, following bladder C-fiber desensitization, suppresses involuntary detrusor contractions dependent upon a sacral micturition reflex [de Groat et al., 1997]. The C-fiber micturition reflex is usually inactive but it was shown that it is enhanced in patients with chronic spinal-cord lesions above sacral segments [de Groat et al., 1997] in those with chronic bladder outlet obstruction [Chai et al., 1998] and in those with IDO [Silva et al., 2002]. In the bladders of NDO patients, the enhancement of the micturition reflex is accompanied by an increase in the number of sub-urothelial C-fibers expressing TRPV1 [Brady et al., 2004]. Curiously, NDO patients who responded better

to intravesical RTX exhibited a significant decrease in the density of TRPV1 immunoreactive fibers, whereas non-responders experience a non-significant variation [Brady et al., 2004]. A decrease in TRPV1 expression in urothelial cells of NDO patients was also demonstrated after intravesical application of RTX [Apostolidis et al., 2005].

Changes in sub-urothelial C-fiber innervation expressing neuropeptides [Smet et al., 1997] or TRPV1 [Liu et al., 2007] were also reported in patients with sensory urgency. In IDO patients, responders to intravesical RTX are closely associated with the over-expression of the receptor in the bladder mucosa [Liu et al., 2007]. In women with sensory urgency, TRPV1 mRNA expressed in trigonal mucosa was not only increased but also inversely correlated with the bladder volume at first sensation of filling during cystometry further indicating that TRPV1 plays a role in premature bladder sensation [Liu et al., 2007].

b) Intravesical capsaicin

Intravesical capsacin for NDO was studied in six non-controlled [Fowler et al., 1992; Fowler et al., 1994; Geirsson et al., 1995; Das et al., 1996; Igawa et al., 1996, Cruz et al., 1997, De Ridder et al., 1997] and 1 controlled clinical trial [de Seze et al., 1998]. Capsaicin was dissolved in 30% alcohol and 100-125 ml (or half of the bladder capacity if lower than that volume) of 1-2 mM solutions were instilled into the bladder and left in contact with the mucosa for 30 minutes. Best clinical results were found among patients with incomplete spinal cord lesions, in whom clinical improvement could be observed in up to 70-90% the patients [Fowler et al., 1994, Cruz et al., 1997; De Ridder et al., 1997]. In patients with complete spinal cord lesions the success rate was much lower [Geirsson et al., 1995].

Only one small randomized controlled study compared capsaicin against 30% ethanol, the vehicle solution. Ten patients received capsaicin and found a significant regression of the incontinence and urge sensation. In contrast, only 1 among the 10 patients that received ethanol had clinical improvement [de Seze et al., 1998].

The pungency of alcoholic capsaicin solutions has prevented the widespread use of this compound. In particular, the possibility of triggering autonomic dysreflexia with capsaicin, especially in patients with higher spinal cord lesions has progressively restrained its use. The relevance of capsaicin might however be back with a recent observation by de Séze et al. [2006] with a new capsaicin formulation. They conducted a double blind placebo controlled study with a glucidic solution of capsaicin in 33 NDO patients. The glucidic-capsaicin treated group showed improvement both in symptoms and urodynamic parameters above the comparator arm [de Sèze et al., 2006]. The global tolerance of this new capsaicin formulation was excellent.

c) RTX in NDO

Resiniferatoxin (RTX) has the advantage over capsaicin in being much less pungent [Cruz et al., 1997]. Intravesical RTX application in NDO patients was evaluated in five small open-label studies [Cruz et al., 1997; Kuo, 2003; Lazzeri et a., 1997; Lazzeri et al., 1998; Silva et al., 2000]. Different RTX concentrations, 10 nM, 50 nM, 100 nM and 10 μM were tested. RTX brought a rapid improvement or disappearance of urinary incontinence in up to 80% of the selected patients and a 30% decrease in their daily urinary frequency.

Furthermore, RTX also increased the volume to first detrusor contraction and maximal cystometric capacity. In general, in patients receiving 50-100 nM RTX the effect was long-lasting, with a duration of more than six month being reported. In patients treated with 10 μM doses, transient urinary retention may occur [Lazzeri et al., 1998].

In a recent placebo-controlled study, the urodynamic effects of RTX in NDO patients were specifically evaluated. Only in the RTX arm was a significant increase in first detrusor contraction and maximal cystometric capacity found [Silva et al., 2005]. RTX also caused a significant improvement in urinary frequency and incontinence [Silva et al., 2005].

RTX, 600 nM was compared against BONT-A (Botox®, 300U) in a study involving 25 patients with NDO due to chronic spinal cord injury. Both neurotoxins were capable of significantly reducing the number of daily incontinence episodes and improving maximum bladder capacity, although BONT-A turned out to be more effective [Giannantoni et al., 2004].

d) RTX in IDO

The first study with intravesical RTX in IDO patients was designed as a proof-of-concept study and involved 13 patients. Intravesical RTX 50 nmol/L was associated with an improvement in volume to FDC from 170 ± 109 mL to 440 ± 153 mL at 30 days, and to 391 ± 165 mL at 90 days. An increase in mean MCC from 291 ± 160 mL to 472 ± 139 mL at 30 days and to 413 ± 153 mL at 90 days was also observed (**Figure 14**). These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency [Silva et al., 2002]. Subsequent small open label studies confirmed these observations using either a single high (50-100 nM) or multiple low (10 nM) dose approaches [Kuo et al., 2003; Dinis et al., 2004; Kuo et al., 2005].

The effect of RTX on refractory IDO was evaluated in two randomized clinical trials. One, involved 54 patients randomized to receive four weekly instillations of a low concentration RTX solutions (10 nmol/L) or the vehicle

solution, 10% ethanol in saline [Kuo et al., 2006] Three months after completing the four intravesical treatments, the RTX treated group had 42.3% and 19.2% of patients feeling much better or improved, respectively. This was significantly more than in the placebo group, 14.2% and 7.1% respectively. At six months treatment remained effective in 50% patients in the RTX group but only in 11% in the placebo group [Kuo et al., 2006]. Such clinical and urodynamic findings could not be reproduced in another study in which patients were randomly assigned to receive a single intravesical dose of 100 ml of either RTX 50 nM or placebo. Patients were followed-up only for four weeks. During this period a single 50 nM intravesical dose of RTX was not better than placebo for the treatment of women with IDO and urgency incontinence [Rios et al., 2007].

e) RTX and urgency

The involvement of bladder C-fibers in IDO has led some investigators to explore the role of these sensory afferents to the genesis of urgency. In a non-controlled study involving 12 male patients with LUTS associated with benign prostate enlargement (BPE), mean International Prostate Symptom Scores (IPSS) halved following intravesical administration of RTX (50 nmol/L). The decrease in IPSS was largely due to improvements in scores related to urgency, in addition to improvement in nocturia and frequency [Dinis et al., 2005]. In another open-label study 15 patients with intractable urgency and frequency, with or without urgency incontinence or bladder pain/discomfort, and without urodynamic evidence of DO received one single 50 nM RTX solution. A trend towards an improvement of urgency was noticed [Apostolidis et al., 2006]. In a more recent study involving first a placebo instillation and one month later a 50 nM RTX administration to 23 patients with refractory urgency, a significant decrease in the number of episodes of urgency were detected after RTX treatment when compared with the placebo treatment [Silva et al., 2007].

At the moment and probably in the near future, a lack of stable preparations of RTX available for easy bladder instillation will make further investigation of the compound difficult. Different origins of the vanilloid and different ways for preparation and storage of the solutions might have caused substantial differences in the amount of active compound effectively administered to the patients. In addition, RTX adheres to plastics, another reason to the enormous discrepancies have been observed among RTX studies, with some claiming good results and others not demonstrating any superiority of RTX over placebo. Development of new, user-friendly formulations is needed.

Capsaicin and RTX will also face the concurrence of small molecule TRPV1 antagonists that act as a blockade of TRPV1 receptors rather than desensitizing them. Some of these compounds are already entering preliminary clinical trials. The interested reader might find an extensive review on small molecule TRPV1 antagonists elsewhere [Szallasi et al., 2006]. Very recently an experimental study was presented showing that one of these compounds (GRC 6211) active by oral route could reduce frequency of bladder reflex contractions as well as spinal c-fos expression in rat models of cystitis (**Figure 15**). Interestingly in the optimal therapeutic doses, this TRPV1 antagonist had no effect on the bladder activity of intact animals [Cruz et al., 2008; Charrua et al., 2008].

X. OTHER DRUGS

1. BACLOFEN

Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex in several points along its central pathway [De Groat, 1997; Pehrson et al., 2002]. As a GABA agonist on GABA(B) receptors, baclofen was used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier [Taylor and Bates, 1979]. To overcome this inconvenience, intrathecal baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [Bushman et al., 1993]. Baldo et al. [2000] could find a rapid (24 hours) and persistent increment in the volume to first detrusor contraction and of the maximal cystometric whereas maximal detrusor pressure decreased. At ten days the volume to first detrusor contraction had increased from 143 ml to 486 ml. Contrasting with the limited published clinical experience, some recent experimental data may revive the GABAergic system as a target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of GABA(B) receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium [Pehrson et al, 2002]. In spinally intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes whereas intrathecal application of baclofen induces urethral relaxation during isovolumetric bladder contractions. These results indicate not only that GABA receptor activation in the spinal cord exerts inhibitory effects on DSD after SCT but also that decreased activation of GABA(A) receptors due to hypofunction of GABAergic mechanisms in the spinal cord might be responsible at least in part for the development of DSD after spinal cord transaction (SCT) [Miyazato et al., 2008a]. These findings are reinforced by the observation that glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased after

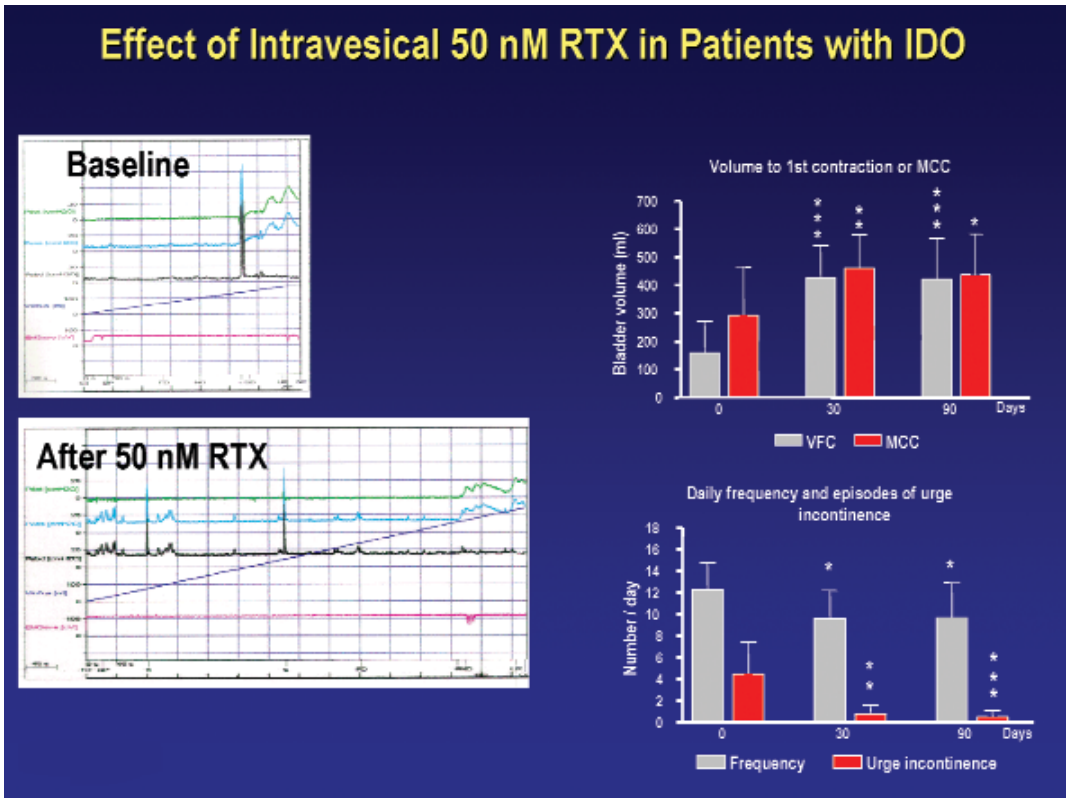

Figure 14 : Effect of intravesical resiniferatoxin in patients with idiopathic DO

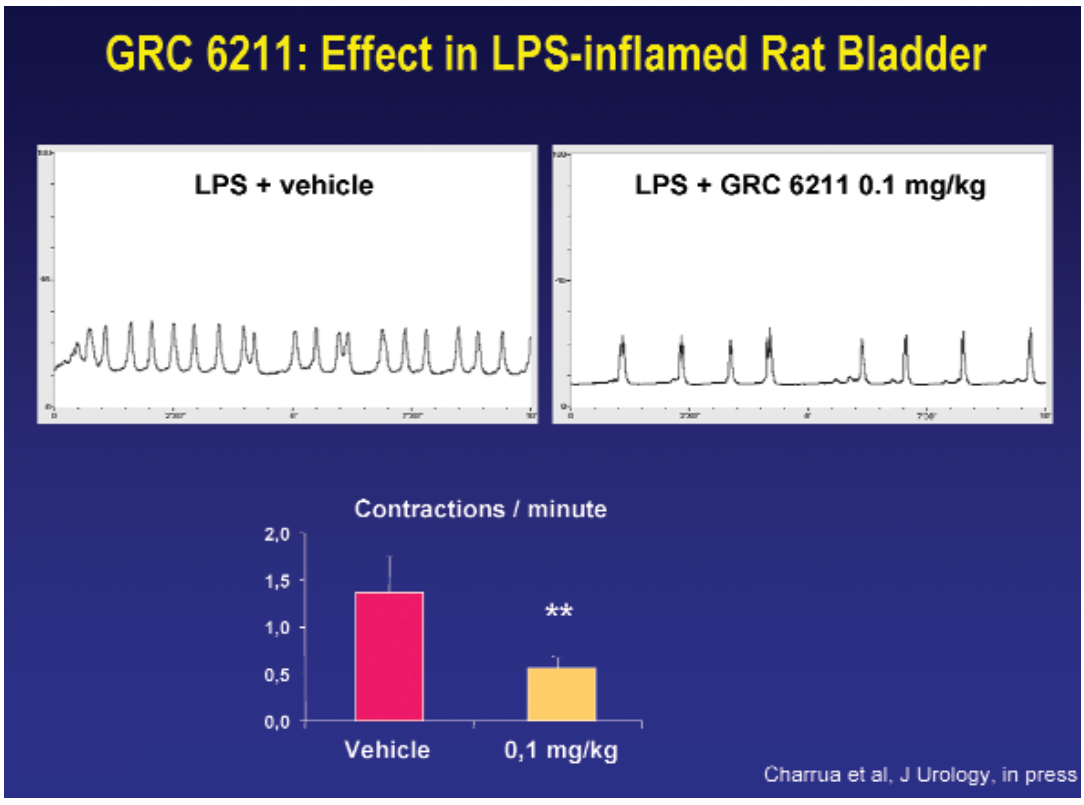

Figure 15 : Effects of the TRPV1 receptor antagonists, GRC-6211, on rat spinal c-fos expression induced by instillation of acetic acid into the bladder. Unpublished information, courtesy F. Cruz

spinal cord transection. Therefore, stimulation of spinal GABAergic mechanisms can be useful for the treatment of detrusor overactivity after spinal cord injury [Miyazato et al., 2008b]. For assessment, see Table 2.

XI. COMBINATIONS

Combining the current α_1-AR antagonists with other agents might theoretically provide improved symptom relief. One such example is the combination of α_1-AR antagonists with 5-α reductase inhibitors, which has proven to improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery [McConnell et al., 2003, Roehrborn et al., 2008]. Other combinations have also been tested with varying degrees of success. Traditionally muscarinic receptor antagonists have been contraindicated in patients with BPH due to fears of urinary retention. However, this dogma has been questioned and several studies have been performed in which α_1-AR antagonists are combined with muscarinic receptor antagonists with promising results [Athanasopoulus et al., Lee et al., 2004; 2005; 2008; Ruggieri et al, 2006; Kaplan et al., 2006; Novara et al., 2006; Mc Vary, 2007; Rovner et al., 2008]. Speculatively, several other combinations can be suggested [Andersson, 2008].

XII. FUTURE POSSIBILITIES

1. PERIPHERALLY ACTING DRUGS

a) Vitamin D_3 receptor analogues

Rat and human bladders were shown to express receptors for vitamin D [Crescioli et al., 2005], which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D_3 have also been shown to inhibit benign prostatic hyperplasia (BPH) cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [Crescioli et al., 2002; 2003; 2004]. Experiments in rats with bladder outflow obstruction [Schröder et al., 2006] showed that one of the analogues, BXL-628 (elocalcitol), at non-hypercalcemic doses, did not prevent bladder hypertrophy, but reduced the decrease in contractility of the bladder smooth muscle which occurred with increasing bladder weight [Schröder et al., 2006]. The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [Morelli et al., 2007]. Upregulation of his pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO [Peters et al., 2006; Christ and Andersson, 2007]. The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that elocalcitol was able to arrest prostate growth within 12 weeks in men aged>or=50 years with prostatic volume > or = 40 ml [Colli et al., 2006]. In an RCT enrolling 120 female patients with OAB, where the primary endpoint was an increase in the mean volume voided, a significant increase vs placebo (22% vs 11%) was demonstrated [Colli et al., 2007]. Whether or not vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB, requires further RCTs.

2. CENTRALLY ACTING DRUGS

Many parts of the brain seem to be activated during storage and voiding [see, Griffiths 2007; Fowler et al., 2008; Griffiths and Tadic, 2008], and there is increasing interest in drugs modulating the micturition reflex by a central action [Andersson and Pehrson, 2003]. Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples. However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OAB, since selective actions may be difficult to obtain. Holstege [2005], reviewing some of the central mechnisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that “the problem in OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level.”

a) Gonadotropin-releasing hormone antagonists

The beneficial effects of the 5α-reductase inhibitors, finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example, antiandrogens or gonadotropin-releasing hormone (GNRH; also known as luteinizing hormone-releasing hormone: LHRH) agonists is either poor or at the expense of unacceptable side effects such as medical castration associated with hot flushes, decrease of potency and libido, and negative effects on bone density following long-term androgen ablation [Schroeder et al. 1986; Peters et al 1987; Bosch et al., 1989; Eri and Tveter, 1993]. With LHRH antagonists submaximal, non-castrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus avoiding medical castration.

Debruyne et al. [2008] demonstrated in a phase 2 RCT that the LHRH antagonist cetrorelix, given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS $\geq$ 13, peak urinary flow rates 5-13 ml/s), rapidly caused a significant improvement in the mean IPSS: the peak decrease was -5.4 to -5,9 vs -2,8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug

offered a safe and effective treatment of male LUTS. Further studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

b) Gabapentin

Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [Striano and Striano 2008]. It was originally designed as an anticonvulsant GABA (y-aminobutyric acid) mimetic capable of crossing the blood-brain barrier [Maneuf et al., 2003]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [Maneuf et al., 2003]. It has been suggested that it acts by binding to a subunit of the $\alpha_2\delta$ unit of voltage dependent calcium channels [Gee et al., 1996; Striano and Striano, 2008]. Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone et al. [2006] reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim et al. [2004] studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other $\alpha_2\delta$ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives.

c) Tramadol

Tramadol is a well-known analgesic drug [Grond and Sablotzski, 2004]. By itself, it is a weak μ-receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ-receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and noradrenaline reuptake [Grond and Sablotzski, 2004]. This profile is of particular interest, since both μ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS/OAB/DO, as shown in a placobo controlled study with duloxetine [Steers et al., 2008].

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction [Pehrson et al., 2003]. Tramadol also inhibited DO induced by apomorphine in rats [Pehrson and Andersson, 2003] – a crude model of bladder dysfunction in Parkinson´s disease. Singh et al. [2008] gave tramadol epidurally and found the drug to increase bladder capacity and compliance, and to delay filling sensations without adverse effects on voiding. Safarinejad and Hosseini [2006] evaluated in a double-blind, placebo-controlled, randomized study, the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100 mg tramadol sustained release every 12 h for 12 weeks. Clinical evaluation was performed at baseline and every two weeks during treatment. Tramadol significantly ($p<001$) reduced the number of incontinence periods per 24 hours from 3.2±3.3 to 1.6±2.8) and induced improvements in urodynamic parameters. The main adverse event was nausea. It was concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the best suitable drug for treatment of LUTS/OAB, the study suggests efficacy for modulation of micturition via the μ-receptor.

d) NK1-receptor antagonists.

The main endogenous tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control [Lecci and Maggi, 2001; Saffroy et al., 2003; Covenas et al., 2003]. NK1 receptor expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via NK1 receptors in the micturition reflex induced by bladder filling has been demonstrated [Ishizuka et al., 1994] in normal, and more clearly, rats with bladder hypertrophy secondary to BOO. Capsaicin-induced detrusor overactivity was reduced by blocking NK1 receptor-expressing neurons in the spinal cord, using intrathecally administered substance P-saponin conjugate [Seki et al., 2002]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 1995a].

In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses, and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction [Gu et al., 2000]. Intracerebroventricular administration of NK1 and NK2 receptor antagonists to awake rats suppressed detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 2000]. Taken together, available information suggests that spinal and supraspinal NK1 and NK2 receptors may be involved in micturition control.

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting [Massaro and Lenz, 2005], significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed

incontinence (with predominantly urgency urinary incontinence), as shown in a well designed pilot RCT [Green et al., 2006]. The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total urinary incontinence and urgency incontinence episodes, and urgency episodes. Aprepitant significantly ($p<0.003$) decreased the average daily number of micturitions (-1.3±1.9) compared with placebo (-0.4±1.7) at 8 weeks. The average daily number of urgency episodes was also significantly ($p<0.047$) reduced (-23.2±32%) compared to placebo (-9.3±40%), and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. The results of this initial proof of concept study suggest that NK-1 receptor antagonism holds promise as a potential treatment approach for OAB.

C. DRUGS USED FOR TREATMENT OF STRESS URINARY INCONTINENCE

Many factors seem to be involved in the pathogenesis of stress urinary incontinence (SUI): urethral support, vesical neck function, and function of the nerves and musculature of the bladder, urethra, and pelvic floor [DeLancey, 1997; Mostwin et al., 2005]. Anatomical factors cannot be treated pharmacologically. However, women with SUI have lower resting urethral pressures than age-matched continent women [Henriksson et al, 1979; Hilton et al, 1983], 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 [Andersson, 1993; Andersson and Wein, 2004]. A contributing factor to SUI, mainly in elderly women with lack of estrogen, may be lack of mucosal function. The pharmacological treatment of SUI aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated muscles. Several drugs may contribute to such an increase [Andersson, 1988; Zinner et al., 2004], but relative lack of efficacy or/and side effects have limited their clinical use. For assessments, see **Table 4**.

Table 4. Drugs used in the treatment of stress incontinence. Assessments according to the Oxford system (modified)

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

I. α-ADRENCEPTOR AGONISTS

Several drugs with agonistic effects on α-ARs have been used in the treatment of SUI (Table 4). However, ephedrine and norephedrine (phenylpropanolamine; PPA) seem to have been the most widely used [Andersson et al., 2002]. The original Agency for Healthcare Policy and Research Guidelines (Agency for Healthcare Policy and Research, 1992) 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. The most recent Cochrane review on the subject [Alhasso et al., 2005] assessed randomized or quasi-randomized controlled trials in adults with stress urinary incontinence which included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in two, norepinephrine in three, clenbuterol in three, terbutaline in one, eskornade in one and RO 115-1240 in one). The authors concluded “there was weak evidence to suggest that use of an adrenergic agonist was better than placebo treatment”. The limited evidence suggested that such drugs were better than placebo in reducing the number of pad changes and incontinence episodes, and in improving subjective symptoms. There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination.

Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25% of subjects reported such effects, but when these consisted of effects due to adrenergic stimulation, they caused discontinuation in only 4 % of the total.

The date of the most recent amendment to this review is listed as 15 May 2007; no new trials were identified at that time. The update of 2005 [Alhasso et al., 2005] included seven new randomized controlled trials over the 2003 report, cited in the last consultation. The final statement on "what's new" reads, "The conclusions still provide limited support for the use of adrenergics but side effects may cause dropout, and some side effects may be dangerous. Further trials are needed".

Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [Andersson et al., 2002]. Kernan et al. [2000] 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 [Bent et al., 2003] 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 US decreed such a ban, a move which has survived legal appeal.

Midodrine and methoxamine stimulate α_1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate and the clinical usefulness seems to be limited by adverse effects [Alhasso et al., 2003; Radley et al., 2001; Weil et al., 1998].

Attempts continue to develop agonists with relative selectivity for the human urethra. Musselman et al. [2004] reported on a phase two randomized crossover study with Ro 115-1240, a peripheral active selective α-$_{1A/L}$-AR adrenoceptor partial agonist [Blue et al., 2004] in 37 women with mild to moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug.

II. β-ADRENOCEPTOR ANTAGONISTS

The theoretical basis for the use of ß-AR antagonists in the treatment of stress incontinence is that blockade of urethral ß-ARs may enhance the effects of noradrenaline on urethral α-ARs. Propranolol has been reported to have beneficial effects in the treatment of stress incontinence [Gleason et al., 1974; Kaisary, 1984] but there are no RCTs supporting such an action. In the Gleason et al. [1974] study the beneficial effects become manifest only after 4 to 10 weeks of treatment; a phenomenon difficult to explain. Donker and Van der Sluis [1976] reported that ß-blockade did not change UPP in normal women. Although suggested as an alternative to ß-AR agonists in patients with SUI and hypertension, these agents may have major potential cardiac and pulmonary side effects of their own, related to their therapeutic ß-AR blockade.

III. β-ADRENOCEPTOR AGONISTS

ß-AR stimulation is generally conceded to decrease urethral pressure [Andersson, 1993], but ß$_2$-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 [Fellenius et al., 1980]. Some ß-AR agonists also stimulate skeletal muscle hypertrophy – in fast twitch more so than slow twitch fibers [Kim et al., 1992]. Clenbuterol has been reported to potentiate the field stimulation induced contraction in rabbit isolated periurethral muscle preparations, an action which is suppressed by propanolol and greater than that produced by isoprotererol [Kishimoto et al., 1991]. 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. [1994] reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs, abolished by ß-AR blockade.

Yasuda et al. [1993] 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 maximum urethral closure pressure (MUCP) was from 46.0± 18.2 cm H_2O to 49.3± 19.1 cm H_2O, versus a change of -1.5 cm H_2O in the placebo group. 56/77 patients in the clenbuterol group reported some degree of improvement versus 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. [2000] investigated the effects of clenbuterol on 61 female patients with stress incontinence in a 12-week randomized study, comparing drug therapy to pelvic floor exercises. The frequency and volume of stress incontinence and the patient's own impression were used as the basis for

the assessment of efficacy. The improvement of incontinence was 76.9%, 52.6%, and 89.5% in the respective groups. In an open study, Noguchi et al. [1997] reported positive results with clenbuterol (20 mg twice daily for one month) in nine of 14 patients with mild to moderate stress incontinence after radical prostatectomy. No subsequent published reports have appeared. Further well-designed RTCs documenting the effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence.

IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS

1. IMIPRAMINE

Imipramine, among several other pharmacological effects, inhibits the re-uptake of noradrenaline and serotonin in adrenergic nerve endings. In the urethra this can be expected to enhance the contractile effects of noradrenaline on urethral smooth muscle. Gilja et al [1984] reported in an open study on 30 women with stress incontinence that imipramine, 75 mg daily, produced subjective continence in 21 patients and increased mean maximal urethral closure pressure (MUCP) from 34 to 48 mm Hg. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement.

Lin et al. [1999] assessed the efficacy of imipramine (25 mg imipramine three times a day for three months) as a treatment in 40 women with genuine stress incontinence. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of "successful treatment" was 60% (95% CI 11.8-75.2). There are no RCTs on the effects of imipramine on SUI. No subsequent published reports have appeared.

2. DULOXETINE

As mentioned previously, duloxetine is a combined serotonin and noradrenaline reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Thor et al., 1995; Katofiasc et al., 2002]. The sphincteric effects were reversed by α_1-AR (prazosin) and $5HT_2$ serotonergic (LY 53857) receptor antagonism, while the bladder effects were mediated by temporal prolongation of the actions of serotonin and noradrenaline in the synaptic cleft (**Figure 16**) (Fraser et al, 2003). Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 hours [Sharma et al., 2000].

There are many studies, including RCTs, documenting the effects of duloxetine in SUI [Norton et al., 2002; Dmochowski et al., 2003; Millard et al., 2004; Van Kerrebroeck et al., 2004; Cardozo et al., 2004; Kinchen et al., 2005; Ghoneim et al., 2005; Hurley et al., 2006; Castro-Diaz et al., 2007; Bump, 2008]. A Cochrane review of the effects of duloxetine for stress urinary incontinence in women is available, the last substantive amendment listed as 25 May 2005 [Mariappan et al., 2005]. Fifteen reports were deemed eligible for analysis, nine primary studies and six additional reports related to one or two of the primary references. An additional analysis "performed under the auspices of the Cochrane Incontinence Group" was performed on just the nine primary trials comparing duloxetine and placebo, and published separately [Mariappan et al., 2007]. The results can be summarized as follows. Subjective "cure" in the duloxetine 80 mg daily (40 mg twice daily) was higher than in the placebo group (10.8 % vs 7.7%, overall relative risk (RR) = 1.42; 95% confidence interval (CI), 1.02-1.98; p = 0.04). The estimated absolute size of effect was about three more patients cured of every 100 treated. Objective cure data, available from only one trial, showed no clear drug/placebo difference. Duloxetine showed greater improvement in I-QoL (weighted mean difference (WMD) for 80 mg: 4.5; 95% CI 2.83-6.18, p < 0.00001). Patient global impression of improvement (PGI-I) data also favored the drug (RR for better health status 1.24, 95% CI 1.14-1.36; p < 0.00001). Adverse effects in six trials were analyzed. These were reported by 71% of drug subjects and 59% of those allocated to placebo. Nausea was the most common adverse event and the incidence ranged from 23 to 25% and was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness and insomnia, overall RR 1.30 (95% CI, 1.23-1.37). Across these six trials 17% in the drug group withdrew, 4 % in the placebo arm. In the 2007 article the authors conclude by saying that further research is needed as to whether management policies incorporating duloxetine are clinically effective and cost effective compared to other current minimally invasive and more invasive approaches in patients with varying severity of SUI, and that "longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications". Hashim and Abrams [2006] suggested that in order to reduce the risk of nausea, begin with a dose of 20 mg twice daily for two weeks, then to increase to the recommended 40 mg twice daily dosage.

Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in the European Union (European Medicines Agency, Scientific Discussion, 2005) for women with moderate to severe incontinence (defined as 14 or more episodes per week). It was withdrawn from the Food and Drug Administration (FDA) consideration process in the United States for the treatment of SUI, but is approved for the treatment of major depressive disorder (20-30 mg twice daily

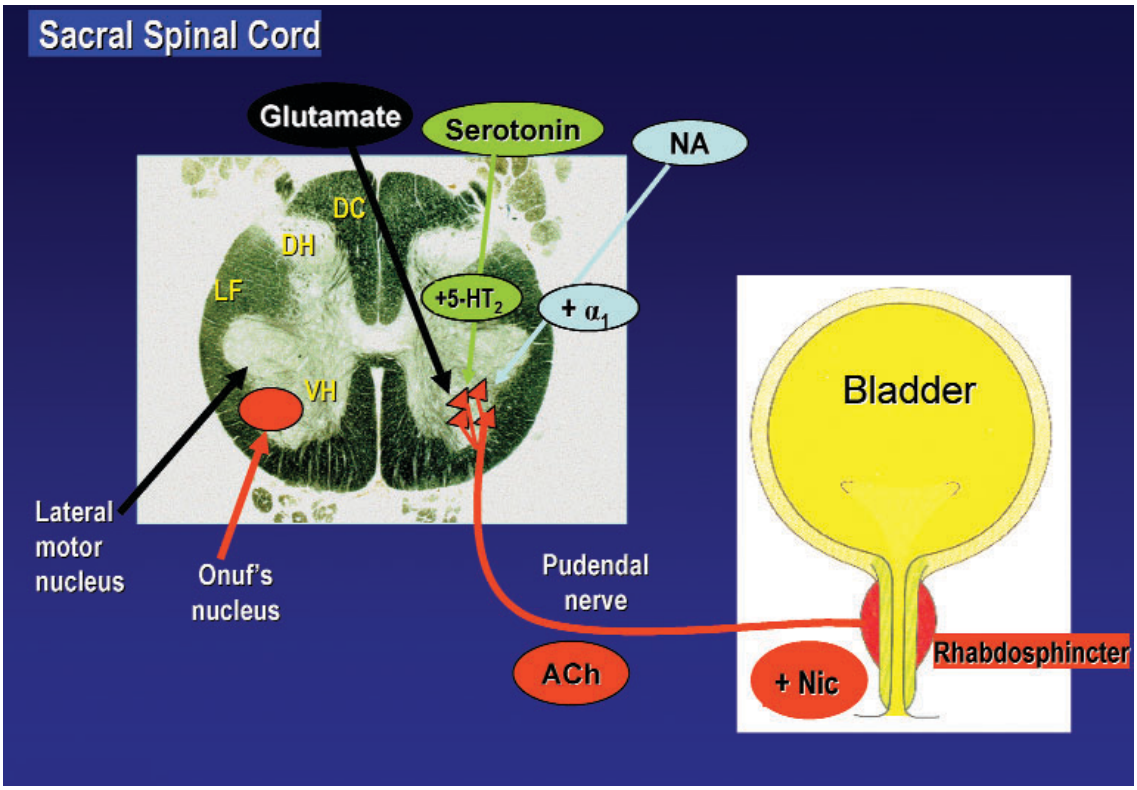

Figure 16 : Mode of action of duloxetine. The striated urethral sphincter is innervated by the pudendal nerve, which contains the axons of motor neurons whose cell bodies are located in Onuf's nucleus. Glutamate exerts a tonic excitatory effects on these motor neurons, and this effect is enhanced by noradrenaline (NA) and serotonin (5-HT), acting on α1- adrenoceptors and 5-HT2-receptors, respectively. By inhibition of the reuptake of noradrenaline and serotonin, duloxetine increases the contractile activity in the striated sphincter (nicotinic receptors: + Nic). DC = dorsal commissure; DH = dorsal horn; VH = ventral horn; LF = lateral funiculus; ACh = acetylcholine

initially, 60 mg once daily maintenance), diabetic peripheral neuropathic pain (60 mg once daily), and generalized anxiety disorder (60 mg once daily). The product information contains a "black box" warning of "increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders", noting also that "depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide" (Prescribing Information, revised December 2007, Eli Lilly and Company, Indianapolis, Indiana 46285).

Other warnings and precautions in the United States Product Information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease), orthostatic hypotension, serotonin syndrome (general statement regarding selective serotonin reuptake inhibitors (SSRIs) and SNRIs), abrupt discontinuation (may result in dizziness, paresthesias, irritability and headache), inhibitors of CYP1H2 or thioridazine (do not administer concomitantly), potent inhibitors of CYP2D6 (may increase concentration), and others.

3. MALE STRESS URINARY INCONTINENCE

Although a problem of significant magnitude, especially after total prostatectomy for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention. Tsakiris et al. [2008] searched for articles on this subject published between 1966 and June 2007 and did a generalized database search in addition. Nine trials were identified using α-AR agonists, ß$_2$-AR antagonists or SNRIs.

Only one of these included a comparison arm [Filocamo et al., 2007], 40 mg twice daily duloxetine plus pelvic floor exercises vs pelvic floor exercises (PFE) with placebo. The results suggested a positive effect of drug, but were a bit confusing. Of those patients completing the four-month trial (92/112) 78% of the drug treated patients vs 52% of those in the placebo group were dry. However, one month after the end of the study, the corresponding figures were 46% vs 73%, a shift still observed two months later.

The authors of the review article suggest further larger and well designed studies on duloxetine for this potential usage.

D. DRUGS USED FOR TREATMENT OF OVERFLOW INCONTINENCE

Urinary incontinence most often results from too much pressure generated by the bladder and/or too little resistance generated by the bladder outflow tract during the storage phase of the micturition cycle (urgency incontinence and stress urinary incontinence, respectively). More rarely, incontinence can also occur in the presence of too little pressure and/or too much resistance being developed which can lead to a markedly distended bladder and urinary retention and, secondarily, to overflow incontinence [Abrams et al., 2002].

Based upon theoretical reasoning, animal studies [Kamo et al., 2005; Gu et al., 2004] or reports of drugs which can cause overflow incontinence [Anders et al., 1985], a variety of medical approaches to the treatment of overflow incontinence have been proposed [Chutka and Takahashi, 1998; Hampel et al., 2005].

These include direct or indirect muscarinic receptor agonists and α_1-AR antagonists. The use of the former is based upon the idea that stimulation of muscarinic receptors may overcome a hypo-contractile state of the detrusor. However, a recent systematic review of controlled clinical studies on the use of direct and indirect parasympathetic agonists in patients with an underactive detrusor has shown that these drugs do not exhibit consistent benefit and may even be harmful [Barendrecht et al., 2007]. In contrast, the use of α_1-AR antagonists has repeatedly been shown to beneficial in patients with acute urinary retention [McNeill et al., 2004; 2005].

However, neither parasympathomimetic drugs nor α_1-AR antagonists have ever been tested systematically in the treatment of overflow incontinence. Accordingly, a Medline search using the keyword “overflow incontinence” did not yield a single randomized controlled trial for its treatment, and not even a case series with a meaningful number of patients was retrieved. Therefore, it must be concluded that there is no empirical basis to select medical treatments for overflow incontinence and all previously recommended treatments must be rated as “expert opinion” at best. Moreover, any medical treatment for overflow incontinence will have to be evaluated as compared to catherization or surgery but also for such comparison no clinical data are available.

E. HORMONAL TREATMENT OF URINARY INCONTINENCE

I. ESTROGENS

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 women 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 all of which play a part in the maintenance of a positive urethral pressure 1) epithelium, 2) vasculature, 3) connective tissue, 4) muscle.

Two types of estrogen receptor, (α and β) have been identified in the trigone of the bladder, urethra and vagina as well as in the levator ani muscles and fascia and ligaments within the pelvic floor [Smith et al., 1990; Copas et al., 2001; Gebhardt et al., 2001]. After the menopause, estrogen receptor α has been shown to vary depending upon exogenous estrogen therapy [Fu et al., 2003]. In addition exogenous estrogens affect the remodeling of collagen in the urogenital tissues resulting in a reduction of the total collagen concentration with a decrease in the cross linking of collagen in both continent and incontinent women [Falconer et al., 1998; Keane et al., 1997]. Studies in both animals and humans have shown that estrogens also increase vascularity in the peri-urethral plexus which can be measured as vascular pulsations on urethral pressure profilometry [Robinson et al., 1996; Endo et al., 2000; Versi and Cardozo, 1986].

2. ESTROGENS FOR STRESS URINARY INCONTINENCE

The role of estrogen in the treatment of stress urinary incontinence has been controversial despite a number of reported clinical trials [Hextall, 2000]. Some have given promising results but this may have been because they were small observational and not randomized, blinded or controlled. The situation is further complicated by the fact that a number of different types of estrogen have been used with varying doses, routes of administration and duration of treatment. For assessment, see Table 4.

Fantl et al. [1996] treated 83 hypo-estrogenic women with urodynamic stress incontinence and/or detrusor overactivity with conjugated equine estrogens 0.625 mg and medroxyprogesterone 10 mg cyclically for three months. Controls received placebo tablets. At the end of the study period the clinical and quality of life variables did not change significantly in either

group. Jackson et al. [1996] treated 57 post menopausal women with urodynamic stress or mixed incontinence with estradiol 2 mg or placebo daily for six months. There was no significant change in objective outcome measures although both the active and placebo groups reported subjective benefit.

There have been two meta-analyses performed. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee the use of estrogens to treat all causes of incontinence in post menopausal women was examined [Fantl et al., 1994]. Of 166 articles identified, which were published in English between 1969 and 1992, only six were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with urodynamic stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost, maximum urethral closure pressure increased significantly but this result was influenced by only one study showing a large effect.

In the second meta-analysis Sultana and Walters [1990] reviewed eight controlled and 14 uncontrolled prospective trials and included all types of estrogen treatment. They also found that estrogen therapy was not an efficacious treatment for stress urinary incontinence but may be useful for the often associated symptoms of urgency and frequency. Estrogen when given alone therefore does not appear to be an effective treatment for stress urinary incontinence.

Several studies have shown that estrogen may have a role in combination with other therapies e.g. α-AR agonists. However, PPA (the most widely used α-AR agonist in clinical practice) has now been restricted or banned by the US Food and Drug Administration (FDA). In a randomized trial Ishiko et al. [2001] compared the effects of the combination of pelvic floor exercise and estriol (1 mg per day) in 66 patients with post meno-pausal stress urinary 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 incontinent 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 could be used as first line treatment for mild stress urinary incontinence. Unfortunately this has not been reproduced in other clinical trials.

Thus even prior to the more recently reported secondary analyses of the heart and estrogens/ progestogen replacement study (HERS) [Grady et al., 2001] and Women's Health Initiative (WHI) [Hendrix et al., 2005] it was already recognized that estrogen therapy had little effect in the management of urodynamic stress incontinence [Al-Badr et al., 2003; Robinson and Cardozo, 2003].

3. ESTROGENS FOR URGENCY URINARY INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS

Estrogen has been used to treat post menopausal urgency and urgency incontinence for many years but there have been few controlled trials to confirm that it is of benefit [Hextall, 2000; for assessment, see Table 2]. A double blind multi centre study of 64 post menopausal women with "urgency syndrome" failed to show efficacy [Cardozo et al., 1993]. All women underwent pre-treatment urodynamic investigation to ensure that they had either "sensory urgency" or DO. They were randomized to treatment with oral estriol 3 mg daily or placebo for three months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Estriol produced subjective and objective improvements in urinary symptoms, but was not significantly better than placebo.

Another recent randomized controlled trial from the same group using 25 mg estradiol implants confirmed the previous findings [Rufford et al., 2003], and furthermore found a high complication rate in the estradiol treated patients (vaginal bleeding).

Evidence from large clinical trials

The HERS study included 763 post menopausal women under the age of 80 years with coronary heart disease and intact uteri [Grady et al., 2001]. It was designed to evaluate the use of estrogen in secondary prevention of cardiac events. In a secondary analysis 1525 participants who reported at least one episode of incontinence per week at baseline were included. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxy-progesterone acetate in one tablet (N=768) or placebo (N=757) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged or worsened. The results showed that incontinence improved in 26% of the women assigned to placebo compared to 21% assigned to hormones whilst 27% of the placebo worsened compared with 39% of the hormone group (P=0.001).

This difference was evident by four months of treatment, for both urgency and stress urinary 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 progestogen therapy was associated with worsening urinary incontinence in older post menopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.

The Women's Health Initiative (WHI) was a multi centre double blind placebo controlled randomized clinical trial of menopausal hormone therapy in 27347 postmenopausal women age 50-79 years enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23296 participants at baseline and one year. The women were randomized based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg per day of conjugated equine estrogen (CEE) plus 2.5 mg per day of medroxyprogesterone acetate (CEE+MPA), whereas those who had undergone hysterectomy received estrogen alone (CEE). At one year hormone therapy was shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline. The risk was highest for stress urinary incontinence CEE+MPA: RR, 1.7 95% continence interval) CI (1.61-2.18); CEE alone RR 2.15 mg, 95% CI, 1.77-2.62, followed by mixed urinary incontinence CEE+MPA: RR 1.49 95% CI 1.10-2.01. On CEE alone RR was 1.79 95% CI, 1.26-2.53. The combination of CEE and MPA had no significant effect on developing urgency urinary incontinence RR, 1.15; 95% CI, 0.99-1.34 but CEE alone increased the risk, RR 1.32; 95% CI, 1.10-1.58. For those women experiencing urinary incontinence at baseline frequency worsened in both active groups CEE+MPA; RR, 1.38 95% CI 1.28-1.49; CEE alone: RR, 1.47 95% CI, 1.35-1.61. Quantity of urinary incontinence worsened at one year in both active groups, CEE+MPA: RR, 1.20 95% CI, 1.06-1.76; CEE alone: RR, 1.59 95% CI, 1.39-1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities CEE+MPA: RR 1.18 95% CI, 1.06-1.32. CEE alone: RR 1.29 95% CI, 1.15-1.45 at one year. Thus based on this secondary analysis of data from a huge study conjugated equine estrogen alone or in combination with medroxyprogesterone acetate was shown to increase the risk of urinary incontinence amongst continent women and worsen urinary incontinence amongst asymptomatic women after one year of therapy.

The Nurses Health Study [Grodstein et al., 2004] was a biennial postal questionnaire starting in 1976. In 1996, 39436 post menopausal women aged 50-75 years who reported no urinary leakage at the start of the study were followed up for four years to identify incident cases of urinary incontinence. 5060 cases of occasional and 2495 cases of frequent incontinence were identified. The risk of developing urinary incontinence was increased amongst post menopausal women taking hormones compared to women who had never taken hormones (oral estrogen: RR1.54 95% CI 1.44, 1.65; transdermal estrogen: RR1.68, 95% CI 1.41, 2.00; oral estrogen with progestin: RR1.34, 95% CI 1.24, 1.44; transdermal estrogen with progestin: RR1.46, 95% CI 1.16, 1.84). After cessation of hormone therapy there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

CONCLUSIONS

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 estrogen either alone or in combination with progestogen has yielded poor results. The current level 1 evidence against the use of estrogens for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events, and therefore the secondary analyses have only been based on self reported symptoms of urinary leakage without any objective data. Despite this all of these large randomized controlled trials show a worsening of pre-existing urinary incontinence both stress and urgency, and an increased new incidence of urinary incontinence with both estrogen and estrogen plus progestogen. However, the majority of patients in all of these studies were taking combined equine estrogen and this may not be representative of all estrogens taken by all routes of administration.

In a systematic review of the effects of estrogens for symptoms suggestive of an overactive bladder the conclusion was that estrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration [Cardozo et al., 2004].

It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency and urgency incontinence may be a manifestation of urogenital atrophy in older post menopausal women rather than a direct effect on the lower urinary tract [Robinson and Cardozo, 2003]. Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal estrogen therapy there is currently no evidence that estrogens with or without progestogens should be used in the treatment of urinary incontinence.

II. OTHER STEROID HORMONE RECEPTOR LIGANDS

Progesterone and progestogens are thought to increase the risk of urinary incontinence. Lower urinary tract symptoms especially stress urinary incontinence, have been reported to increase in the progestogenic phase of the menstrual cycle [Hextall et al., 2001]. In similar studies progesterone has been shown to increase β-AR activity leading to a decrease in the urethral closure pressure in female dogs [Raz et al., 1973]. However, in the WHI there appeared to be no difference whether or not progestin was given in addition to estrogen [Hendrix et al., 2005].

Selective estrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both estrogenic and anti estrogenic effects. In the clinical trials of levormeloxifene there was a fourfold increase in the incidence of incontinence leading to cessation of the clinical trial [Hendrix et al., 2001]. However raloxifene has not been shown to have any effect at all on urinary incontinence [Waetjen et al., 2004].

There are no reported clinical trials evaluating the effect of androgens, and in particular testosterone, on urinary incontinence in women.

III. DESMOPRESSIN

The endogenous hormone vasopressin (also known as anti-diuretic hormone) fulfils two main functions, i.e. it can contract vascular smooth muscle and can stimulate water reabsorption in the renal medulla. These functions are mediated by specific vasopressin receptors of which two major subtypes exist, the V_1 and the V_2 receptors of which the V_2subtype is particularly important for the anti-diuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to a central diabetes insipidus, and genetic defects in the gene encoding the V_2 receptors can cause nephrogenic diabetes insipidus [Insel et al., 2007]. Accordingly, a (relative) lack of vasopressin is believed to be important in the pathophysiology of polyuria, specifically nocturnal polyuria, which can lead to symptoms such as nocturia [Matthiesen et al., 1996]. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioural factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist.

Based upon these considerations, vasopressin receptor agonists have been explored for the treatment of the symptom nocturia (both in children and in adults) and, more recently, for the treatment of OAB in general. Most studies related to the treatment of nocturia with vasopressin analogues have been performed using desmopressin, which shows selectivity for anti-diuretic over vasopressor effects and is available in formulations for oral, parenteral and nasal administration; an oral lyophilisate formulation [Vande Walle et al., 2006] has recently been approved in some countries. Vasopressin receptor agonists with pronounced vasopressor effects such as terlipressin have mainly been tested in other indications, e.g., acute oesophageal variceal haemorrhage.

The use of desmopressin in children with nocturnal enuresis has been comprehensively reviewed by the Cochrane Collaboration in 2002 [Glazener and Evans, 2008]. Their analysis included 47 randomized controlled trials involving 3448 children, of whom 2210 received desmopressin. According to this analysis desmopressin was effective relative to placebo in reducing bed-wetting (for example at a dose of 20 µg there was a reduction of 1.34 wet episodes/night (95% CI 1.11; 1.57), and children were more likely to become dry with desmopressin (98%) than with placebo (81%). However, there was no difference to placebo after discontinuation of treatment, indicating that desmopressin suppresses the symptom enuresis but does not cure the underlying cause. Moreover, based upon limited data, there was no clear dose-related effect, and there were too few studies to conclusively compare oral vs. nasal administration.

A Medline search using the terms “desmopressin” and “enuresis” did not yield additional studies which would change these conclusions. However, not all children respond sufficiently to desmopressin treatment, and some studies indicate that non-responders may benefit from other medications including tricyclic antidepressants or loop diuretics whereas muscarinic receptor antagonists may be ineffective in such children [De Guchtenaere et al., 2007; Neveus and Tullus, 2008].

Other studies have explored a possible role of desmopressin in the treatment of nocturia in adults. The Medline search for such studies used the terms “desmopressin” and “nocturia” and was limited to clinical studies on de novo nocturia, i.e. excluded subjects in whom childhood enuresis persisted into adulthood. Early studies have mainly investigated the use of desmopressin in the treatment of nocturia in the context of multiple sclerosis. One study with single dose administration reported reductions of nocturnal polyuria, but by design did not assess nocturia [Eckford et al., 1995]. Three placebo-controlled double-blind studies with small patient numbers (16-33 patients total per study) reported a significant reduction of nocturia [Eckford et al., 1994; Valiquette et al., 1996; Hilton et al., 1983]. For example, in the study of Valiquette et al. [1996] performed in patients with multiple sclerosis, the number of nocturia episodes were reduced from 2.35 to 1.09 and the maximum hours of uninterrupted sleep form increased from 3.74 to 5.77 hours. Other controlled studies of similar size, mostly performed in crossover designs, and with treatment for up to two weeks used daytime micturition frequency and urgency incontinence within the first six hours after desmopressin administration rather than nocturia as their primary endpoint and consistently reported efficacy of desmopressin [Kinn and Larsson, 1990; Fredrikson, 1996; Hoverd and Fowler, 1998]. While desmopressin treatment was generally well tolerated, at least in one study, four out of 17 patients discontinued treatment due to asymptomatic or minimally symptomatic hyponatremia [Valiquette et al., 1996].

Accordingly, desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients [Cvetkovic and Plosker, 2005]. In a small open-label study desmopressin was also reported to reduce nocturnal polyuria in spinal cord injury patients [Zahariou et al., 2007]. Other studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurological damage. Most studies had a short double-blind period of only two to three weeks. The recruited patient populations were based upon different criteria including having at least two nocturia episodes per night or having nocturnal polyuria. The early studies mostly used desmopressin given either orally [Asplund et al., 1999] or intranasally [Hilton and Stanton, 1982; Cannon et al., 1999], and tended to be very small (?25 patients). The original intranasal formulation has meanwhile been withdrawn from the market in several countries due to side effects and unpredictable absorption.

Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1003 screened patients, and applied higher oral doses (0.1-0.4 mg) for three weeks of double-blind treatment in adults [Mattiasson et al., 2002; Lose et al., 2004; van Kerrebroeck et al., 2007]. The three short-term placebo-controlled studies were of identical design and were designed to identify the most effective dose regimen as well as establishing criteria for selecting those patients most likely to respond safely to desmopressin. A total of 632 patients entered the dose-titration phase with 422 patients entering the double-blind phase of the three NOCTUPUS trials. The aim of the titration phase was to describe the antidiuretic effect in patients with nocturnal polyuria. It has been argued that while these studies consistently demonstrated efficacy over placebo in reducing nocturia episodes, they were performed in patients who were known to be desmopressin responders based upon initial dose-titration phases. To avoid this bias, all patients in the NOCTUPUS trials were washed out following the dose-titration and in order to be randomized it was a requirement that these patients should be back to baseline on their nocturnal diuresis before inclusion in the double-blind phase. Patients on desmopressin had a reduction in mean number of nocturnal voids (from 2.4-2.7 to 1.6-2.0), an increase in mean duration of the first sleep period (from 181-196 to 247-272 minutes) and a decrease in mean nocturnal diuresis (from 1.35 and 1.5 to 0.82 tand 0.9 ml per minute [Hashim and Abrams; 2008].

The efficacy of desmopressin for the treatment of nocturia was also confirmed in a long-term (10-12 months) open-label study involving 249 patients, which was an extension to the above mentioned randomized studies in known desmopressin responders [Lose et al., 2004]. The number of nocturnal voids was decreased throughout the study in males to 1.3-1.6 from a baseline of 3.1 and in females from 2.9 to 1.2-1.3. After the one-month follow-up at the end of the trial when treatment was stopped, the number of nocturnal voids increased following cessation of desmopressin. The mean duration of the first sleep period gradually increased in males from 157 minutes at baseline to 288 minutes at 12 months and in females from 142 at baseline to 310 minutes at 12 months. After follow-up the mean duration of the first sleep period decreased confirming that increased sleep is a real treatment related benefit of desmopressin. There was an improvement in QoL with more than 50% decrease in patients reporting nocturia as the most bothersome symptom as assessed by the ICSmale and BFLUTS questionnaires.

An open-label pilot study in a nursing home setting also reported beneficial effects of desmopressin [Johnson et al., 2006]. Taken together these data demonstrate that oral desmopressin treatment at doses of 0.1-0.4 mg reduces nocturia more effectively than placebo in known desmopressin responders. Hyponatremia appears to occur in few cases only and rarely becomes symptomatic. As the symptom of nocturia can result from many causes, it has also been studied whether desmopressin may be beneficial in patients characterized not only by nocturia. In a small, non-randomized pilot study of men believed to have BPE, desmopressin was reported to improve not only nocturia but also to reduce overall International Prostate Symptom Score (IPSS) [Chancellor et al., 1999].

An exploratory, placebo-controlled double-blind study in women with daytime urinary incontinence has reported that intranasal administration of 40 µg desmopressin increased the number of leakage-free episodes after drug administration [Robinson et al., 2004]. One double-blind, placebo-controlled pilot study in patients with OAB treated with 0.2 mg oral desmopressin reported a reduction in daytime voids and urgency episode along with an improvement of quality of life, in the first eight hours of the morning after taking desmopressin [Hashim et al., 2008]. These data indicate that desmopressin may be effective in storage symptoms, not limited to nocturia (Level 2, Grade C), and desmopressin may be used as a ‘designer’ drug in the treatment of OAB and incontinence during the daytime. Further studies are required to address this concept using the new oral lypophilisate ‘Melt’ formulation either on its own or in combination with antimuscarinics and/or alpha blockers in patients with OAB and/or BPE.

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL. However, one of the main clinically important side effects of demopressin usage is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache,

anorexia, nausea, and vomiting to loss of consciousness, seizures and death. The risk of hyponatremia seems to increase with age, cardiac disease, and increasing 24-hour urine volume [Rembratt et al., 2003] and has been reported in a meta-analysis to be about 7.6% [Weatherall et al., 2004].

Currently, there are no predictive factors about who may be at increased risk of developing hyponatraemia. However, to reduce the risk of hyponatremia, it is recommended that patients older than 79 years or with a 24-hour urine volume more than 28 ml/kg should not be given desmopressin [Rembratt et al., 2006]. In those over 65 years, serum sodium levels should be checked at baseline and at three days and seven days after commencing treatment or changing dose. It is probably good medical practice that these serum sodium measurements are also applied to those under 65 years of age, as well as checking sodium levels at three weeks post treatment or change of dose as there is the potential for levels of sodium to meanchange within a three week period [Callreus et al., 2005]. One study showed that hyponatraemia can develop after six months of administration, although not clinically significant [Bae et al., 2007], and therefore serum sodium levels may be checked at six months following administration and then six monthly thereafter. Long-term use of desmopressin does not seem to affect baseline antidiuretic hormone secretion [Bae et al., 2007]. The fluid intake will need to be limited to a minimum from one hour before the dose until eight hours afterwards and there needs to be periodic blood pressure and weight measurements to monitor for fluid overload. Desmopressin is currently the only medication licensed and available for the treatment of nocturia. It is currently licensed for the treatment of nocturia in the oral 'Melt' form and in the oral tablet form. For assessment, see Table 2.

F. CONSIDERATIONS IN THE ELDERLY

Almost all randomized controlled trials of antimuscarinics for urinary incontinence include older adults, however only two efficacy sub-analyses of older adults have been reported. The first, TOLT-IR 2 mg twice daily vs. placebo, revealed a significant decrease of 0.7 episodes of incontinence per day (an approximate 25% reduction) among 131 participants with urgency incontinence (mean age 75, range 62-92) [Malone-Lee et al., 2001]. A second, larger study comparing older adults (mean age 74 $\pm$ 6) to younger adults (mean age 51$\pm$ 10) taking TOLT-ER 4 mg, showed equivalent efficacy for the two age groups in reducing incontinence episodes (a mean decrease of 12 episodes per week, an approximate 55% reduction from baseline), with both groups showing significantly greater improvement compared to placebo (placebo response: younger 6, older 7 episodes per week) [Zinner et al., 2002].

A number of explanations exist for why antimuscarinic agents may show reduced efficacy for urgency incontinence in the elderly in the practice setting compared to the research setting. Exclusion criteria for antimuscarinic research trials generally include consumption of other antimuscarinic agents or cytochrome P450 3A4 inhibitors. In practice, older adults are a heterogeneous group, often consuming many medications that may desensitize or alter the response of the individual to antimuscarinics. As well, there is a higher prevalence of concomitant BPE among older men, with storage symptoms showing a variable response to antimuscarinics. Failure to acknowledge the multifactorial nature of urinary incontinence in the elderly often leads to sub-optimal treatment. Urgency symptoms may be exacerbated by consumption of caffeinated beverages, pelvic floor muscle weakness, diuretics or other functional and systemic dysfunctions. Treatment must address all possible etiologies, and not be limited to a solitary intervention.

The side effect profile of antimuscarinics appears to be the same for older and younger patients. Dry mouth is the most frequent adverse effect prompting discontinuation of the drug [Zinner et al., 2002]. Other more serious side effects, such as prolongation of the Q-T interval with some antimuscarinics, have not been systematically studied in the elderly population. The M_2 receptor antimuscarinics in particular have the potential to increase resting heart rate (a predictor of mortality in the elderly), however the clinical significance of this remains uncertain [Andersson and Olshansky, 2007]. In practice, older patients may already be taking other antimuscarinic drugs and thus may be habituated or intolerant to the addition of another medication in the same class and the resultant cumulative antimuscarinic load. A number of commonly used medications in the elderly possess antimuscarinic properties [Chew et al., 2008]. These include, among others, amytriptyline, clozapine, olanzepine, paroxetine, furosemide, hydrocodone, lansoprazole, levofloxacin, and metformin.

Of particular concern in the elderly is the possibility that antimuscarinic agents used to treat urgency incontinence may induce subtle or not so subtle cognitive impairment. In experimental studies, administration of scopolamine has been shown to impair memory and attention in older adults [Flicker et al., 1992; Sperling et al., 2002]. Older adults are also prone to develop hallucinations and confusion with scopolamine, and experience significantly greater impairments in delayed memory and psychomotor speed compared to younger individuals.

Antimuscarinic drugs have also been associated with the presence of mild cognitive impairment, a precursor

of dementia. The Eugenia study of aging randomly recruited 372 adults 60 years and older from Montpellier, France, and showed that antimuscarinic drug users displayed significantly poorer reaction time, attention, immediate and delayed visuospatial memory, narrative recall, and verbal fluency than did non drug users [Ancelin et al., 2006]. Oxybutynin in particular, has been shown to elicit cognitive impairments in four case reports and one small experimental study [Donellan et al., 1997; Katz et al., 1998]. The experimental study, using a double-blind, placebo-controlled cross-over design, tested a convenience sample of 12 healthy continent older adults, and revealed cognitive decrements on seven of fifteen cognitive measures resulting from oxybutynin use [Katz et al., 1998]. Impairments were observed in verbal learning, memory, reaction time, attention, concentration and psychomotor speed. In a separate sleep study, oxybutynin was found to significantly alter EEG patterns compared to placebo [Todorova et al., 2001]. There have also been several published case reports documenting the acute onset of delirium following initiation of tolterodine, in incontinent adults with and without dementia [Womack and Heilman, 2003; Salvatore et al., 2007; Edwards et al., 2002; Williams et al., 2004; Tsao et al., 2003]. These deficits resolved upon discontinuation or dose reduction of tolterodine. Two studies have been conducted using darifenacin, but only in continent volunteers [Lipton et al., 2005; Kay et al., 2006]. In the first study of 129 older adults aged 65-84, no significant effects on cognition were observed (memory scanning sensitivity, speed of reaction time, and word recognition) compared with placebo [Lipton et al., 2005]. In the second study, darifenacin was compared to oxybutynin and placebo in a randomized multicentre double-blind parallel-group 3-week study design using 150 healthy volunteers aged 60-83 [Kay et al., 2006]. Darifenacin produced no impairments compared to placebo at 3-weeks, but oxybutynin caused significant memory deterioration in delayed recall compared to the other two groups. Darifenacin was associated with significantly slower reaction times than placebo in the Divided Attention Test, but not in other tests of information processing speed. Oxybutynin also reduced accuracy scores for immediate recall in one of three tests. In the absence of more definitive data linking antimuscarinics and cognition impairment, clinicians are suggested to proceed with caution in prescribing these medications and fully weigh the risk-benefit ratio in light of other therapeutic options that can be equally effective for urgency and mixed incontinence in the elderly. If antimuscarinics are to be prescribed, a short cognitive screen (such as the Montreal Cognitive Assessment) or even a full neuropsycho-logical test battery for those patients who are concerned or at risk, before and after initiating therapy might reveal whether subtle impairments have been induced. This is especially pertinent because patients are often unaware of their memory deficits [Kay et al., 2006]. A proxy informant, such as the patient's spouse or a relative, may be able to provide more reliable information on possible cognitive changes resulting from the drugs.

A frequently asked clinical question is whether antimuscarinic agents used to treat incontinence should be contraindicated in patients with dementia already taking cholinesterase inhibitors, as the mechanisms of these two medications are diametrically opposed. No studies have examined the cognitive consequences of antimuscarinics in patients with dementia. However, a number of small studies have shown the reverse mechanism to be true, that cholinesterase inhibitors used to improve cognition in Alzheimer's disease precipitate urinary incontinence [Hashimoto et al., 2000]. A Japanese study followed 94 patients with mild to moderate dementia treated with donepezil [Hashimoto et al., 2000]. Seven patients developed urinary incontinence, although the event was transient in most patients. In Scotland, among 216 patients with Alzheimer's disease initiating treatment with a cholinesterase inhibitor, incontinence was precipitated in 6.6%, and those with existing incontinence worsened [Starr, 2007]. Epidemiologic studies also show associations between cholinesterase inhibitors and incontinence [Gill et al., 2005; Roe et al., 2002]. In a large population-based cohort study of 44,884 adults with dementia carried out in Canada, those who were dispensed cholinesterase inhibitors were more likely to subsequently receive an antimuscarinic drug for incontinence compared to those not receiving cholinesterase inhibitors (hazard ratio 1.55, 95% confidence interval 1.39-1.72) [Gill et al., 2005]. This finding was confirmed by a separate study in the U.S. documenting a two-fold risk of taking oxybutynin in dementia patients treated with donepezil compared to those not treated with donepezil [Roe et al., 2002]. This evidence suggests the competing mechanisms of the antimuscarinics and cholinesterase inhibitors may indeed have clinical consequences in some, but not all patients. Should an adverse effect be suspected, then alternate therapeutic options should be pursued. None of the other drug classes used to treat stress, urgency or overflow incontinence have undergone rigorous evaluation in the elderly, however a number of general guidelines apply. Use of α-AR agonists and tricyclic antidepressants are discouraged in the elderly due to blood pressure considerations. Uncontrolled systolic hypertension could occur with the former agents and orthostatic hypotension leading to falls with the latter. There is no evidence that hormonal agents are of benefit for urgency or stress incontinence in older women, although local estrogens may be indicated to treat dysuria resulting from concomitant vaginal atrophy. Finally, removal of any offending agents that could be contributing to incontinence (benzodiazepines, narcotics, diuretics) should be considered.

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