minimised by performing a limited resection [1015] or by performing TURP within 2 years of brachytherapy [1012]. In the latter study, two of 24 patients (8%) that underwent TURP within 2 years of treatment were incontinent and 5 of 14 patients (36%) that underwent TURP 2 years or more after brachytherapy were incontinent (p=0.04). However, others suggest that delaying TURP until 5 years after radiation can actually reduce the risk of incontinence [1016-1018].

V. CONCLUSIONS

Incontinence in the male as in the female can be broadly divided into causes related to bladder and/or sphincter dysfunction. The pathophysiology of incontinence as it relates specifically to the male is fairly well described; however advances in science and anatomy will undoubtedly provide a more intricate understanding in the future. For example, the causes of sphincter insufficiency are known (i.e. damage to muscle, nerve and/or supporting structures) but clinicians are not able to accurately assess the exact cause of sphincter insufficiency in any given patient. Therefore much of our understanding of post treatment incontinence "pathophysiology" is derived from reports of incontinence (incidence/prevalence) after surgery or radiation. In addition investigators have not adequately defined the incidence of incontinence related to interventions for prostatic disease, whether benign or malignant. Some work has been undertaken to understand and discriminate the issue of pre- and post operative related incontinence, but because of the shortened hospitalization those prospective investigations, which are mandatory for the understanding of the physiological functioning and the pathophysiology, which might become clinically significant after the intervention. Problems have been two-fold: first in defining incontinence and what is bothersome/significant and second in accurately reporting data. New technologies for the treatment of BPH have provided us with Level 1 evidence regarding the incidence of incontinence in trials comparing new technology to TURP and **Level 2** evidence through meta-analysis and prospective series. Data regarding the incidence of post-radical prostatectomy and postradiation incontinence has been less robust and of a lower quality - **level 2-4.**

H. CAUSE OF TRANSIENT INCONTINENCE IN OLDER ADULTS

I. URINARY INCONTINENCE

Transient causes probably account for one-third of incontinent cases among community-dwelling older people (>65 years old), up to one-half of cases among acutely-hospitalised older people, and a significant proportion of cases among nursing home residents [1019-1023]. Transient urinary incontinence rises suddenly, lasts less than six months, and results from reversible causes [1024]. Most causes of transient incontinence in the older population lie outside the lower urinary tract but two points are worth emphasising. First, the risk of transient incontinence is increased if, in addition to physiologic changes of the lower urinary tract, the older person also suffers from pathological changes [1025, 1026]. Overflow incontinence is more likely to result from an anticholinergic agent in a person with a weak or obstructed bladder, just as urgency incontinence is more likely to result from a loop diuretic in someone with detrusor overactivity and/or impaired mobility [1027, 1028].

This fact may explain why some controversy persists regarding some causes of transient incontinence. It also emphasises that continence depends on the integrity of multiple domains-mental state, mobility, manual dexterity, medical factors, and motivation, as well as lower urinary tract function. Although in younger individuals incontinence usually results from lower urinary tract dysfunction alone, incontinence in older patients often results from deficits in multiple domains that together result in incontinence [1023, 1029]. Attention to any one or more of these risk factors can restore continence or at least improve it. Second, although termed "transient," these causes of incontinence may persist if left untreated, and so they cannot be dismissed merely because the incontinence is of long duration.

1. QUALITY OF DATA

In older people, continence status may not be absolute, especially in those who are frail. Infrequent leakage of small amounts may appear and disappear, and reporting accuracy varies as well [1030]. Sometimes the changing status of incontinence is the initial symptom of LUTS, neurological disorder (Parkinson's disease, MS etc.), cardiac changes or diabetes. Furthermore, ethical constraints and methodological issues preclude robust investigations of the conditions commonly impugned as causes of transient incontinence. Thus, it is not surprising that evidence supporting the association between these conditions and transient incontinence consists predominantly of case reports and case series.

2. RESULTS OF LITERATURE REVIEW

Transient causes of incontinence in older people are shown in **Table 6** and can be recalled using the mnemonic DIAPPERS (Delirium, Infection, Atrophic vaginitis, Pharmaceuticals, Psychological condition, Excess urine output, Reduced mobility, Stool impaction) [1024, 1031-1033].

Table 6: Transient Incontinence in Older Adult DIAPPERS

Delirium
Infection
Atrophic vaginitis
Pharmaceuticals
Psychological condition
Excess urine output
Reduced mobility
Stool impaction

a) Delirium

"D" is for delirium, a confusional state characterised by fluctuating inattentiveness and disorientation. Its onset occurs over hours to days, as contrasted with dementia, which develops over years. Delirium can result from almost any medication and from virtually any acute illness, including congestive heart failure, deep vein thrombosis, or infection. Many of these conditions may present atypically in older patients, and if the patient becomes confused because of them, incontinence may be the first abnormality detected [1034]. Delirium leads the list because, if unrecognised, it is associated with significant mortality [1035]. Thus, in this case, meticulous medical evaluation - not cystometry - is crucial [1036].

b) Urinary infection

Symptomatic urinary infection is another cause of incontinence, although it is supposing uncommon one [1022]. However, asymptomatic urinary infection, is much more common in older people [1037, 1038]. Women with recurrent urinary tract infection had the highest increase in UI by 230% for weekly UI [1039] and for monthly UI [1040], 220% for UI in the past year [936], and by 470% for ever having UI [1041]. In addition Arya at al. reported that women with recurrent UTIs have greater urinary frequency and increased perceived bladder sensation in the absence of an active infection than control women [1042].

c) Atrophic vaginitis

Atrophic vaginitis in older women is frequently associated with lower urinary tract symptoms, which occasionally include incontinence [1043]. As many as 80% of such women attending an incontinence clinic are reported to have physical evidence of atrophic vaginitis, characterised by vaginal mucosal atrophy, friability, erosions, and punctuate haemorrhages. While the evidence supporting the use of oestrogens in lower urinary tract dysfunction remains controversial there are considerable data to support their use in urogenital atrophy and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritus and dyspareunia, greater improvement in cytological findings, and higher serum oestradiol levels [1044]. Atrophic vaginitis has been associated with urgency and occasionally a sense of "scalding" dysuria, but both symptoms may be relatively unimpressive. More recent epidemiological and clinical studies have called these beliefs into question since they have demonstrated an association with systemic oestrogen treatment and the onset of incontinence [Sievert et al ICI-RS paper 2012]. Unfortunately, limitations in their design allow for the possibility of both bias and confounding factors. Further research is warranted.

d) Medications

Pharmaceuticals are one of the most common causes of incontinence in older people, with several categories of drugs commonly implicated [1045, 1046]. Of note, many of these agents are also used in the treatment of incontinence, underscoring the fact that most medications used by older people are "double-edged swords." The first category of relevant drugs is the long-acting sedative/hypnotics, such as diazepam and flurazepam, which can cloud an older patient's memory. "Loop" diuretics, such as furosemide or bumetanide, by inducing a brisk diuresis, can also provoke leakage. Drugs with anticholinergic side effects are a particular problem and include major tranquilizers, antidepressants, anti-Parkinsonian agents (e.g., benztropine mesylate or trihexyphenidyl), first generation (sedating) antihistamines, antiarrhythmics (disopyramide), antispasmodics, and opiates. By decreasing detrusor contractility, they can cause urinary retention and overflow incontinence. They also can cause confusion. Anticholinergic agents are particularly important to ask the patient about for two reasons. First, older patients may often take more than one of them at a time. Second, they are contained in many non-prescription preparations that older people frequently take without consulting a physician.

Adrenergically-active agents have also been associated with incontinence. Many alpha-adrenoreceptor antagonists (used mainly for treatment of hypertension) block receptors at the bladder neck and may induce stress incontinence in women [1047]. Older women are particularly at risk because their urethral length and closure pressure normally decline with age. Thus, prior to considering other interventions for stress incontinence in a woman taking such a drug, substitution of an alternative agent should be tried and the incontinence re-evaluated. Calcium channel blockers can cause incontinence. As smooth muscle relaxants, they can increase residual volume, especially in older adults with impaired detrusor contractility. The increased residual urine may occasionally lead to stress incontinence in women with a weak urethral sphincter, or to overflow incontinence in men with concurrent urethral obstruction. Finally, angiotensin converting enzyme inhibitors, by inducing cough (the risk of which is age-related), may precipitate stress incontinence in older women whose urethra has shortened and sphincter weakened with age [1048].

e) Diuresis

Excess urinary output can also cause incontinence, especially in individuals with impaired mobility, mental state, or motivation, particularly if they also have detrusor overactivity. Causes of excess output include excess intake, diuretics (including theophylline-containing fluids and alcohol), and metabolic abnormalities (e.g., hyperglycemia and hypocalcaemia). Nocturnal incontinence can be caused or exacerbated by disorders associated with excess nocturnal excretion, such as congestive heart failure, peripheral venous insufficiency, hypoalbuminemia (especially in malnourished older people), and drug induced peripheral oedema associated with NSAIDs, thiazolidinediones, and some calcium channel blockers (e.g., dihydropyridines such as nifedipine, isradipine, and nicardipine). In addition certain foods are natural diuretics like asparagus, parsley, beetroot, grapes, green beans, leafy greens, pineapple, pumpkin, onion, leeks, and garlic, as well as juices such as orange juice. The role of caffeine and timing of drinking fluids (e.g. in the evening or before bedtime) is still not clear, but should nonetheless be considered a possible contributing cause for nocturia and nocturnal incontinence, whereas it is known to increase the bowel motility [1049-1051].

f) Restricted mobility

Restricted mobility is an easily understood but frequently overlooked cause of incontinence [1052]. In addition to obvious causes, restricted mobility may be associated with orthostatic or postprandial hypotension, poorly-fitting shoes, poor physical state, or fear of falling, all of which are common geriatric conditions. All of these reasons together with restricted mobility might be the cause of incontinence due to nocturia.

g) Nocturia

For frail/older people with bothersome nocturia, assessment should focus on identifying the potential underlying cause(s), including (GR: C):

- Nocturnal polyuria;
- Primary sleep problem (including sleep apnoea);
- Conditions resulting in a low voided volumes (e.g. elevated post-voiding residual) co-morbidity.

Post-void residual (PVR) volume

A post-void residual volume (PVR) is impractical to obtain in many care settings. However, there is compelling clinical experience for measuring PVR in selected frail/ older persons with:

- Diabetes mellitus (especially if longstanding);
- Previous episodes of urinary retention or history of high PVR;
- Recurrent UTIs;
- Medications that impair bladder emptying (e.g. anticholinergics);
- Chronic constipation;
- Persistent or worsening UI despite treatment with antimuscarinics;
- Previous urodynamic study demonstrating detrusor underactivity and/or bladder outlet obstruction (GR: C).

h) Faecal impaction

II. FAECAL INCONTINENCE

1. BACKGROUND

The prevalence of faecal incontinence in older adults ranges from 3.7-27% in community dwelling elderly persons to over 50% in nursing home residents [602, 603, 605, 606, 636, 637, 672, 709, 1053, 1054]. In addition faecal incontinence is a common reason for referral of elderly persons to a nursing home. [565, 1055] Underreporting is an issue with both urinary and faecal incontinence [656, 1054, 1056, 1057]; memory-loss and dementia exacerbate that the problem in the elderly. While the prevalence is fairly well documented, the percentage of those people who have transient as opposed to long-term incontinence is not well known. There is significant financial and social cost associated with management of faecal incontinence in the community and nursing homes [607, 656, 1058-1062]. Identifying transient and remediable causes would benefit patients, caregivers and the health care system. One confounding aspect in the discussion of transient incontinence is the largely unknown natural history of faecal incontinence. It is clear that the symptom is intermittent in some patients and spontaneously resolves in others. As noted earlier in this chapter, continence for stool is a complex mechanism involving the consistency and transit time of stool, rectal capacity and pelvic floor function. Rectal capacity and pelvic floor function are less likely to undergo transient changes but stool consistency, transit time of the intestinal tract and other medical conditions may change. It is well established that the prevalence of faecal incontinence increases with age, even if the mechanism is not completely understood; the increase in prevalence suggests progressive deterioration of some aspect of anorectal function [602-604, 606, 607, 636, 640, 656]. Theoretically, alternations in stool consistency, transit time and medical conditions would be more likely to result in incontinence in the elderly although that there is minimal confirmatory data.

The literature on transient faecal incontinence is limited with a dominance of case series and retrospective reports. Some information is inferred from data from large studies of prevalence and risk factors. Treatment recommendations are frequently based upon an empirical rather than evidence-based approach.

2. CAUSES

Faecal incontinence occurs when the propulsive forces in the colon and rectum overwhelm the resistant forces of the pelvic floor. Continence for stool requires the receipt and recognition of the urge to defaecate, mobility to reach the toilet in time, and the ability to postpone defaecation until reaching the bathroom.

Delaying defaecation requires sufficient rectal capacity and compliance and adequate neurologic and anal sphincter function.

a) Altered mental status

Acute medical illness, hospitalisation, surgery and medications such as opiates and sedatives may result in delirium or disorientation in the elderly. The reported rates of mental status changes to as high as 74% after surgery and from 11 to 42% during medical hospitalisation [1063, 1064]. In a systematic review of delirium associated with medication, opiods, benzodiazepines, and dihydropyridines were found to clearly increase the risk of delirium. There was uncertainty regarding antihistamines, tricyclic antidepressants, anti-Parkinson mediations, steroids and non-steroidal anti-inflammatory medication [1065]. Delirium, confusion and other transient changes in cognitive function may impair a patient's ability to recognise the urge to defaecate and/or their motivation to remain continent. The limited investigations of the relationship between delirium and incontinence studied patients with chronically altered mental status; any relationship of acute delirium and/or confusion with faecal incontinence is inferred from those data. Studies of the impact of delirium on continence show that delirium plays an important role in the development of incontinence [670, 708]. The impact of altered mental status on continence has also been inferred from studies showing improvement in continence with scheduled toileting programs [1066, 1067]. Ignoring the urge to defaecate combined with the effect of medications may result in faecal impaction followed by incontinence. Delirium may require the use of restraints. Need for a restraint has been reported as an independent factor in incontinence [709].

b) Impaired mobility

Lack of adequate mobility may prevent a patient from reaching the bathroom in time to avoid incontinence. In addition to the causes described in the urinary incontinence section, musculoskeletal ailments, such as arthritis and bone fractures, occur more commonly in the elderly and limit mobility. During the recovery phase from joint replacements ambulation may be slow and unsteady. Acute neurological conditions such as stroke may affect a patient's gait as well as debilitated states from other illness. Faecal incontinence is fairly common (up to 30% in first week) immediately after a stroke; with rehabilitation, the rate decreases [605, 681, 1068]. The use of anti-cholingeric medication and requiring assistance to reach the toilet were significant independent factors [681]. For patients temporarily requiring assistance to reach the bathroom, the timeliness of the assistant may affect their continence.

c) Stool consistency

Change in stool consistency affects continence; both constipation and diarrhoea may result in faecal incontinence.

d) Diarrhoea

Loose stool is clearly a risk factor for incontinence [606, 608, 636, 640, 674, 1054, 1068-1070]; one study identified loose stool as the most important independent risk factor [607]. Any condition or medication resulting in loose stools may also lead to incontinence including acute infection, intestinal inflammatory processes, medication and supplements (**Table 7**). Medications with the side effects of diarrhoea and/or steatorrhea may result in faecal incontinence. **Table 8** lists the medications, which cause diarrhoea or steatorrhoea with reasonable frequency.[605, 1071, 1072] Laxatives and the medications used for bowel preparation for colonoscopy and surgery frequently result in temporary incontinence in older patients.

Although rarely described in the literature, intuitively cessation of the causative medication should decrease the incontinence. In a case report, withdrawal of the offending medication, metformin, resolved the incontinence.[648]

e) Constipation

Paradoxically faecal incontinence may occur in patients with faecal impaction. [641, 662, 1073-1075] Immobility, inadequate dietary and fluid intake, depression, metabolic disorders neurological conditions, connective tissue disorders and medications contribute to constipation.[641, 662] Impaction may result in overflow incontinence with loose stool leaking around the faecal bolus. [663] Evaluation of impacted patients compared to elderly controls revealed similar resting and squeeze pressures although both groups had lower pressures than younger healthy controls. However perianal and rectal sensation was impaired in 74% of the impacted patients.[613, 1076] The theory is the patients with impaired sensation do not experience the urge to defaecate with the typical volume of stool. The stool bolus causes the usual reflex relaxation of the internal anal sphincter but the lack of perception prevents the normal contraction of the external sphincter muscle. Incontinence is often aggravated by the use of laxatives to relieve constipation.

Table 7:Causes of Loose Stool

Infection
• Acute viral or bacterial gastroenteritis
• Clostridium difficile colitis
Inflammation
• Ischaemic colitis
• Inflammatory bowel disease flare (ulcerative colitis, Crohn's colitis)
• Microscopic colitis
Medications
• Supplements/dietary elements
• Caffeine
• Fructose
• High dose probiotics
• Magnesium
• Omega-3 fatty acids
• Orlistat
Tube feedings

Table 8: Medications causing diarrhoea

Alpha-glucosidase inhibitors
Antibiotics
Antiretroviral therapy
Biguanides (e.g. Metformin)
Bile acids
Chemotherapy agents
Cholinergic drugs
Colchicine
Diacerein
Digoxin
Immunosuppressive agents
Mesalamine
Metocopramide
Non-steroidal anti-inflammatory agents
Orlistat
Osmotic laxatives
Prostaglandins
Selective serotonin reuptake inhibitors
Ticlopidine
Tyrosine kinase inhibitors

III. SUMMARY

Apart from data for alpha-adrenergic agents (**Level of Evidence = 2**), the level of evidence for most of these causes is Level 3-4. Nonetheless, because many are easily addressed and contribute to morbidity beyond the lower urinary tract and perianal area, they are worth identifying even if the evidence is not strong.

IV. RECOMMENDATIONS

Despite the lack of robust data about the incidence and causes, transient urinary and faecal incontinence are clinically common problems. Since in most cases treatment is relatively straightforward, it is important to consider the causes discussed in this section when elderly patients present with new onset incontinence. Moreover, addressing them may improve the incontinence even if it does not eliminate it, and it may make the incontinence more amenable to subsequent therapy. (**Grade of recommendation C**)

V. RESEARCH PRIORITIES

Further research should be performed on the mechanisms, prevalence, incidence, and remission rates of each of the known causes of transient incontinence, and possible additional causes should be identified as well. Since the clinical circumstances of older people are heterogeneous, studies should be conducted among several subgroups, including independent and homebound and community-dwelling older people, bedbound and mobile institutionalised older people and acutely hospitalised older people.

LIST OF ABBREVIATIONS

ACS	American College of Surgeons
ANS	Autonomic Nervous System
ACh	Acetylcholine
AChE	Acetylcholinesterase
ASR	Anal Sphincter Rupture
ATP	Adenosine Triphosphate
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
CNS	Central Nervous System
CI	Confidence Interval
cAMP	Cyclic Adenosine Monophosphate
DO	Detrusor Overactivity
DM	Diabetes Mellitus
DSD	Detrusor Sphincter Dyssynergia
EMG	Electromyography
EAS	External Anal Sphincter
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IAS	Internal Anal Sphincter
ICI	International Consultation on Incontinence
IPSS	International Prostate Symptom Score
ISD	Intrinsic Sphincter Deficiency
LAM	Levator Ani Muscle
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NGF	Nerve Growth Factor
OAB	Overactive Bladder
OR	Odds Ratio
PMC	Pontine Micturition Centre
PFD	Pelvic Floor Dysfunction
PFM	Pelvic Floor Muscle
POP	Pelvic Organ Prolapse
POP-Q	Pelvic Organ Prolapse Quantification
PNTML	Pudendal Nerve Motor Terminal Motor Latency
RRP	Radical Retropubic Prostatectomy
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative Risk
SSRI	Selective Serotonin Re-uptake Inhibitor
SUI	Stress Urinary Incontinence
TURP	Transurethral Prostatectomy
TUIP	Transurethral Incision of the Prostate
TTX	Tetrodotoxin
VLPP	Valsalva Leak Point Pressure
UI	Urinary Incontinence
USI	Urodynamic Stress Incontinence

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Committee 8

Pharmacological Treatment of Urinary Incontinence

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CONTENTS

Pharmacological Treatment of Urinary Incontinence

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Christopher R Chapple, Linda Cardozo, Francisco Cruz, Christian Gratzke, Kyu-Sung Lee, Cara Tannenbaum, Alan J Wein

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. These structures form 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; see, Andersson and Michel., 2011]. 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, 2012].

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 2007; 2011c; Colli et al., 2007; Athanasopoulos and Cruz, 2011].

In this report, we update the recommendations from the 2008 International Consensus meeting [Andersson et al., 2009]. The most relevant information obtained since the last meeting is briefly 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].

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

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

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 (**Figures1-4**). 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; Beckel and Holstege, 2011]. Studies in humans and animals have identified areas in the brainstem and diencephalon (**Figure 5**) that are specifically implicated in micturition control, including Barrington's nucleus or the pontine micturition center (PMC) in the dorsomedial pontine tegmentum [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 [Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Griffiths et al., 2007; 2008; Hruz et al., 2008; Mehnert et al., 2008; Tadic et al., 2008; Griffiths, 2011].

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. These nerves are parts of reflex pathways, which either keep the bladder in a non-contracted 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; Beckel and Holstege, 2011]. 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].

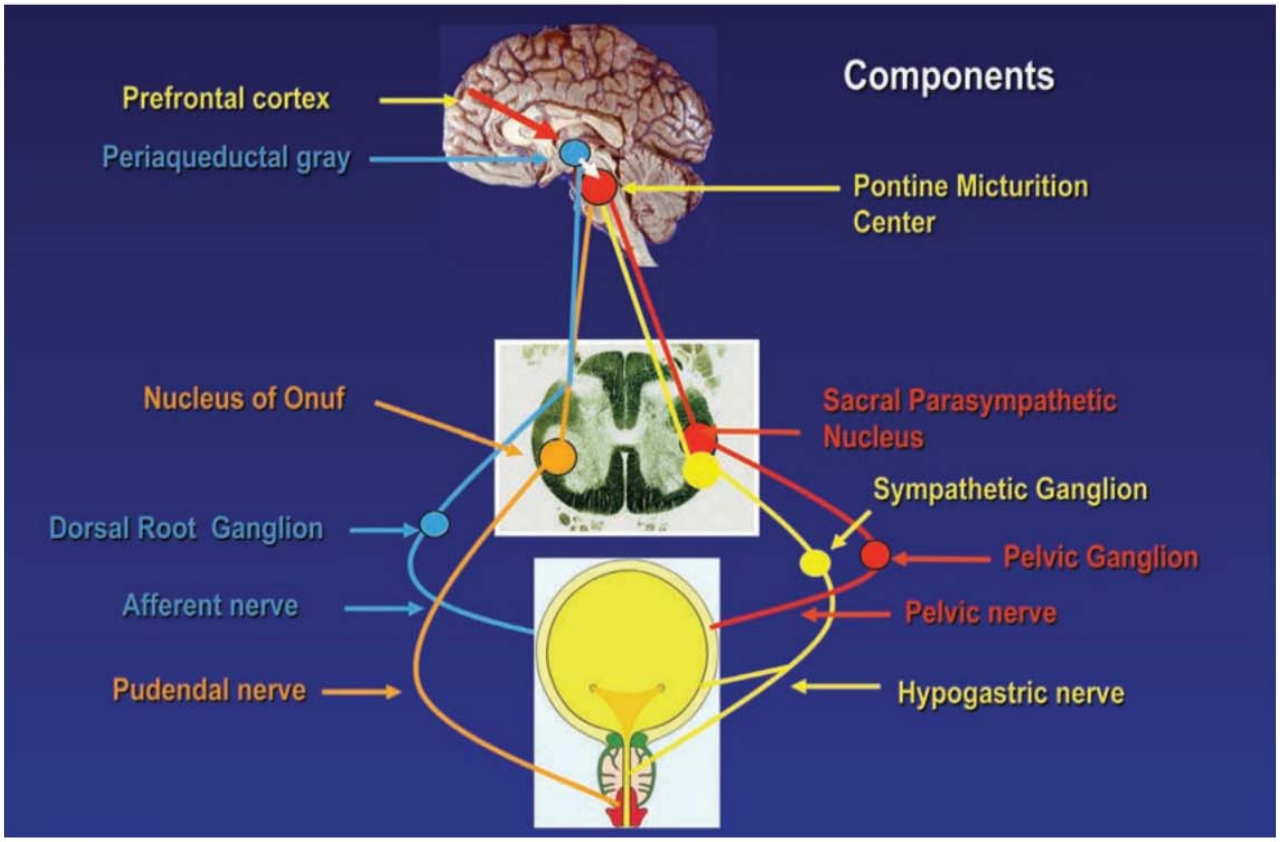

Figure 1 : Components of the micturition reflex.

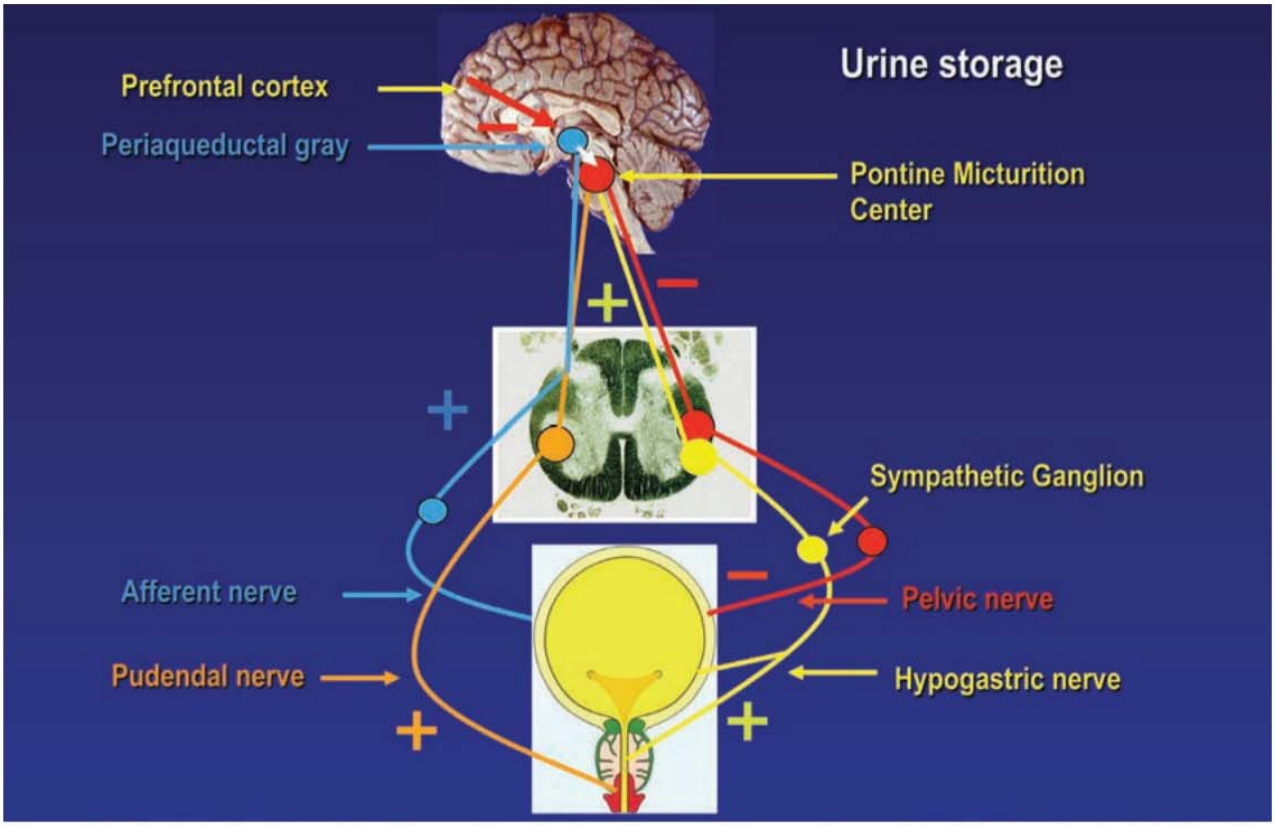

Figure 2 : Activity in the micturition reflex during storage. The pontine micturition center is inhibited by impulses from the prefrontal cortex, afferent impulses unable to initiate micturition. Activities in the hypogastric and pudendal nerves keep the bladder relaxed and the outflow region contracted.

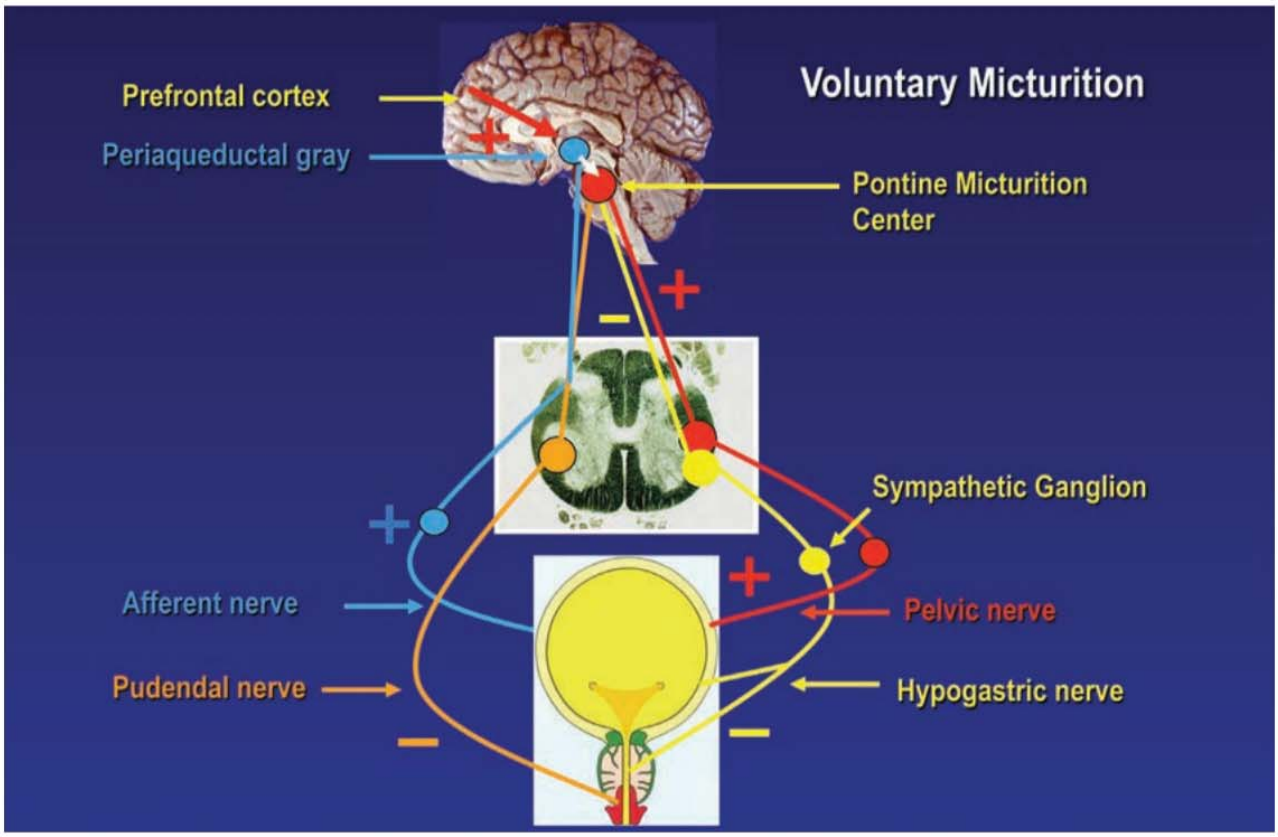

Figure 3 : Activity in the micturition reflex during voluntary voiding. The inhibitory impulses from the prefrontal cortex pontine micturition center are removed and afferent impulses are able to initiate micturition. Activities in the hypogastric and pudendal nerves are inhibited, the outflow region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

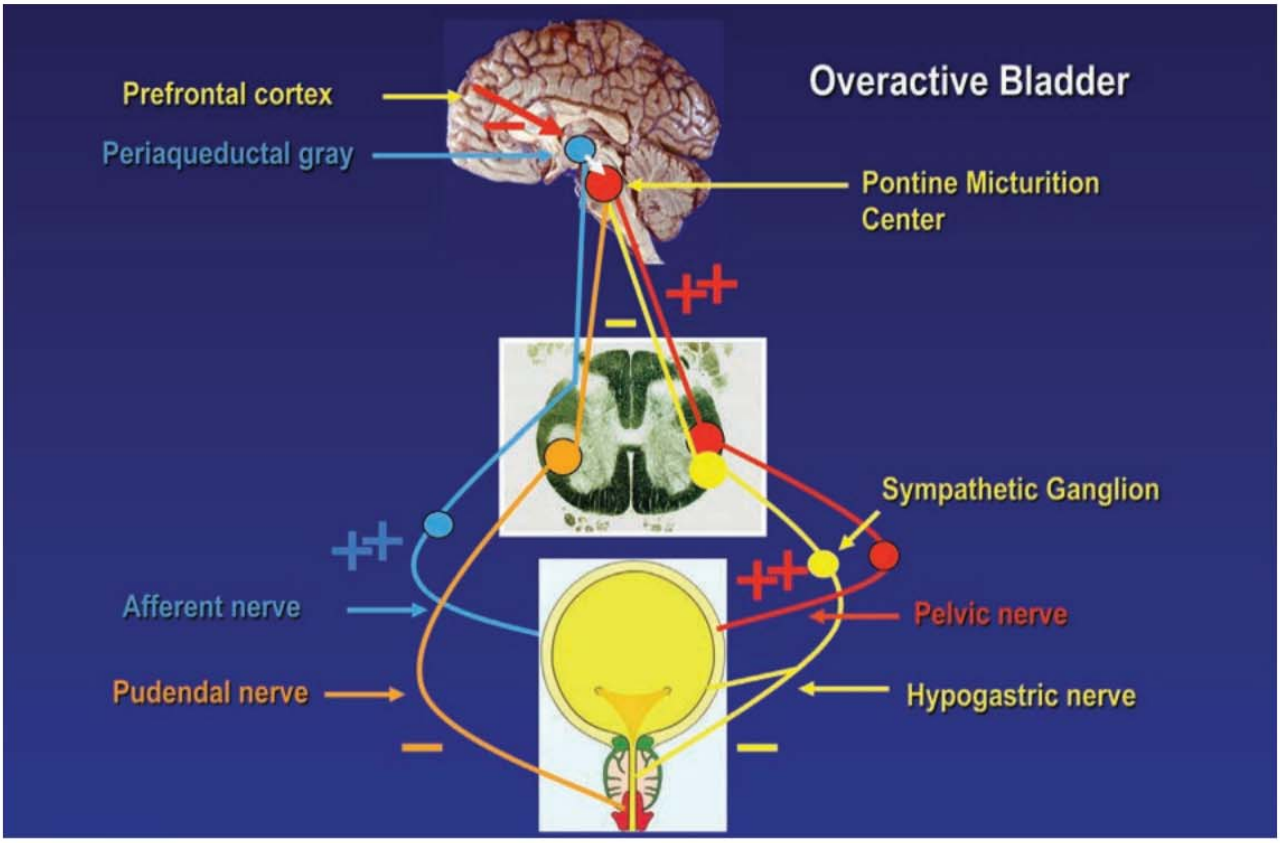

Figure 4 : Detrusor overactivity. Despite the inhibitory impulses from the prefrontal to the cortex pontine micturition center the enhanced (?) afferent impulses are able to initiate micturition.

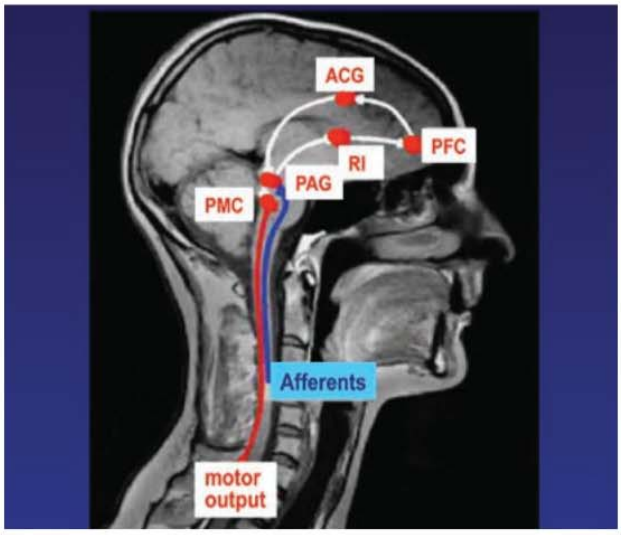

Figure 5: Simplified model of the supraspinal control system of micturition. Secondary bladder afferents synapse in the Periaqueductal Gray (PAG) and are relayed to the Insula (RI), forming the substrate for sensation. Insula representation may have slight right-sided predominance. The Anterior Cingulate Gyrus (ACG) is responsible for monitoring, arousal, and efferent output to the PAG and the Pontine Micturition Center (PMC). The prefrontal cortex (PFC) is involved in voluntary decision about voiding and generates efferent signals to control ACG and ultimately PMC. PMC provides motor output to cause voiding. Modified from Griffiths and Tadic, Neurourol Urodyn, 2008;27:466-474

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 [Beckel and Holstege, 2011]. 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].

The ***somatic*** innervation of the urethral rhabdosphincter and of some perineal muscles (for exam-

ple compressor urethrae and urethrovaginal sphincter), is provided by the pudendal nerve [Beckel and Holstege, 2011]. 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 [Kanai and Andersson, 2010]. 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, 2012]. 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]. In a Finnish study, taking into account bother, the prevalence of clinically meaningful OAB was was much lower than reported in these studies [Vaughan et al., 2011].

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, as can be seen in various neurological disorders, such as multiple sclerosis, cerebrovascular disease, Parkinson's disease, brain tumors, and spinal cord injury [Andersson and Pehrson, 2003; Ouslander, 2004; Banakhar et al., 2012; Wein and Dmochowski, 2012]. 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, 2011].

V. BLADDER CONTRACTION

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle [Andersson and Wein, 2004] (**Figure 6**). 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) [Ford and Cockayne, 2011]. 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; Ford and Cockayne, 2011]. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that P2X1 receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder. Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells [de Groat and Yoshimura, 2001]. P2X3 receptors, which have been identified in small-diameter afferent neurons in dorsal root ganglia, have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus

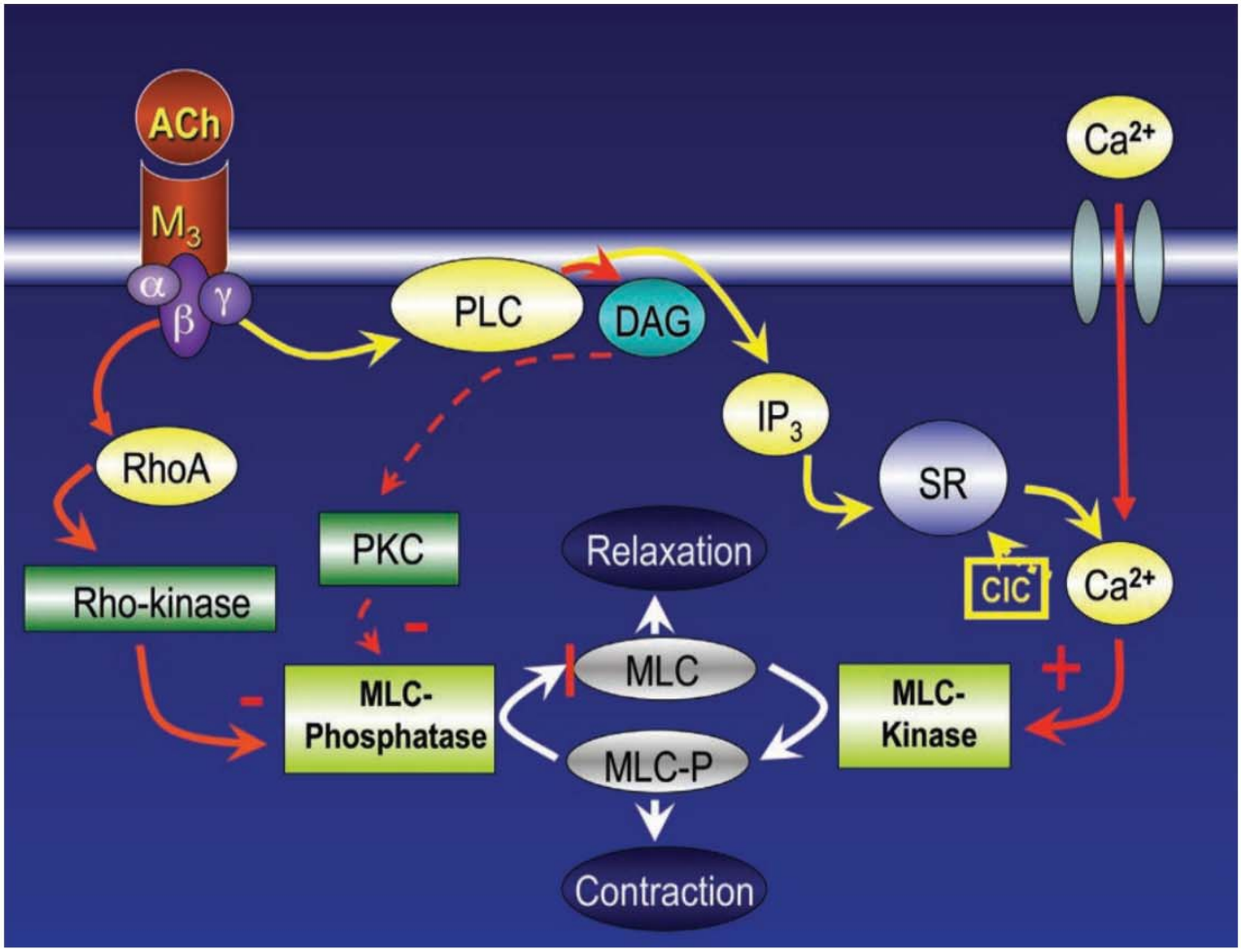

Figure 6: Muscarinic M3 receptor-mediated detrusor activation. Calcium influx and activation of the Rhokinase system are the main pathways mediating activation of the contractile system in the detrusor.

of afferent nerves. In P2X3 knockout mice, afferent activity induced by bladder distension was significantly reduced [Cockayne et al., 2000; Ford et al., 2006; Ruggieri et al., 2006; Ford and Cockeyne, 2011]. 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 [Andersson, 2006].

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, Andersson, 2011]. Five subtypes of muscarinic receptors have been cloned in humans and other mammalian species, which are designated M1-5 [Caulfield and Birdsall 1998]. Based upon structural criteria and shared preferred signal transduction pathways, the subtypes can be grouped into M1, M3 and M5 on the one hand and the subtypes M2 and M4 on the other. The former prototypically couple via pertussis toxin-insensitive Gq 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 Gi 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 M2 and M3 receptors, with the former dominating quantitatively [Abrams et al., 2006: Hegde, 2006, Andersson, 2011]. Inhibitory pre-junctional muscarinic receptors have been classified as M2 in the rabbit and rat, and M4 in the guinea-pig, rat and human [d´Agostini et al., 2000; see Andersson, 2011] bladder. These receptors appear to be of the M1 subtype in the rat and rabbit urinary bladder, but have also been detected in human bladders. The muscarinic facilitatory mechanism seems to be upregulated (M3 receptors) in overactive bladders from chronic spinal cord transected rats.

Apparently, most muscarinic receptors in the bladder are found on the smooth muscle cells of the detrusor. While the detrusor expresses far more M2 than M3 receptors, it appears that detrusor contraction under physiological conditions is largely if not exclusively mediated by the M3 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., 2000; 2002; Stengel et al., 2002; Ehlert et al., 2007]. Under physiological conditions M2 receptor-selective stimulation causes little contraction [Schneider et al., 2005a], but rather appears to act mainly by inhibiting β-adrenoceptor-mediated detrusor relaxation [Hegde et al., 1997; Ehlert et al., 2007; Matsui et al., 2003]. It has been proposed that M2 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 M3 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 M2 and M3 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]. Muscarinic receptor blockade in urothelial cells may also reduce ATP release induced by strech [Young et al., 2012]. 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.

Assuming an 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].

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**). Helfand and coworkers showed that in a cohort of 7,244,501 patients over 45 years with an OAB diagnosis, 24.4% of these were treated mainly with antimuscarinic agents; 75.6% went untreated. Only 25.6% of those treated were men. [Helfand et al., 2009]. 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 irrespective of location [Abrams and Andersson, 2007; Andersson 2011b] (**Figure 7**). 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, 2007]. 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 (**Figure 8**), there is little evidence for a significant reduction of the voiding contraction [Finney et al., 2006]. 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] (**Figure 9**).

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

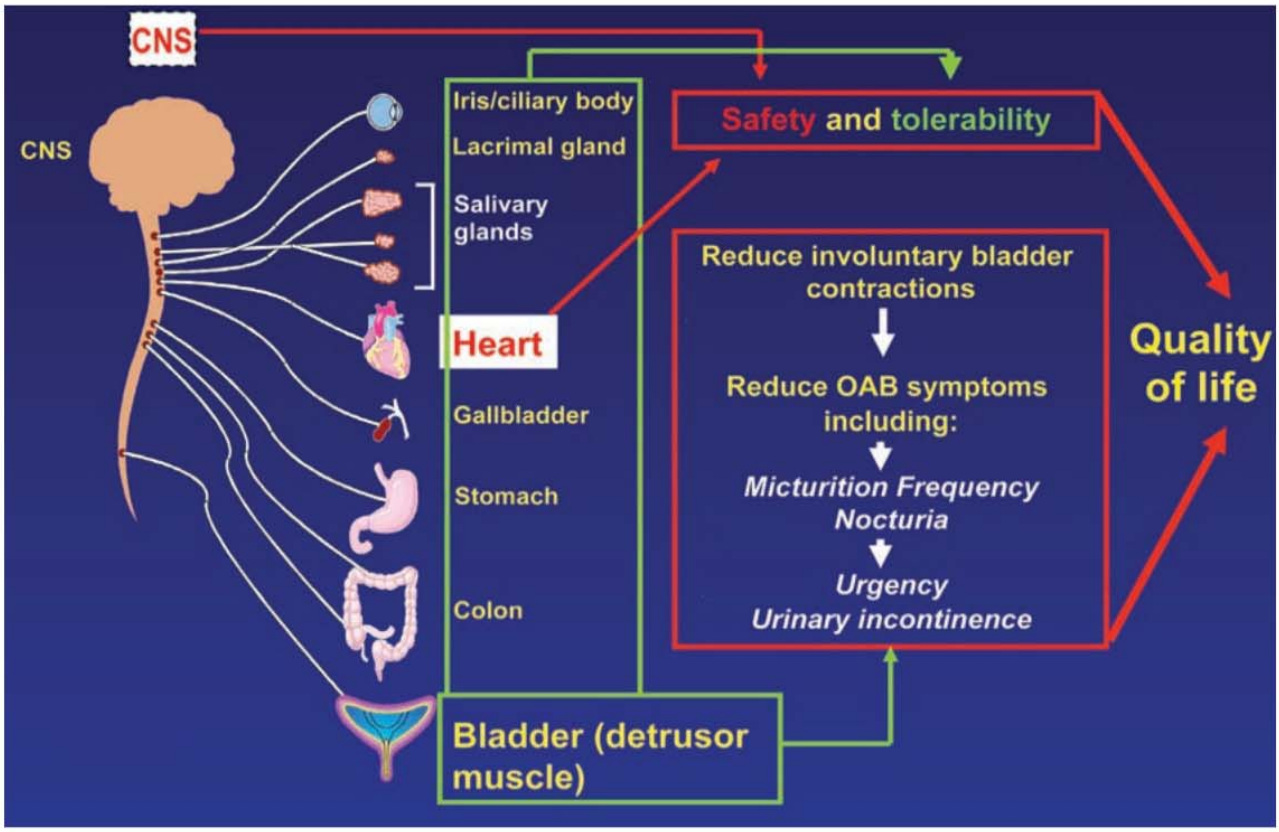

Figure 7: Important sites of action of antimuscarinics.

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

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

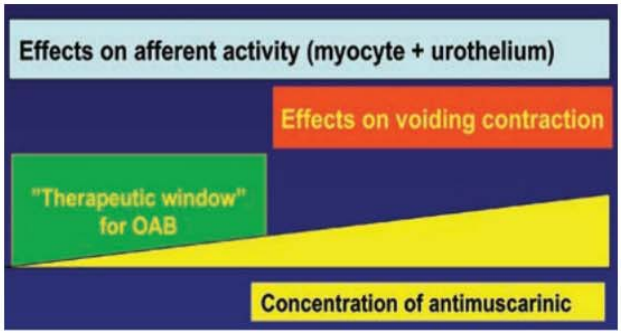

Figure 8: Rationale for use of antimuscarinics for treatment of OAB/DO. Blockade of muscarinic receptors at both detrusor and nondetrusor sites may prevent OAB symptoms and DO without depressing the contraction during voiding. The «Therapeutic window for OAB» can be obtained in most patients with recommended doses of antimuscarinics

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 (by increasing detrusor smooth muscle tone) 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 darifenacin, that is compensated by active transport out of the CNS by the product of the MDR1 gene. 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, increases in heart rate, 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. Some antimuscarinics and their active metabolites are excreted in urine in amounts that may affect the mucosal muscarinic receptors from the luminal side. This has not yet been demonstrated to imply superior clinical efficacy [Andersson et al., 2008b].

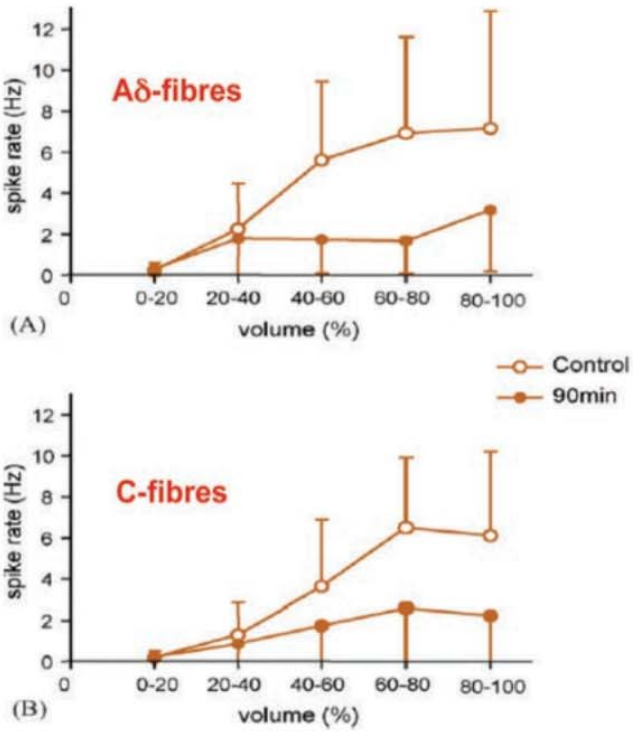

Figure 9: Influence of darifenacin on volume-related nerve activity in Aδ afferents (A) and C afferents (B) in the rat pelvic nerve. From Iijima et al. Eur Urol. 2007 Sep;52(3):842

Antimuscarinics are still the most widely used treatment for urgency and urgency incontinence [Andersson, 2004, Andersson et al., 2009]. However, currently used drugs lack selectivity for the bladder, and effects on other organ systems 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].

1. ANTIMUSCARINICS WITH "SPECIFIC" ACTION

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

a) 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.

Assessment

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**.

b) 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 M3 receptor antagonist. In vitro, it is selective for human cloned muscarinic M3 receptors relative to M1, M2, M4 or M5 receptors. Theoretically, drugs with selectivity for the M3 receptor can be expected to have clinical efficacy in OAB/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes [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].

The time-to effect with darifenacin was analyzed in a pooled analysis of efficacy and safety data fom 1,059 patients participating in three double-blind 12-week studies Khullar et al [2011]. Darifenacin significantly improved all OAB symptoms as early as 6 to 8 days.

One of the most noticeable clinical effects of antimuscarinics is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin, on the 'warning time' associated with urinary urgency. Warning time was defined as the time from the first sensation of urgency to the time of voluntary micturition or incontinence. This was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks' washout, 2 weeks' medication-free run-in and a 2-week treatment phase [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].

Since darifenacin is a substrate for the P-glycoprotein drug efflux transporter [Miller et al., 2011;

Chancellor et al., 2012], which is present both in the blood-brain and blood-ocular barriers, several clinical studies have been devoted to investigate possible effect of darifenacin on cognition. Neither in healthy volunteers (19-44 years) and healthy subjects (>60 years), nor in volunteers 65 years or older, could any effect of darifenacin (3.75-15mg daily) be demonstrated, compared to placebo [Kay and Wesnes, 2005; Lipton et al., Kay et al., 2006; Kay and Ebinger 2008; Chancellor et al., 2012].

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 Tmax 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].

Assessment

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

c) 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, Malhotra et al., 2009a]. 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]. The bioavailability of fesoterodine, averaging 52%, was independent of food intake and the drug may be taken with or without a meal [Malhotra et al., 2009b]. Peak plasma concentration of 5-HMT is reached at 5 h following oral administration and has a half-life of 7–9 h [Malhotra et al., 2008]. The suggested starting dose, 4 mg/day, can be used in patients with moderately impaired renal or hepatic function due to the combination of renal excretion and hepatic metabolism of 5-HMT [Malhotra et al., 2009c; de Mey et al., 2011].

The clinical efficacy and tolerability of fesoterodine have been documented in several RCTs [Chapple et al., 2007; Nitti et al., 2007; Dmochowski et al., 2010; Herschhorn et al., 2010; Kaplan et al., 2010; Nitti et al., 2010; see Dell'Utri et al., 2012]. In a multicenter, double-blind, double-dummy RCT with tolterodine ER, 1132 patients were enrolled and received treatment [Chapple et al., 2007]. The trial showed that both the 4 and 8 mg doses of fesoterodine were effective in improving symptoms of OAB, with the 8 mg dose having a greater effect at the expense of a higher rate of dry mouth. There appeared to be little difference between fesoterodine 4 mg and tolterodine ER. Only one subject from the fesoterodine 8 mg group and one subject from the tolterodine ER group withdrew from the study due to dry mouth. The dose-response relationship was confirmed in another study that pooled data from two phase III RCTs [Khullar et al., 2008]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and urge UI as recorded by 3-day bladder diary, offering the possibility of dose titration.

A head to head placebo controlled trial has been completed comparing fesoterodine 8mg to tolterodine extended release 4mg and placebo [Herschorn et al., 2010]. The study randomized 1,590 patients to assess the primary outcome of reduced urgency incontinence episodes at 12 weeks. Fesoterodine produced statistically significant improvements in urgency incontinence episodes, complete dry rates (64.0% vs. 57.2%, p = 0.015), mean voided volume per void (+32.9 ml vs. +23.5 ml, p = 0.005), and in patients' assessments of bladder related problems as measured by OAB questionnaire (except sleep domain), Patient Perception of Bladder Condition (40% vs. 33% with > 2 point improvement, p < 0.001), and Urgency Perception Scale (46% vs. 40% with improvement, p = 0.014) compared with tolterodine. The clinical significance of these statistically significant findings is questionable as there was no difference between agents with respect to number of micturitions, urgency episodes, and frequency-urgency sum per 24 hours. The improved efficacy of fesoterodine came at the cost of greater dry mouth (27.8% vs. 16.4%), headache (5.6% vs. 3.4 %), constipation (5.4% vs. 4.1%), and withdrawal rates (6% vs. 4%). Nonetheless, this first head to head trial comparing two drugs in class supports the use of fesoterodine 8mg for additional benefit over tolterodine ER 4 mg.

Wyndaele et al. [2009] reported the first flexible-dose open-label fesoterodine trial, which was conducted at 80 different centres worldwide and comprised 516 participants (men and women) >18 years who self-reported OAB symptoms for at least 3 months

before screening and had been treated with either tolterodine or tolterodine ER within 2 years without symptom improvement. Approximately 50% opted for dose escalation to 8 mg at week 4. Significant improvements from baseline to week 12 were observed in micturitions, urgency urinary incontinence episodes, micturition-related urgency episodes and severe micturition-related urgency episodes per 24 h. Significant improvements from baseline were observed in QoL parameters. Dry mouth (23%) and constipation (5%) were the most common adverse events; no safety issues were identified.

The largest double-blind, double-dummy, flexible-dose fesoterodine RCT, which was conducted at 210 different centres with a total of 2,417 patients enrolled, was performed by Kaplan et al. [2010]. All patients were healthy, >18 years of age and self-reported OAB symptoms for at least 3 months. The 960 patients who received fesoterodine 8 mg showed significantly greater mean improvements at week 12 in most efficacy parameters (diary variables) than those receiving either tolterodine ER or placebo; UUI and urgency episodes, micturition frequency and MVV. No statistically significant changes were shown in reduction of nocturnal micturitions compared with the tolterodine group, whereas when comparing the mean changes in nighttime micturition with the placebo group a significant difference was found. This phase III study confirmed the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for improving of UUI and urgency episodes and 24-h micturitions but not for MVV and nocturia. In another RCT of flexible-dose fesoterodine, Dmchowski et al. reported statistically significant improvements at week 12 in the mean number of micturition per 24 h and in both UUI and urgency episodes. Between groups, difference in nocturnal micturition was not statistically significant.

Nitti et al. [2010] determined whether the presence of DO in patients with OAB and urgency urinary incontinence was a predictor of the response to treatment with fesoterodine in a phase 2 randomized, multicentre, placebo-controlled trial. They concluded that regardless of the presence of DO, the response to fesoterodine treatment was dose-proportional and associated with significant improvements in OAB symptoms, indicating that the response to OAB pharmacotherapy in patients with UUI was independent of the urodynamic diagnosis of DO.

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 Chapple et al., 2007; Nitti et al., 2007] 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. In a post hoc analysis of data pooled from these studies, significant improvements in all KHQ domains, ICIQ-SF scores, and bladder related problems were observed at months 12 and 24 compared to open label baseline [Kelleher et al., 2011]. The authors concluded that treatment satisfaction was high throughout the open-label treatment regardless of gender and age.

Malhotra et al. [2010] performed a thorough QT study to investigate the effects of fesoterodine on cardiac repolarization in a parallel-group study. Subjects were randomly assigned to receive double-blind fesoterodine 4 mg, fesoterodine 28 mg, or placebo or open-label moxifloxacin 400 mg (positive control) for 3 days. Electrocardiograms (ECGs) were obtained on Days -1 (baseline), 1, and 3. The primary analysis was the time-averaged changes from baseline for Fridericia's-corrected QT interval (QTcF) on Day 3. Among 261 subjects randomized to fesoterodine 4 mg (n = 64), fesoterodine 28 mg (n = 68), placebo (n = 65), or moxifloxacin 400 mg (n = 64), 256 completed the trial. The results indicated that fesoterodine is not associated with QTc prolongation or other ECG abnormalities at either therapeutic or supratherapeutic doses.

Assessment

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

d) Imidafenacin

Imidafenacin (KRP-197/ONO-8025, 4-(2-methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide) is an antagonist for the muscarinic ACh receptor with higher affinities for M3 and M1 receptors than for the M2 receptor. Metabolites of imidafenacin (M-2, M-4 and M-9) had low affinities for muscarinic ACh receptor subtypes [Kobayashi, Yageta et al. 2007]. The drug blocks pre- as well as postjunctional muscarinic receptors and was shown to block both detrusor contractions and acetylcholine release [Murakami, Yoshida et al. 2003]. The receptor binding affinity of imidafenacin in vitro was found to be significantly lower in the bladder than submaxillary gland or colon [Yamada, Seki et al. 2011], and in rats orally administered imidafenacin distributes predominantly to the bladder and exerts more selective and longer-lasting effect here than on other tissues. Whether this can be translated to the human situation has to be established before claims of clinical bladder selectivity can be made.

Imidafenacin is well absorbed form the gastrointestinal tract and its absolute bioavailability in human is 57.8% [Ohmori, Miura et al. 2007; Ohno, Nakade et al. 2008]. It is rapidly absorbed with maximum plasma concentration occuring 1-3h after oral administration [Ohno, Nakade et al. 2008]. Metabolites in the plasma are produced mainly by

first-pass effects. The major enzymes responsible for the metabolism of the drug are CYP3A4 and UGT1A4. The oxidative metabolism is reduced by concomitant administration of CYP3A4 inhibitors. In contrast, imidafenacin and its metabolites have no inhibitory effect on the CYP-mediated metabolism of concomitant drugs [Kanayama, Kanari et al. 2007].

Kitagawa et al. [Kitagawa, Kuribayashi et al. 2011] reported that the subjective efficacy of imidafenacin was observed from 3 days after the commencement of administration and that mean total OABSS decreased gradually during 2 weeks after administration.

A randomized, double-blind, placebo-controlled phase II dose-finding study in Japanese OAB patients was performed to evaluate the efficacy, safety/tolerability, and dose-response relationship of imidafenacin [Homma, Yamaguchi et al. 2008]. Overall, 401 patients were enrolled and randomized for treatment with 0.1 mg of imidafenacin/day (99 patients), 0.2 mg of imidafenacin/day [100], 0.5 mg of imidafenacin/day [101], or a placebo [101]. After 12 weeks of treatment, the number of incontinence episodes was reduced in a dose-dependent manner, and a significant difference between the imidafenacin treatment and the placebo was observed ($P < 0.0001$). Compared with the placebo, imidafenacin caused significant reductions in urgency incontinence, voiding frequency, and urinary urgency, and a significant increase in the urine volume voided per micturition. Imidafenacin was also well tolerated. The incidence of dry mouth in the imidafenacin groups increased dose-dependently. Even though the percentage of patients receiving 0.5 mg/day who discontinued treatment due to dry mouth was high (8.9%), the percentages in the 0.1 mg/day and 0.2 mg/day groups (1.0% and 0.0%, respectively) were comparable with that in the placebo group (0.0%).

A randomized, double-blind, placebo- and propiverine-controlled trial of 781 Japanese patients with OAB symptoms were conducted by Homma et al.[Homma and Yamaguchi 2009]. They were randomized to imidafenacin (324), propiverine [310], or a placebo [147]. After 12 weeks of treatment, a significantly larger reduction in the mean number of incontinence episodes was observed in the imidafenacin group than in the placebo group ($P < 0.0001$). The non-inferiority of imidafenacin compared with propiverine was confirmed for the reduction in using incontinence episodes ($P = 0.0014$, non-inferiority margin: 14.5%). Imidafenacin was well tolerated. The incidence of adverse events with imidafenacin was significantly lower than with propiverine ($P = 0.0101$). Dry mouth, the most common adverse event, was significantly more common in the propiverine group than in the imidafenacin group. There were no significant increases in either the imidafenacin or placebo group in the mean QTc interval, whereas there was a significant increase in the mean QTc interval in the propiverine group ($P < 0.0001$). However, there were no clinical arrhythmia and clinical arrhythmic events in any of the treatment groups.

The long-term safety, tolerability, and efficacy imidafenacin was studied in Japanese OAB patients [Homma and Yamaguchi 2008], of whom 478 received treatment and 376 completed a 52-week program. Imidafenacin was well tolerated, the most common adverse event being a dry mouth (40.2% of the patients). Long-term treatment did not produce an increase in the frequency of adverse events compared with short-term treatment. A significant efficacy of the drug was observed from week 4 through week 52. After 52 weeks, imidafenacin produced mean changes from baseline in the number of incontinence episodes (-83.51%), urgency incontinence episodes (-84.21%), voiding frequency (-2.35 micturitions/day), urgency episodes (-70.53%), and volume voided per micturition (28.99 mL). There were also significant reductions from baseline in all domains of the King's Health Questionnaire. received the treatment and 376 patients completed the 52-week program. Imidafenacin had no significant effects on the corrected QT interval, vital signs, results from laboratory tests, or post-void residual volume.

A 52-week prospective, open randomized comparative study to evaluate the efficacy and tolerability of imidafenacin (0.2 mg/day) and solifenacin (5 mg/day) was conducted in a total of 41 Japanese patients with untreated OAB [Zaitsu, Mikami et al. 2011]. They were randomly assigned to imidafenacin and solifenacin groups. There was no difference in OABSS and KHQ scores between the two groups, but the severity and incidence of adverse events caused by the drugs showed increased differences between the groups with time. The severity of dry mouth and the incidence of constipation were significantly lower in the imidafenacin group ($P = 0.0092$ and $P = 0.0013$, resp.). An important limitation of this study is the low number of patients. Only 25 patients (17 males 8 females) were available for long-term analysis.

Assessment.

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

e) 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 overactivitycontractions [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.

Assessment

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.

f) 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 significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) Cmax and AUC0-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]. Supporting an effect on sensory function by solifenacin, 15 women with DO receiving 10 mg/day of the drug showed an increase in the area under the bladder-volume sensation curve [Lowenstein et al., 2011] Solifenacin also increased maximum bladder capacity, a finding in agreement with other studies Tanaka et al., 2010; Hsiao et al., 2011].

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 in solifenacin trials and these findings demonstrate efficacy as early as one week. The 5 mg, 10 mg, and 20 mg dosing groups experienced statistically significant increases in volume voided; the 10 mg solifenacin dose was associated with statistically 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 was 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.

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

A number of studies and reviews have further documented the effects of solifenacin [Cardozo et al., 2006; Chapple et al., 2006; 2007; Maniscalco et al., 2006, see also Chapple et al., 2008; Novara et al., 2008; Toglia et al., 2009; Vardy et al., 2009; Serels et al., 2010; Luo et al., 2012], including men with OAB without bladder outlet obstruction [Kaplan et al., 2010;] 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. A positive impact on nocturia and sleep quality in patients with OAB treated with solifenacin has also been reported in other studies [Takao et al., 2011; Yokoyama et al., 2011] 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 (> 65 years) patients, and also showed a high level of persistence in a 40 week extension trial [Wagg et al., 2005]. Post-hoc analysis of two12-week, open lable, flexible-dosing studies on 2645 patients over 65 years of age with OAB, revealed that solifenacin was associated with improvements in measures assessing patients’ perception of their bladder problems, symptom bother, and aspects of health-related quality of life [Capo et al., 2011]. Solifenacin was equally well tolerated in younger (<65 years) and older (>65 years) patients [Herschorn et al., 2001]. An exploratory pilot study with single doses of solifenacin 10 mg to 12 elderly volunteers suggested no clear propensity to impair cognitive functions [Wesnes et al., 2009].

Improvement of QoL by solifenacin treatment has been documented in several studies [Kelleher et al., 2005; Garely et al., 2006]. In 30 patients with mutiple sclerosis, van Rey and Heesakkers [2011] improved OAB symptoms as well as neurogenic disease-specific QoL measures.

Information on solifenacin treatment in children is scarce. In a prospective open label study in 72 children (27 with neurogenic bladders) Bolduc et al.[2010] improved urodynamic capacity and im-

proved continence.Chart review of 138 children with therapy resistant OAB treated with solifenacin increased mean voided volume and improved continence [Hoebeke et al., 2009]

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".

Assessment

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

g) Tolterodine tartrate

Tolterodine is 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.

Animal experiments have suggested that antimuscarinics may affect signaling from the bladder [Andersson, 2011b]. Cirfirming data in humans were found by Vijaya et al. [2012]. In a randomized, placebo-controlled study, they evaluated the effect of tolterodine on urethral and bladder afferent nerves in women with DO in comparison to placebo, by studying the changes in the current perception threshold (CPT). They found a significantly increased CPT value at 5 (described as urgency) and 250 Hz upon both urethral and bladder stimulation after 1 week of treatment. When compared with placebo, women taking tolterodine had significantly increased bladder CPT values at 5 Hz (P-value <0.05).

Tolterodine is available as immediate-release (TOLT-IR; 1 or 2 mg; twice daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability [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 33% and 28% 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 (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 qd 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 the effects on heart rate of TOLT-ER 4 mg/day with those of darifenacin 15 mg/day in healthy volunteers. They found that tolterodine, but not darifenacin, significantly increased mean heart rate per 24 hours. The proportion of subjects with an increase >5 beats/min was significantly greater in those receiving TOLT-ER (25% than with darifenacin (8.9%).

Hsiao et al. [2011] compared the urodynamic effects, therapeutic efficacy and safety of solifenacin [5 mg] versus tolterodine ER [4 mg] treatment inwomen with the OAB syndrome. Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy and adverse events, however, tolterodine had a greater effect in increasing heart rate than solifenacin.

In a prospective, open study, Song et al. [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. In a 16-week, multicenter, open label study tolterodine extended release plus behavioral intervention resulted in high treatment satisfaction and improved bladder diary variables in patients who had previously been treated and were dissatisfied with tolterodine or other antimuscarinics [Klutke et al., 2009].

Abrams et al. [2006] studied the safety and tolerability of tolterodine for the treatment of OAB symptoms in men with BOO. They found that tolterodine did not adversely affect urinary function in these men. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. It was suggested that antimuscarinics can be safely administered in men with BOO. Lee et al. [2008] reviewed the safety and efficacy of antimuscarinic agents in treating men with BOO and OAB and emphasized their safety and efficacy. They also concluded that combination therapy of antimuscarinic and α1-AR antagonists improves the symptoms effectively without increasing the incidence of acute urinary retention.

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 α1-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]. A large, 26-week, multicenter, randomized, double-blind, placebo-controlled, three-period crossover study enrolled women aged ≥ 18 years that were diagnosed with OAB and reported ≥ 8 micturitions/24 hr and ≥ 4 urgency episodes/week on 5-day bladder diary at baseline [Marencak et al.2011]. Subjects were randomized to 1 of 10 treatment sequences and received three of five treatments, each for 4 weeks with 4-week washout periods: standard-dose pregabalin/tolterodine ER (150 mg twice daily [BID]/4 mg once daily [QD], n=102), pregabalin alone (150 mg BID, n=105), tolterodine ER alone (4 mg QD, n=104), low-dose pregabalin/tolterodine ER (75 mg BID/2 mg QD, n=105), and placebo (n=103). Subjects completed 5-day diaries at the end of treatment and washout periods. The primary endpoint was change from baseline to week 4 in mean voided volume (MVV) per micturition. Baseline-adjusted changes in MVV were significantly greater after

treatment with standard-dose pregabalin/tolterodine ER (39.5 ml) versus tolterodine ER alone (15.5 ml; P<0.0001), and with pregabalin alone (27.4 ml) versus tolterodine ER alone (P=0.005) and placebo (11.9 ml; P=0.0006). Treatments were generally well tolerated; discontinuation rates due to adverse events were 4%, 2%, 5%, 0%, and 1% with standard- and low-dose pregabalin/tolterodine ER, pregabalin,tolterodine ER, and placebo, respectively. See further section on Combinations].

Assessment

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

h) 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 since it is a substrate for the drug-efflux transporter P-glycoprotein, which restricts its entry into the brain [Gever et al., 2009]. This was demonstrated by Staskin et al. [2010], showing that trospium chloride levels in CSF samples were undetectable on Day 10 at steady-state peak plasma concentration concurrent with measureable peak plasma values. Clinically, trospium seems to have no negative cognitive effects [Fusgen and Hauri, 2000; Todorova et al., 2001; Widemann et al., 2002; Staskin et al., 2010; Chancellor et al., 2012].

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; 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 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) and urgency incontinent episodes 59% compared to placebo (-1.29; 44%). It significantly increased average volume per void (32 ml; placebo: 7.7) ml, and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (-0.43; placebo: 0.17) - and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%) and headache (6.5%; placebo 4.6%). In a large US multicenter trial with the same design, and including 658 patients with OAB, Rudy et al. [2006] confirmed the data by Zinner et al [2004], both with respect to efficacy and adverse effects.

Dose escalation seems to improve therapeutic efficacy. In a 12-week, randomised, double-blind, phase IIIb study including 1658 patients with urinary frequency plus urgency incontinence received trospium chloride 15 mg TID (n = 828) or 2.5 mg oxybutynin hydrochloride TID (n = 830). After four weeks, daily doses were doubled and not readjusted in 29.2% (242/828) of patients in the trospium group, and in 23.3% (193/830) in the oxybuytnin group, until the end of treatment. At study end, there were no relevant differences between the “dose adjustment” subgroups and the respective “no dose adjustment” subgroups (trospium: P = 0.249; oxybutynin: P = 0.349). After dose escalation, worsening of dry mouth was higher in both dose adjusted subgroups compared to the respective “no dose adjustment” subgroups (P < 0.001). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups [Bödeker et al., 2010].

An extended release formulation of trospium allowing once daily dosing, has been introduced [Silver et al., 2010], and and its effects tested in controlled trials [Staskin et al., 2008; Dmochowski et al., 2008; Chancellor et al., 2010; MacDiarmid et al., 2011; Sand et al., 2011a; b; c; Zinner et al., 2011]. These studies demonstrated similar efficacy as found with previous formulations, but include experiences in e.g., elderly patients (>75 years), obese patients, and in patients who use multiple concomitant medications. The most frequent side effects were dry mouth (12.9% ; placebo 4.6) and constipation (7.5%; placebo 1.8) [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, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium does not seem to be absorbed [Walter et al., 1999], thus offering an opportunity for treatment with minimal systemic antimuscuscarinic effects.

Assessment

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

2. ANTIMUSCARINICS WITH “MIXED” ACTION

Some drugs used for treatment of the OABsyndrome/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 Ca2+ channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action. Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsade de pointes) in some patients [Connolly et al., 1991; Stewart et al., 1992].

a) 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