metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander et al. [1988]. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation [Hughes et al., 1992; Douchamps et al, 1988].

Oxybutynin has several pharmacological effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent [Kachur et al., 1988]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions [Waldeck et al., 1997; Nilvebrant et al., 1988]. The drug was shown to have slightly higher affinity for muscarinic M1 and M3 receptors than for M2 receptors [Nilvebrant et al., 1986; Norhona-Blob et al., 1991], but the clinical significance of this is unclear.

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other anti-muscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR, and the advantage of the newer formulations lies in improved dosing schedules and side-effect profile [Appell et al., 2001; Diokno et al., 2003; Dmochowski et al., 2002]. An extended release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability. Some of the available formulations of oybutynin were overviewed by McCrery and Appell [2006].

Immediate-release oxybutynin (OXY-IR). Several controlled studies have have shown that OXY-IR is effective in controlling DO, including neurogenic DO [Yarker et al., 1995; Andersson and Chapple, 2001]. The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff et al. [1998] summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52% and the mean reduction in frequency per 24 h was 33% (data on placebo not presented). The overall "subjective improvement" rate was reported as 74 % (range 61% - 100%). The mean percent of patients reporting an adverse effect was 70 (range 17% - 93%). Oxybutynin, 7.5 to 15 mg/day, significantly improved quality of life of patients suffering from overactive bladder in a large open multicenter trial. In this study, patients´ compliance was 97% and side effects, mainly dry mouth, were reported by only 8% of the patients [Amarenco et al., 1998]. In nursing home residents (n=75), Ouslander et al. [1995] found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double blind, cross-over trial. On the other hand, in another controlled trial in elderly subjects (n=57), oxybutynin with bladder training was found to be superior to bladder training alone [Szonyi et al., 1995].

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

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose-limiting [Baigrie et al., 1988; Jonville et al., 1992]. The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence [Hussain et al., 1998]; no changes were found. It cannot be excluded that the commonly recommended dose 5 mg x 3 is unnecessarily high in some patients, and that a starting dose of 2.5 mg x 2 with following dose-titration would reduce the number of adverse effects [Amarenco et al., 1998].

Extended release oxybutynin (OXY-ER). This formulation was developed to decrease liver metabolite formation of desethyloxybutynin (DEO) with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy [see Arisco et al., 2009]. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 hours distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared to OXY-IR. DEO is still formed through the hepatic cytochrome P-450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR [Appell et al., 2003]. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [Chancellor et al., 2001].

The effects of OXY-ER have been well documented [Siddiqui et al., 2004]. In the OBJECT study [Appell et al., 2001], the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose

of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6 to 6.1%; TOLT-IR 24.1 to 7.8), total incontinence (OXY-ER from 28.6 to 7.1%; TOLT-IR 27.0 to 9.3), and frequency (OXY-ER from 91.8 to 67.1%; TOLT-IR 91.6 to 71.5) and both medications were equally well tolerated. The basic study was repeated as the OPERA study [Diokno et al., 2003] with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg) and the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urgency incontinence, however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should no longer be compared with ER entities of the other.

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

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

In a multicentre, prospective, observational, flexible-dosing Korean study, Yoo et al. [2012] investigate the prescription pattern and dose distribution of OXY-ER in patients the OAB syndrome in actual clinical practice. The dosage of for each patient was adjusted after discussions of efficacy and tolerability between doctor and patient, over a 12 week treatment period. Efficacy was measured by administering the Primary OAB Symptom Questionnaire (POSQ) before and after treatment. Patients were also administered, the patient perception of treatment benefit (PPTB) questionnaire at the end of the study. Of the 809 patients enrolled, 590 (73.2%) continued to take study medication for 12 weeks. Most patients were prescribed 5–10 mg/day oxybutynin ER as both starting and maintenance doses, with a dose escalation rate of only 14.9%. All OAB symptoms evaluated by the POSQ were improved; 94.1% of patients reported benefits from treatment and 89.3% were satisfied.

Transdermal oxybutynin (OXY-TDS). Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study [Davila et al., 2001] comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study [Dmochowski et al., 2002] the 3.9-mg daily dose patch significantly (vs placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 ml; placebo from 175 to 182 ml). Furthermore, dry mouth rate was similar to placebo (7% vs 8.3%). In a third study [Dmochowski et al., 2003] OXY-TDS was compared not only to placebo but to TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14% and erythema in 8.3% with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

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

Dmochowski et al. [2005] analyzing the combined results of two RCTs concluded that transdermal

oxybutynin was shown to be efficacious and well tolerated. The most common sytemic side effect was dry mouth (7.0 % vs placebo 5.3%). Application site erythema occurred in 7% and pruritus in 16.1 %. Also Cartwright and Cardozo [2006], reviewing published and presented data concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower that with oral antimuscarinics – however, this benefit was offset by the rate of local skin reaction. The reviews of Sahai et al. [2008] and Staskin and Salvatore [2010] largely confirmed these conclusions, which also have been supported by further studies [Cartwright et al., 2011].

Oxybutynin topical gel. Given the efficacy and tolerability of the transdermal application, limited only by skin site reactions, a gel formulation was developed. oxybutynin topical gel (OTG) was approved by the US FDA in January 2009. OTG is applied once daily to the abdomen, thigh, shoulder, or upper arm area [Staskin et al., 2009]. The 1 gram application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations and a "favorable" N-desethyloxybutynin metabolite: oxybutynin ratio believed to minimizing antimuscarinic side effects [Staskin and Robinson, 2009]. In a multicenter RCT, 789 patients (89% women) with urgency-predominant incontinence were assigned to OTG or placebo once daily for 12 weeks [Staskin et al., 2009]. The mean number of urgeny episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes per day versus 2.5 in the placebo arm ($P < 0.0001$). Urinary frequency decreased by 2.7 episodes per day and voided volume increased by 21 mL (versus 2.0 episodes [$P = 0.0017$] and 3.8 mL [$P = 0.0018$], respectively, in the placebo group). Dry mouth was reported in 6.9% of the treatment group versus 2.8% of the placebo group. Skin reaction at the application site was reported in 5.4% of the treatment group versus 1.0% in the placebo arm. It was felt that improved skin tolerability of the gel over the OXY transdermal patch delivery system was secondary to lack of adhesive and skin occlusion. The gel dries rapidly upon application and leaves no residue; person-to-person transference via skin contact is largely eliminated if clothing is worn over the application site [Dmochowski et al., 2011]. The evolution of the transdermal gel allows greater patient tolerability and improved compliance. This was confirmed by Sand et al. [2012] showing that in 704 women with OAB OTG significantly reduced the number (mean ± standard deviation) of daily incontinence episodes (OTG, -3.0 ± 2.8 episodes; placebo, -2.5 ± 3.0 episodes), reduced urinary frequency, increased voided volume, and improved select health-related quality-of-life domains vs placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4%) than with placebo (2.8%).

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

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

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

Assessment.

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

b) Propiverine hydrochloride

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

Propiverine has combined antimuscarinic and calcium antagonistic actions [Haruno, 1992; Tokuno et al., 1993]. The importance of the calcium antagonistic component for the drug´s clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes. The effects of propiverine on cardiac ion channels and action potentials were investigated by Christ et al., [2008]. Propiverine blocked in a concentration-dependent manner HERG channels expressed in HEK293 cells, as well as native I(Kr) current in ventricular myocytes of guinea pig. However, action potential duration was not prolonged in guinea-pig and human ventricular

tissue, and the investigators concluded that their results did not provide evidence for an enhanced cardiovascular safety risk with the drug .

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff et al [1998] collected 9 randomized studies on a total of 230 patients, and found a 17% reduction in micturitions per 24 hours, a 64 ml increase in bladder capacity, and a 77% (range 33-80%) subjective improvement. Side effects were found in 14 % (range 8-42%). In patients with neurogenic DO, controlled clinical trials have demonstrated propiverine´s superiority over placebo [Stöhrer et al., 1999]. Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate and placebo [Wehnert et al., 1989], and propiverine, oxybutynin and placebo [Wehnert et al., 1992; Madersbacher et al., 1999], have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared [Stöhrer et al., 2007]. The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin.

Also in children and adolescents with neurogenic DO, propiverine was found to be effective [Schulte-Baukloh et al., 2006; Grigoleit et al., 2006], with a low incidence rate of adverse events: <1.5% [Grigoleit et al., 2006]. A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5–10 yr was performed by Marschall-Kehrel et al. [2009]. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy parameter; secondary endpoints included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well-tolerated: 23% of side-effects were reported for propiverine and 20% for placebo.

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

Madersbacher et al. [1999] compared the tolerability and efficacy of propiverine (15 mg three times daily) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin. Dorschner et al. [2000] investigated in a double-blind, multicentre, placebo-controlled, randomized study, the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years), suffering from urgency, urgency incontinence or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine – 2 out of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes. The cardiac safety of propiverine was further studied by Donath et al. [2011] in two comprehensively designed mono-centric ECG studies (including 24 healthy females, followed by a second study on 24 male patients with coronary heart disease (CHD) and a pathological Pardee-Q-wave in the ECG). Both studies were placebo-controlled and compared the effects of single (30 mg s.i.d.) and multiple dosing (15 mg t.i.d.) of propiverine hydrochloride in a crossover design over 6 and 13 days, respectively., They were performed to investigate the influence of propiverine hydrochloride and its main metabolite propiverine-N-oxide on cardiac function with regard to QTc prolongation, QTc dispersion and T-wave shape. No negative effects on cardiac safety could be demonstrated.

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

a more pronounced effect on gastrointestinal, cardiovascular, and visual function.

Yamaguchi et al. [2008] performed a multicentre, 12-week, double-blind phase III trial in Japanese men and women with OAB (1593 patients were randomized and 1584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at endpoint in number of voids/24 hours, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence and quality of life (QoL) were examined. It was found that at endpoint, there were greater reductions in mean (SD) voids/24 hours with all drug regimens than with placebo. All active treatments improved the volume voided and QoL vs placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided vs propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg. Wada et al. [2011] performed a prospective nonrandomized crossover study of female OAB patients, assigned alternately to treatment with propiverine (20 mg) for 8 weeks then solifenacin(5 mg) for 8 weeks or solifenacin for 8 weeks then propiverine for 8 weeks. At baseline, 8th week and 16th week, symptoms were assessed using overactive bladder symptom score (OABSS). Of the 121 patients enrolled 83 were analysed. Both drugs were effective. Urgency was further improved after switching from propiverine to solifenacin, but not after switching from solifenacin to propiverine. Solifenacin was better tolerated than propiverine.

In another multicentre, prospective, parallel, doubleblind, placebo-controlled trial, Lee et al. [2009] studied the effects of 30 mg propiverine/day in 264 OAB patients (mean age 52.2 years), 221 of whom had efficacy data available from baseline and at least one on-treatment visit with >75 compliance. The study was focused on improving urgency. Overall, among patients treated with propiverine, 39% rated their treatment as providing 'much benefit', compared with 15 % in the placebo group. Adverse events reported by 32 (22.5%) and 10 (12.7%) patients in the propiverine and placebo group were all tolerable.

Masumori et al. [2011] examined prospectively the efficacy and safety of propiverine in patients with overactive bladder (OAB) symptoms who poorly responded to previous treatment with solifenacin, tolterodine or imidafenacin. Of 73 patients enrolled (29 males and 44 females, median age 71 years), 52 completed the protocol treatment. The OABSS was significantly improved by propiverine treatment. The scores of OAB symptoms (nighttime frequency, urgency and urge incontinence) except daytime frequency also improved significantly. No increase in PVR was observed. The most frequent adverse event was dry mouth (13.7%), followed by constipation (6.8%).

In a non-controlled study in patients with wet OAB the efficacy of propiverine on symptoms and quality of life was confirmed [Komatsu et al. 2009].

Assessment

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

c) Flavoxate hydrochloride

Flavoxate is often discussed as a drug with mixed actions, however, its main mechanism of action may not be antimuscarinic.Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% [Guay, 2003]. The drug is extensively metabolized and plasma half-life was found to be 3.5 h [Sheu et al., 2001]. Its main metabolite (3-methylflavone-8-carboxylic acid, MFCA) has been shown to have low pharmacological activity [Cazzulani et al., 1988; Caine et al., 1991]. The main mechanism of flavoxate's effect on smooth muscle has not been established. The drug has been found to possess a moderate calcium antagonistic activity, to have the ability to inhibit phosphodiesterase, and to have local anesthetic properties; no antimuscarinic effect was found [Guarneri et al., 1994]. Uckert et al. [2000], on the other hand, found that in strips of human bladder, the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable, It has been suggested that pertussis toxin-sensitive G-proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, since intracerebroventricularly or intrathecally administered flavoxate abolished isovolumetric rhytmic bladder contractions in anesthetized rats [Oka et al., 1996].

The clinical effects of flavoxate in patients with DO and frequency, urgency and incontinence have been studied in both open and controlled investigations, but with varying rates of success [Ruffman, 1988]. Stanton [1973] compared emepronium bromide and flavoxate in a double-blind, cross-over study of patients with detrusor overactivity and reported improvement rates of 83% and 66% after flavoxate or emepronium bromide, respectively, both administered as 200 mg 3 times daily. In another double-blind, cross-over study comparing flavoxate 1200 mg/day with that of oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency, and utilising both clinical and urodynamic criteria, Milani et al. [1993] found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects of flavoxate with those of placebo, have not been able

to show any beneficial effect of flavoxate at dosages up to 400 mg three times daily [Briggs et al., 1980; Chapple et al., 1990; Dahm et al., 1995]. In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared to other therapeutic alternatives, is not well documented (**Table 2**).

• ***Assessment***

No RCTs seem to have been performed with flavoxate during the last decade. The scarcity of documented clinical efficacy should be considered before using the drug.

3. CLINICAL USE OF ANTIMUSCARINICS

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned. Herbison et al. [2003] stated in a widely discussed article: "Anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo. The benefits are, however, of limited clinical significance" Large meta-analyses of studies performed with the currently most widely used drugs [Chapple et al., 2005; 2008; Novara et al., 2008], clearly show that antimuscarinics are of significant clinical benefit. Novara et al. [2008] reviewed 50 RCTs and 3 pooled analyses, which they considered of good methodological quality. They concluded that still more clinical studies are needed to decide which of the drugs should be used as first-, second-, or third-line treatment. Reviewing information from more than 12,000 references, Chapple et al. [2008], based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that since the profiles of each drug (see below) and dosage differ, these factors should be considered in making treatment choices.

The durability of the effects of antimuscarinics is not known and the relapse rate of symptoms after discontinuation of treatment has not been systematically studied. In 173 women with OAB symptoms for >6 months, Lee et al.[2011] studied in a prospective, randomized, open-label, trial what happened 3 months after the patients had been successfully treated for 1, 3, or 6-months. The relapse rate was 62%, and the request for treatment was 65 %, indiretly suggesting an efficacy of treatment. None of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine or trospium) is ideal as a first-line treatment for all OAB/DO patients. Optimal treatment should be individualized, implying that the patient´s co-morbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration [Chapple et al., 2008].

To compare the effects of different antimuscarinic drugs for OAB symptoms, Madhuvrata et al. [2012] analyzed 86 trials, 70 with parallel and 16 with cross-over designs (31,249 adults). They concluded that when the prescribing choice is between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. ER preparations of oxybutynin or tolterodine might be preferred to immediate release preparations because there is less risk of dry mouth. Comparing solifenacin and immediate release tolterodine, solifenacin might be preferred for better efficacy and less risk of dry mouth. Fesoterodine might be preferred over ER tolterodine for superior efficacy, but has higher risk of withdrawal due to adverse events and higher risk of dry mouth.

Several studies have documented that the persistence with prescribed antimuscarinic therapy for overactive bladder is low [Kelleher et al., 2005; Basra et al.,2008; Sears et al; Wagg et al., 2012]. The most common causes seem to be lack of efficacy and adverse effects. However, there is some evidence suggesting that the tolerability of the different antimuscarinics may differ. Wagg et al. [2012] analysed prescription data for patients receiving antimuscarinics for treatment of the OAB syndrome over a 12-month period. At 12 months, they found that the proportions of patients still on their original treatment were: solifenacin 35%, tolterodine ER 28%, propiverine 27%, oxybutynin ER 26%, trospium 26%, tolterodine IR 24%, oxybutynin IR 22%, darifenacin 17%, and flavoxate 14%. The longest mean persistence was reported for solifenacin (187 days versus 77 − 157 days for the other treatments). Gomes et al. [2012] compared the persistence of oxybutynin or tolterodine therapy among older patients newly prescribed one of these drugs. This was a retrospective cohort study of Ontarians aged 66 years and older. Persistence with treatment was defined on the basis of refills for the drug within a grace period equal to 50% of the prescription duration. The authors identified 31,996 patients newly treated with oxybutynin and 24,855 newly treated with tolterodine. After 2 years of follow-up, persistence on oxybutynin (9.4%) was significantly lower than that on tolterodine (13.6%, $p < 0.0001$). The median time to discontinuation of oxybutynin and tolterodine was 68 and 128 days, respectively. Kessler et al. [2011] analyzed 69 trials enrolling 26,229 patients with OAB with the aim was to compare adverse events of antimuscarinics using a network meta-analytic approach that overcomes shortcomings of conventional analyses. They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride, but not for oxybutynin orally administered when currently used starting dosages were compared. They concluded that most currently used antimuscarinics seem to be equivalent first choice drugs to start the treatment of OAB, except for oral oxybutynin dosages of ≥ 10 mg/day, which may have more unfavorable adverse event profiles.

Even if the use of antimuscarinics are associated with many adverse effects, they are generally

considered to be 'safe' drugs. However, among the more serious concerns related to their use is the risk of cardiac adverse effects, particularly QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes), and increases in heart rate (HR) [Andersson and Olshansky, 2007; Andersson et al., 2011]. QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart. However, the experiences with terodiline, an antimuscarinic drug that caused torsade de pointes in patients [Connolly et al., 1991; Stewart et al., 1992], have placed the whole drug class under scrutiny.

The parasympathetic actions on the heart (**Figure 10**) opposes the excitatory actions of the sympathetic nervous system, and slows the heart rate (**Figure 11**). An elevated resting HR has been linked to overall increased morbidity and mortality, particularly in patients with cardiovascular diseases. The prevalence of CV comorbidities was found to be significantly higher in patients with than without OAB [Andersson et al., 2010]. Since mean changes in HR reported in population studies might not be applicable to an individual patient, and particularly in patients at risk of cardiac disease, even moderate increases in HR might be harmful. The potential of the different antimuscarinic agents to increase HR and/or prolong the QT time has not been extensively explored for all agents in clinical use. Differences between drugs cannot be excluded, but risk assessments based on available evidence are not possible.

II. DRUGS ACTING ON MEMBRANE CHANNELS

1. CALCIUM ANTAGONISTS

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and thereby contribute to the regulation of smooth muscle tone [Berridge, 2008] Two major groups of calcium channels include the voltage-gated [Caterall et al., 2003] and the store-operated channels [Leung et al., 2008]. While both can contribute to the maintenance of smooth tone in general, store-operated calcium channels apparently contribute only to a limited if any extent to the regulation of bladder smooth muscle tone [Schneider et al., 2004 a; b]. On the other hand, various types of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle including Q-type [Frew and Lundy, 1995] and L-type channels [Wuest et al., 2007]. The latter appears to be of particular importance as inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in

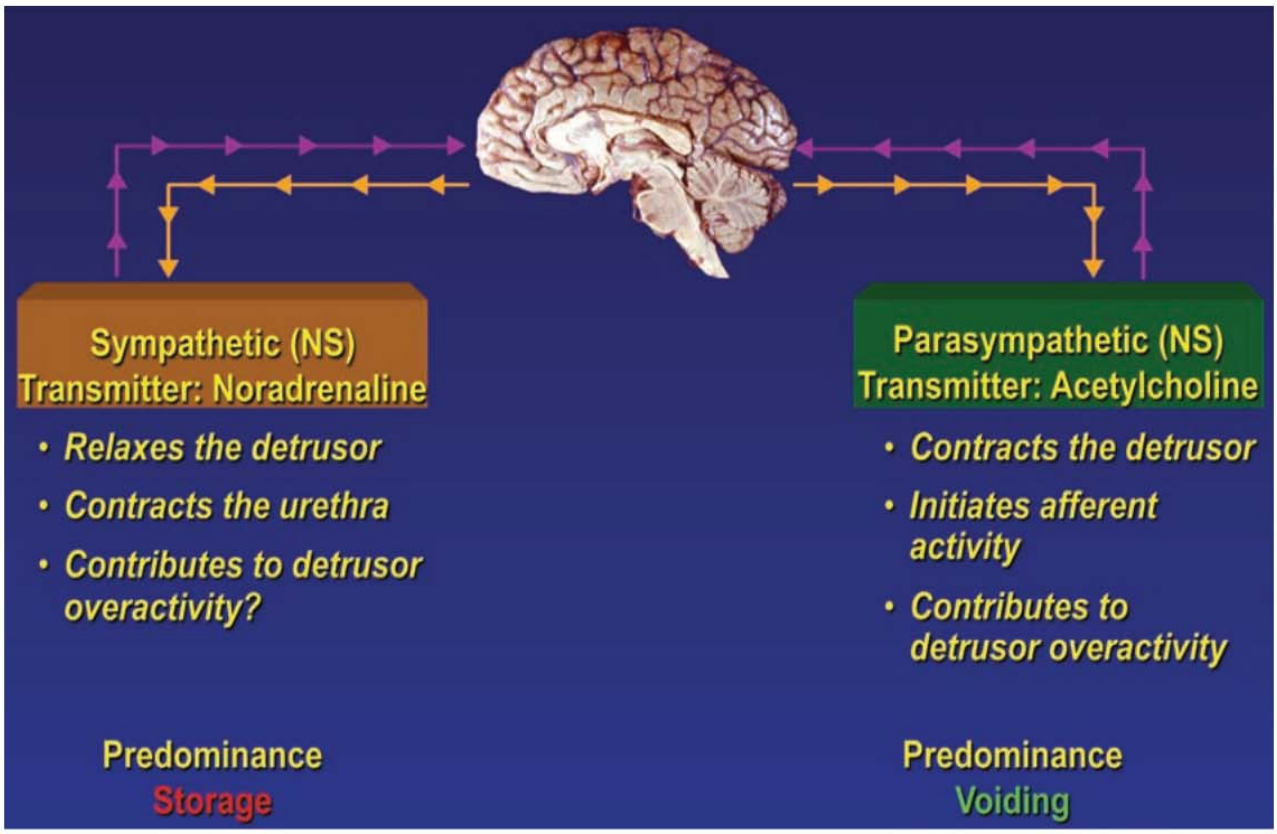

Figure 10 : Cardiac control via the autonomic nervous system. Acetylcholine, released from parasympathetic nerve terminals activate muscarinic receptors that mediate decrease in heart rate, decrease in force of contraction, and decrease in conduction velocity.

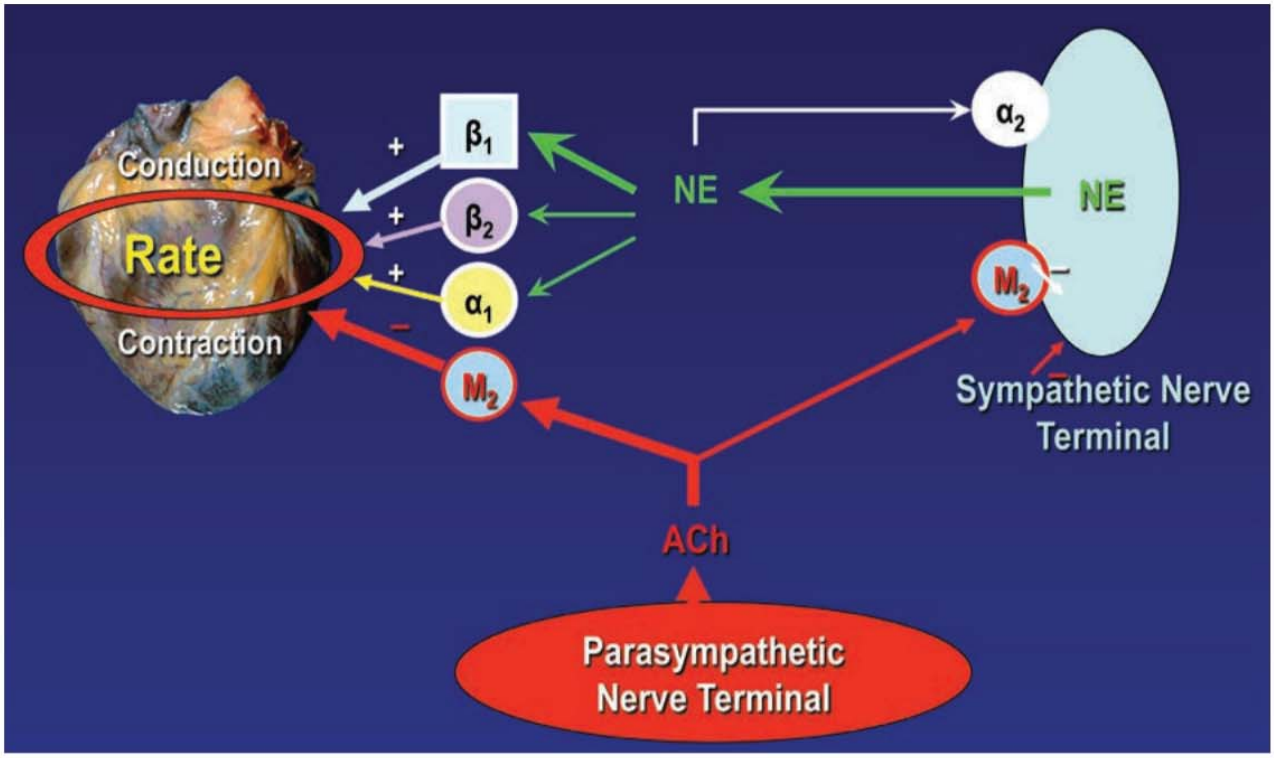

Figure 11: Autonomic receptors controlling heart rate. Acetylcholine, released form parasympathetic nerve terminals, activate muscarinic M2 receptors that mediate a decrease in heart rate. Inhibition of these receptors by antimuscarinics may increase heart rate.

vitro with tissue from multiple mammalian species, including humans [Frazier et al., 2008]. However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species [Wuest et al., 2007]. In confirmation of the role of L-type calcium channels, it has been shown that knock-out mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility [Wegener et al., 2004].

While these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical installation of the calcium channel inhibitor verapamil, the muscarinic receptor antagonists oxybutynin and trospium and placebo to patients with urgency or urgency incontinence. While the two muscarinic receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function [Fröhlich et al., 1998]. In a clinical study of limited size the calcium channel inhibitor nimodipine (30 mg per day) did not significantly improve the number of incontinence episodes as compared to placebo [Naglie et al., 2002]. Larger studies with clinical endpoints related to effects of calcium channel inhibitors have not been reported in incontinent patients (based upon a Medline search using the MeSH terms “calcium channel blockers” and “urinary incontinence”). Moreover, it should be noted that despite a long-standing and wide-spread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro and the lack of clinical data are not fully clear, but it may relate to pharmacokinetic properties of the currently used drugs which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction (**Table 2**). No new information has been added since the assessment in 2008 [Andersson et al., 2009].

2. POTASSIUM CHANNEL OPENERS

In a similar fashion to calcium channels, potassium channels also contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. Numerous types of potassium channels exist [Gutman et al., 2003; Petkov et al., 2012]. With regard to bladder function, ATP-dependent (KATP) and big calcium-activated (BKCa) channels have been studied most intensively. The BKCa channels also appear to be important physiologically as their activation can cause hyperpolarization of bladder smooth muscle cells and by this mechanism they can contribute to the relaxation of bladder smooth muscle by, e.g., β-adrenoceptor agonists [Frazier et al., 2008]. Openers of both KATP [Howe et al., 1995; Hu et al., 1997; Martin et al., 1997] and

BKCa channels [Hu et al., 1997; Sheldon et al., 1997] have been shown to induce bladder smooth muscle relaxation in various mammalian species, but the density of some types of potassium channels may differ markedly between species. Some potassium channel openers have also been shown to suppress non-voiding detrusor contractions in vivo in animal models of DO [Howe et al., 1995; Martin et al., 1997; Tanaka et al., 2003] and this also includes activators of the KCNQ type of potassium channels [Streng et al., 2004]. Although potassium channel openers are believed to mainly act directly on smooth muscle cells [Gopalakrishnan and Shieh, 2004; Petkov et al., 2012], they may also at least in part affect bladder function by modulating the activity of afferent neurones [Tanaka et al., 2003].

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

Another way to use potassium channels to normalize bladder function was suggested by Christ et al. [2001] in a rat model of detrusor hyperactivity. They injected “naked” hSlo/pcDNA3 (maxiK channel) into the bladder and found a significant amelioration of the hyperactivity. As to whether this principle can be therapeutically useful in man is currently under investigation.

III. α-ADRENOCEPTOR (AR) ANTAGONISTS

It is well documented that α1-AR antagonists can ameliorate lower urinary tract symptoms in men [Andersson, 2002; McVary et al., 2011; Oelke et al., 201l; Lepor et al., 2012]. Currently used α1-AR antagonists are considered effective for treatment of both storage and voiding symptoms in men with LUTS associated with or suggestive of BPH [Lepor et al., 2012]. However, in a study where tamsulosin was given alone, or together with tolterodine, to patients with male LUTS and OAB symptoms, monotherapy with the drug was not effective [Kaplan et al., 2006]. In an RCT from Korea, doxazosin monotherapy resulted in only minimal effects in IPSS storage subscore, urgency episodes and no improvement in the patient perception of bladder condition (PPBC) [Lee et al., 2011]. Thus, there is no convincing evidence that α-AR antagonists, given as monotherapy, are effective in patients with storage symptoms only.

A pivotal question is if better efficacy and/or tolerability can be obtained by highly subtype selective drugs than with the commonly used alternatives. α1-ARs include three receptor subtypes, α1A, α1B, and α1D, that are structurally and pharmacologically distinct and have different tissue distributions [Andersson and Gratzke, 2007]. α1A-ARs are the predominant subtype in the human prostate, where they mediate smooth muscle contraction. A fourth subtype, α1L, also present in human prostate, is derived from the same gene as α1A, but α1L- and α1A-receptors have different pharmacologic properties and bind some α-AR antagonists with different affinities. The precise structural relationship between the two subtypes remains to be elucidated.

Selectivity for α1B-AR has been considered disadvantageous from a cardiovascular point of view [Schwinn et al,, 2004; Schwinn and Roehrborn, 2008]. Kojima et al. [2008)] studied the expression of α1-AR in the transitional zone of prostates from 55 patients with BPH, comparing patients treated with tamsulosin presumed to block α1A-ARs and naftopidil presumed to block α1D-ARs. However, the selectivity of naftopidil for α1D- vs α1A-ARs is modest [Take et al., 1998] and its use as a tool to separate between α1-AR subtypes is questionable. Nevertheless, the tamsulosin and naftopidil groups were classified as α1A-AR dominant (22 and 12 patients) and α1D-AR dominant (11 and 16, respectively). The efficacy of tamsulosin and naftopidil differed depending on the dominant expression of the α1-AR subtype in the prostate. Tamsulosin was more effective in patients with dominant expression of the α1A-AR subtype, whereas naftopidil was more effective in those with dominant expression of the α1D-AR subtype. In another study, the same group assessed whether there was a direct correlation between the prostatic expression of α1-AR subtype mRNA and severity of LUTS or bladder outlet obstruction [Kojima et al., 2010]. They found no direct correlation between the expression of α1-AR subtype mRNA in the prostate and severity of LUTS or BOO, although there was a significant regression of this expression with patient age. Kojima et al. [2010] concluded that the expression level of α1-AR subtype mRNA in the prostate could be a predictor of the efficacy of subtype selective α1-AR antagonists in patients with BPH, and

suggested that genetic differences were responsible for the diverse responses to the drugs.

Silodosin (KD-3213), which has a high selectivity for α1A-ARs [Tatemichi et al., 2006a; b; Lepor and Hill, 2010; Yoshida et al., 2011], had clinically good effects on both voiding and storage symptoms in men with BPH [Kawabe et al., 2005; Yoshida et al., 2007; Marks et al., 2009a,b; Chapple et al., 2010; Morganroth et al., 2010; Yoshida et al., 2011]. Chapple et al. [2010] conducted a multicenter double-blind, placebo- and active-controlled parallel group study comparing silodosin, tamsulosin, and placebo. A total of 1228 men ≥50 yr of age with an International Prostate Symptom Score (IPSS) ≥13 and a urine maximum flow rate (Qmax) >4 and ≤15ml/s were selected at 72 sites in 11 European countries. The patients were entered into a 2-wk wash-out and a 4-wk placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg (n=381), tamsulosin 0.4 mg (n=384), or placebo (n=190) once daily for 12 wk. Its overall efficacy was not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo. There was no significant difference between the two α1-AR antagonists and the placebo in terms of Qmax. There was also no difference between the two α-AR antagonists for the QoL parameter, whereas both were better than the placebo. Active treatments were well tolerated, and discontinuation rates due to adverse events were low in all groups (2.1%,1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively).The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α1A-AR antagonism of the drug. The incidence was higher than that observed with tamsulosin (2%); however, only 1.3% of silodosin-treated patients discontinued treatment due to this adverse event. Silodosin treatment improved DO and obstruction grade by decreasing detrusor opening pressure, detrusor pressure at Qmax, bladder outlet obstruction index and Schafer´s obstruction class significantly [Yamanishi et al., 2009]. In a different open, nonblinded prospective study silodosin 8 mg lead to a significant increase in bladder capacity at first desire to void with no significant change in maximum cystometric capacity. In the voiding phase mean detrusor pressure at maximum flow significantly decreased, mean bladder outlet obstruction index decreased significantly and obstruction grade as assessed by the Schaefer nomogram improved significantly [Matsukawa et al., 2009].

It thus seems that selective blockade of α1A-ARs is a clinically effective approach, and silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in male patients with LUTS, even if treatment is associated with a high incidence of ejaculatory dysfunction.

Interest has also been focussed on the α1-ARs (α1D), specifically in the bladder [Schwinn et al., 2004; Schwinn and Roehrborn, 2008], assuming that these receptors were responsible for storage symptoms. However, the inter-relationship between the α1D-ARs in the human detrusor smooth muscle and the pathophysiology of LUTS is unclear. Naftopidil was shown to significantly improve the OAB symptom score [Sakai et al., 2011] and urgency episodes [Yokoyama et al., 2009]. Ikemoto et al. [2003] gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the I-PSS for storage symptoms, tamsulosin monotherapy decreased the I-PSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α1-AR subtypes between the drugs) could not be reproduced in a randomized head to head comparison between the drugs [Gotoh et al, 2005]. Based on available evidence, it therefore cannot be concluded that the α1D-ARs on the detrusor smooth muscle are the main therapeutic target. However, α1D-ARs may have effects on different locations in the bladder beside the detrusor smooth muscle: the detrusor vasculature, the urothelium, and the afferent and efferent nerve terminals and intramural ganglia [Andersson and Gratzke, 2007]. The importance and functional role of this observation remain to be established.

In females, treatment with OAB, α1-AR antagonists seem to be ineffective. In an RCT, comprising 364 women with OAB, no effect of tamsulosin vs placebo could be demonstrated [Robinson et al., 2007]. On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were treated (with modest success) with an α1-AR antagonist [Kessler et al., 2006, Low et al., 2008]. It should be remembered that in women, these drugs may produce stress incontinence [Dwyer and Teele, 1992].

In patients with neurogenic DO, treatment with a1-AR antagonists was moderately successful [Abrams et al., 2003].

IV. β-ADRENOCEPTOR AGONISTS

In isolated human bladder, non-subtype selective β-AR agonists like isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in man [Andersson, 1993]. However, the β-ARs of the human bladder were shown to have functional characteristics typical of neither β1-, nor β2- ARs, since they could be blocked by propranolol, but not by practolol or metoprolol (β1) or butoxamine (β2) [Nergard et al., 1977; Larsen, 1979]. On the other hand, early receptor binding studies using subtype selective ligands, suggested that the β-ARs of the human detrusor are primarily of β2 subtype [Andersson

1993], and favourable effects on DO were reported in open studies with selective β2-AR agonists such as terbutaline [Lindholm and Lose, 1986]. In a double-blind investigation clenbuterol 0.01 mg 3 times daily was shown to have a good therapeutic effect in 15 of 20 women with DO [Gruneberger, 1984]. Other investigators, however, have not been able to show that non-subtype selective β-ARs agonists represent an effective therapeutic principle in elderly patients with DO [Castleden and Morgan, 1980], or in young patients with myelodysplasia and DO [Naglo et al, 1981].

However, three subtypes (β1, β2, and β3) have been identified in the detrusor of most species, including humans [Andersson and Arner, 2004; Michel and Vrydag, 2006]. Also the human urothelium contains all three receptor subtypes [Otsuka et al., 2008]. Studies, using real-time RT-PCR, have revealed a predominant expression of β3-AR mRNA in human detrusor muscle [Nomiya and Yamaguchi, 2003; Michel and Vrydag, 2006, , Igawa et al., 2010] and the functional evidence for an important role in both normal and neurogenic bladders is convincing [Fujumura et al., 1999; Igawa et al., 1999; Takeda et al., 1999; Morita et al., 2000; Igawa et al., 2001; 2010; Biers et al., 2006; Michel and Vrydag, 2006; Badawi et al., 2007; Leon et al., 2008]. The human detrusor also contains β2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in this structure [Andersson and Arner 2004; Michel and Vrydag, 2006; Igawa et al., 2010].

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species, is activation of adenylyl cyclase with the subsequent formation of cAMP (**Figures 12 and 13**). However, there is evidence suggesting that in the bladder K+ channels, particularly BKCa channels, may be more important in β-AR mediated relaxation than cAMP [Hudman et al., 2000; Frazier et al., 2005; Uchida et al., 2005; Frazier et al., 2008]. Aizawa et al. [2010] showed that the β3-AR agonist, CL316,243, could inhibit filling-induced activity in mechanosensitive Aδ-fibers, but not in C-fiber primary bladder afferents of the rat bladder. However, the drug was able to inhibit prostaglandin (PG) E2-induced C-fiber mediated hyperactivity.

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated [Murakami et al., 2007; Otsuka et al., 2008]. Murakami et al. [2007] found that the relaxation responses of the detrusor were not influenced

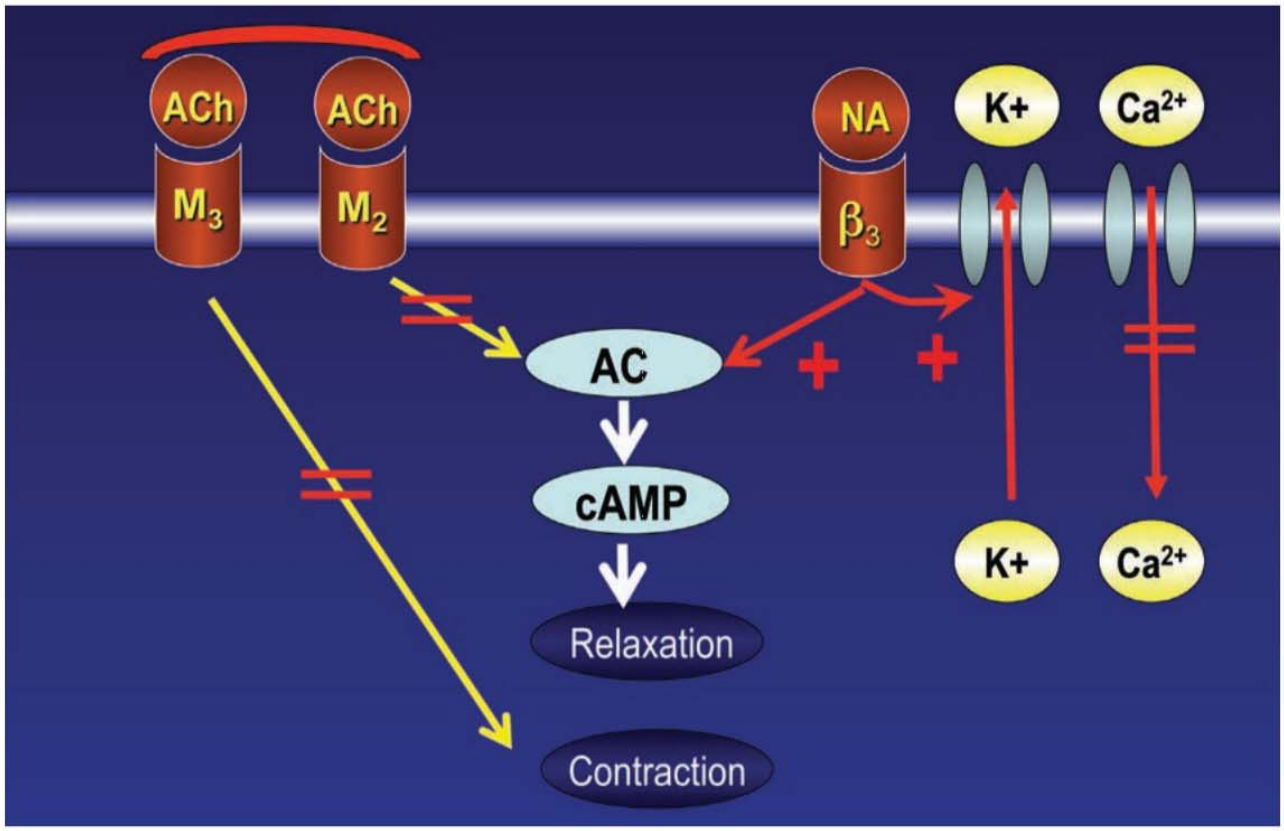

Figure 12 : During bladder filling, there is normally no parasympathetic nervous outflow to the bladder and no release of acetylcholine (ACh). The sympathetic nervous system is active and releases noradrenaline (NA) that via β3 adrenoceptors stimulates adenylyl cyclase (AC) and generation of cyclic AMP (cAMP) which mediates relaxation of the bladder. In addition, β3-adrenoceptor stimulation activate K+ channels, stimulating outflow of K+, which causes hyperpolarisation and inhibition of Ca2+ inflow.

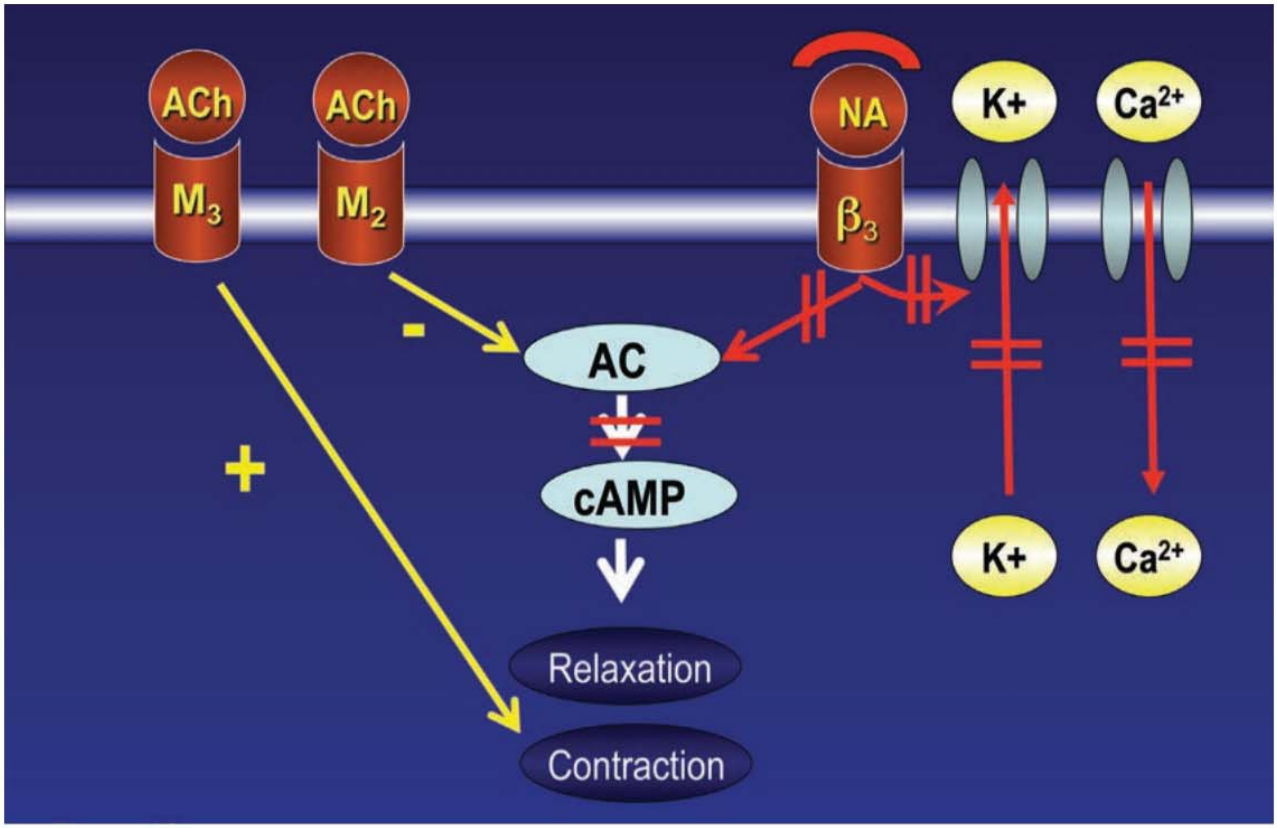

Figure 13: During voiding, the parasympathetic system is activated, releasing acetylcholine (ACh) which causes bladder contraction, directly via muscarinic M3 receptor stimulation, and indirectly by inhibition of adenylyl cyclase (AC) via stimulation of muscarinic M2 receptors. The sympathetic nerve activity is turned off. In vivo exogenous stimulation of the β3-adrenoceptors by β3-adrenoceptor agonists is not sufficient to inhibit the muscarinic receptor mediated activation, which implies that the voiding contraction is not compromised.

by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka et al. [2008]. However, to what extent a urothelial signaling pathway contributes in vitro and in vivo to the relaxant effects of β-AR agonists in general, and β3-AR agonists specifically, remains to be elucidated.

The in vivo effects of β3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [Fujimura et al., 1999; Woods et al., 2001; Takeda et al., 2002; Kaidoh et al., 2002; Igawa et al., 2010]. For example, Hicks et al. [2007] studied the effects of the selective β3-AR agonist, GW427353, in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid evoked bladder hyperactivity, without affecting voiding.

A number of β3-AR selective agonists are currently being evaluated as potential treatment for OAB in humans including GW427353 (solabegron) and YM178 (mirabegron) [Colli et al., 2007; Igawa et al., 2010; Saito et al., 2011; Tyagi and Tyagi, 2011] (**Figure 14**).

Mirabegron. Takusagawa et al. [2012] found that mirabegron was rapidly absorbed after oral administration. It circulates in the plasma as the unchanged form, its glucuronic acid conjugates and other metabolites. Of the administered dose, 55% is excreted in urine, mainly as the unchanged form, and 34% is recovered in feces, almost entirely as the unchanged form. Mirabegron is highly lipophilic and is metabolized in the liver via multiple pathways, mainly by cytochrome P450 3A4 and 2D6 (CYP2D6) [van Gelederen et al., 2009]. In a Phase I pharmacokinetic study, sixteen healthy volunteers, phenotyped as either poor or extensive metabolizers of CYP2D6 were enrolled The volunteers received a 160 mg single oral dose after overnight fasting. Poor metabolizers excreted a slightly higher urinary fraction of mirabegron (15.4±4.2%) than extensive metabolizers (11.7±3.0%). Tmax in both extensive and poor metabolizers was about

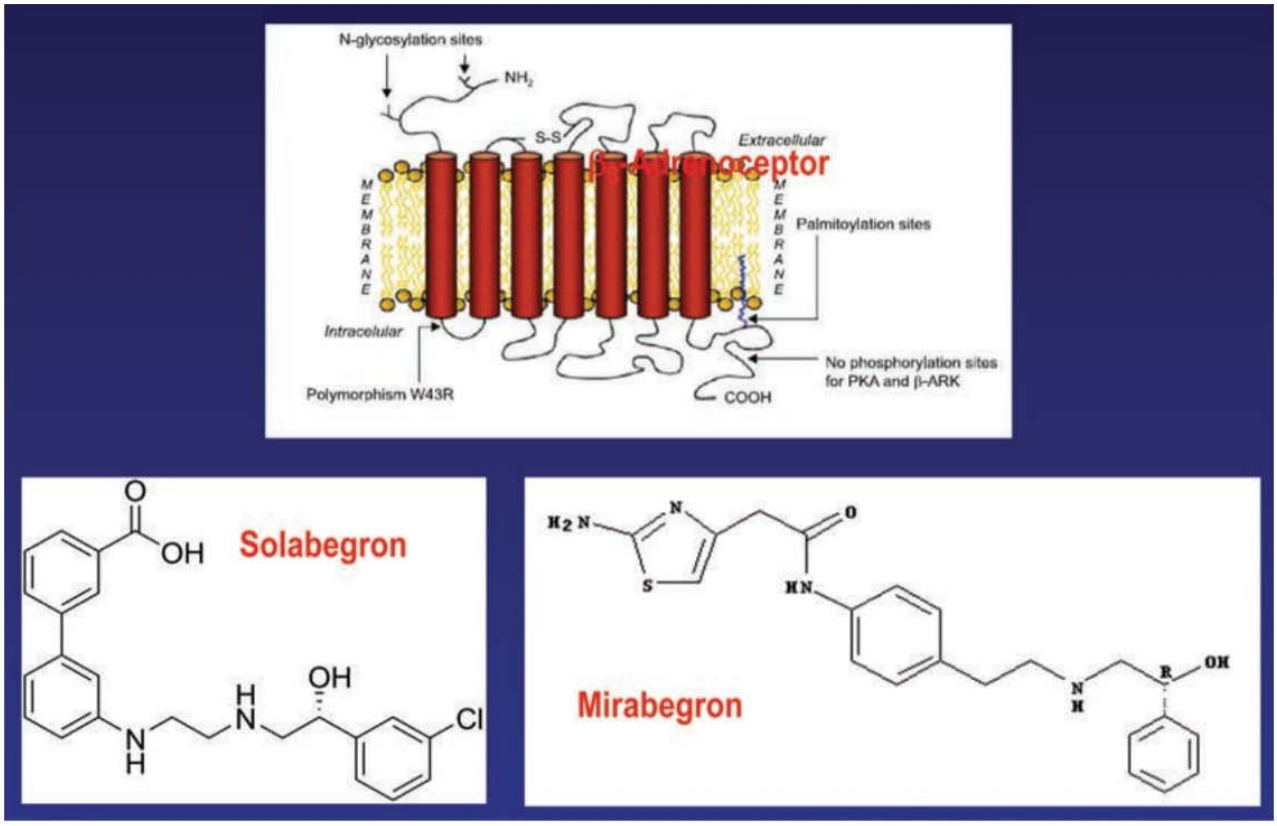

Figure 14: The β3-adrenoceptor is the predominating β-adrenoceptor subtype in the bladder. Stimulation by highly selective β3-adrenoceptor agonists like mirabegron and solabegron may inhibit symptoms of overactive bladder without affecting the ability to empty the bladder.

2 hours and the terminal elimination half-life (t1/2) approximately 23-25 hours.

Chapple et al. [2008] reported the results of a phase IIA trial of mirabegron in patients with OAB. The Blossom trial, conducted in several European countries, was a proof of concept study. It enrolled 314 patients with OAB symptoms - 262 patients were randomly assigned to 4 groups: placebo, mirabegron 100 mg bid, mirabegron 150 mg bid, and tolterodine 4 mg qd for a 4-week treatment period. The primary endpoint was efficacy, and the primary efficacy variable was the change in the mean number of micturitions per 24 hours as recorded on a frequency/volume chart. In both mirabegron groups significant improvements in the mean number of micturitions per 24 hours were found compared with the placebo group (−2.19 and −2.21 vs. −1.18, respectively). Mean volume voided was dose-dependently increased in the mirabegron groups, and the change reached significance in the mirabegron 150 mg group. Urgency episodes per 24 hours decreased significantly in both mirabegron groups compared with the placebo group. No severe adverse events were reported and treatment was generally well tolerated. A small, mean increase in pulse rate with mirabegron 150 mg (5 beats per minute) was demonstrated, but this was not associated with a clinically significant increase in adverse events such as tachycardia and palpitations. This successful phase IIA trial was followed by a phase IIB trial in OAB patients carried out in Europe [Chapple et al., 2010]. This trial was a dose-ranging study of once-daily mirabegron (an extended release formula of mirabegron) with multiple arms (placebo, mirabegron 25 mg, 100 mg, 150 mg, and 200 mg qd, for a 12-week treatment period), and the primary endpoint was to evaluate the dose-response relationship on efficacy. The mean number of micturitions per 24 hours decreased dose-dependently, and the decreases were statistically significant with mirabegron 50 mg, 150, and 200 mg compared with placebo. The mean volume voided per micturition increased dose-dependently, and the increases were significant with mirabegron 50 mg and more. Adverse events were experienced by 45.2% of the patients - the incidence of adverse events was similar among all treatment groups (placebo 43.2% vs. mirabegron 43.8-47.9%). The overall discontinuation rate owing to adverse events was 3.2% (placebo 3.0% vs. mirabegron 2.4-5.3%). The most commonly reported adverse events considered treatment-related was gastrointestinal disorders, including constipation, dry mouth, dyspepsia, and nausea. There was no patient-reported acute retention. No significant difference in ECG parameters between

the groups was demonstrated. However, a small but significant increase in mean pulse rate was observed after mirabegron 100 mg and 200 mg (1.6 and 4.1 beats per minute, respectively), although this was not in associated with an increase in cardiovascular adverse events.

Nitti et al. [2011] reported on a phase III multicentre, randomized, double-blind, parallel-group,placebo-controlled trial of mirabegron in North America. They enrolled 1328 patients ≥18 years with OAB symptoms for ≥3 months. Patients who completed a 2-week, single-blind, placebo run-in and had ≥8 micturitions/24 h and ≥3 urgency episodes/72 h (with or without incontinence) during a 3-day micturition diary period, were randomized to receive placebo, or mirabegron 50 or 100 mg once daily for 12 weeks. Co-primary endpoints were change from baseline to final visit (study end) in the mean number of incontinence episodes/24 h and micturitions/24 h. Efficacy was assessed according to patient micturition diaries and safety assessments included adverse event (AE) reporting. Patients were randomized and received study drug (placebo: n=453; mirabegron 50 mg: n=442; mirabegron 100 mg: n=433). Mean age was 60.1 years, 74.3% were female, 29.7% had urgency incontinence, 38.1% had mixed stress/urgency incontinence with urgency predominant and 32.2%had frequency without incontinence. At the final visit, mirabegron 50 and 100 mg showed statistically significant improvements in the co-primary efficacy endpoints and mean volume voided/micturition compared with placebo. Statistically significant benefits were achieved at the first-measured time point of Week 4. The incidence of AEs was similar across the placebo and mirabegron 50 and 100 mg groups (50.1, 51.6 and 46.9%, respectively). The most common (≥3%) AEs in any treatment group were hypertension (6.6, 6.1 and 4.9%, respectively), urinary tract infection (1.8, 2.7 and 3.7%), headache (2.0, 3.2 and 3.0%) and nasopharyngitis (2.9, 3.4 and 2.5%).

Khullar et al. [2011] performed a similarly designed study i Europe and Australia, enrolling 1978 patients, which included a fourth arm in which tolterodine SR 4 mg was used as a comparator. Like the American study, Khullar et al. [2011] found that mirabegron caused a statistically significant improvements from baseline compared with placebo in the number of urgency incontinence episodes and number of micturions per 24 hours. Mirabegrom 50 and 100 mg was numerically superior to tolterodine in these two key OAB symptoms, but the study was not powered for further analysis. Mirabegrom 50 and 100 mg was well tolerated, no differences being found between the placebo arm and the two mirabegron arms. In particular, the incidence of hypertension or UTI were identical. In contrast with tolterodine, no increased dry mouth incidence was observed with mirabegron.

Mirabegron has been shown to be effective in the treatment of the OAB syndrome and has been approved for clinical use on this indication in Japan. The Japanese label contains a warning: “Avoid administration to patients of reproductive age”. Mirabegron is currently under consideration for approval in Europe (EMA). In the US, the drug was approved in June 2012.

A positive effects of solabegron in patients with the OAB syndrome has also been documented in an RCT [Ohlstein et al., 2012].

V. PHOSPHODIESTERASE (PDE) INHIBITORS

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [Andersson, 1999; Andersson and Wein, 2004]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [Andersson and Arner, 2004]. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach [Andersson et al., 1997; 2007; 2011]. There are presently 11 families of PDEs, some of which preferentially hydrolyse either cAMP or cGMP [Uckert et al., 2006] (**Figure 15**).

As a basis for PDE inhibitor treatment of LUTS, Uckert et al. [2006] investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. In vitro, human detrusor muscle responded poorly to sodium nitroprusside, and to agents acting via the cGMP system [Truss et al., 2000]. However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone [Truss et al., 2001]. Significant dose-dependent relaxations were also induced by human cAMP analogs [Truss et al., 2001]. With these studies as a background, Truss et al. presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders, and not responding to standard antimuscarinic therapy [Truss et al., 2000]. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine only showed statistically significant results for one parameter [Truss et al., 2001]. Studies with other PDE 1 inhibitors than vinpocetin (which may not be an optimal drug for elucidation the principle) do not seem to have been performed.

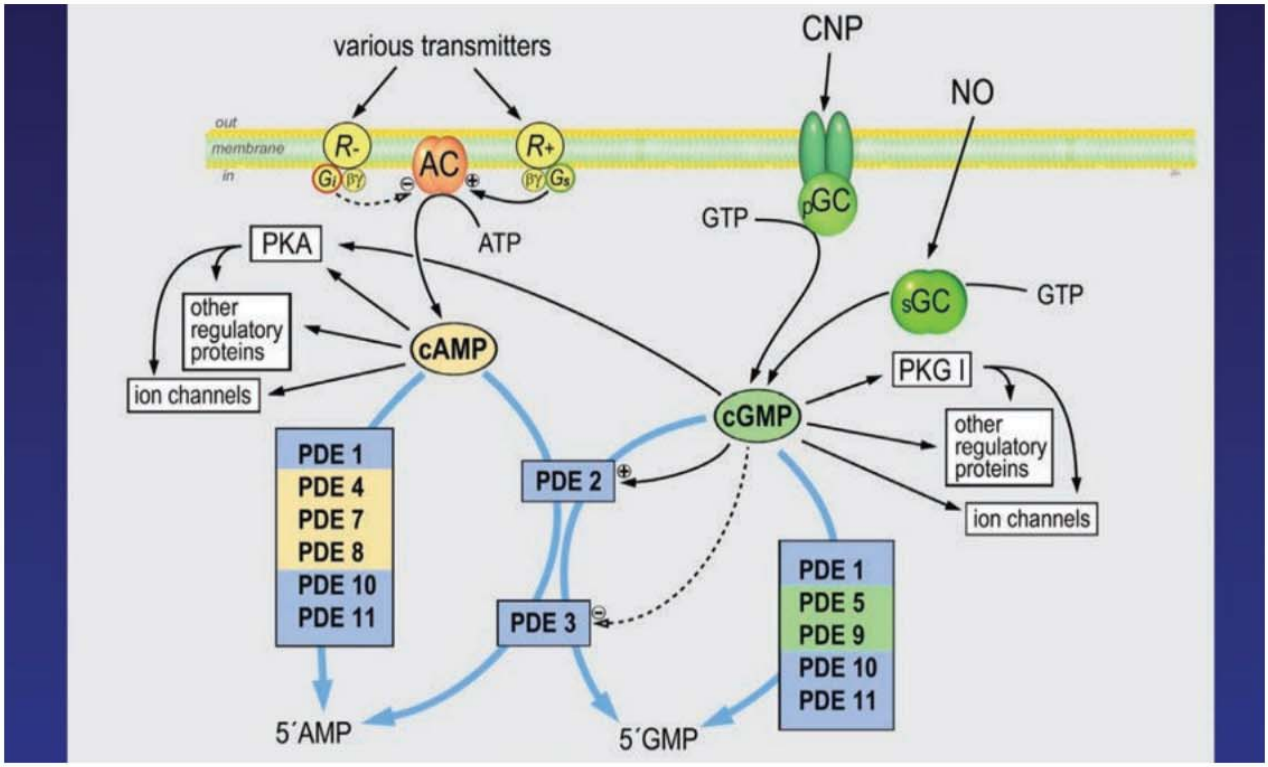

Figure 15: Families of phosphodiesterases (PDE). Inhibitors of both cyclic AMP and cyclic GMP may have inhibitory effects on bladder contraction. However, so far only inhibitors of PDE5 (inhibiting degradation of cyclic GMP) have been clinically useful for treatment of lower urinary symptoms in males.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the in vitro contractile response of guinea pig [Longhurst et al., 1997] and rat [Kaiho et al., 2008] bladder strips, and also suppressed rhythmic bladder contractions of the isolated guinea pig and rat bladder [Gillespie and Drak., 2004; Nishiguchi et al., 2007]. Previous experiences with selective PDE 4 inhibitors showed emesis to be a dose -limiting effect [Giembycz, 2005]. If this side action can be avoided, PDE 4 inhibition seems to be a promising approach.

Oger and co-workers showed that PDE5-inhibitor sildenafil-induced relaxation of human detrusor smooth muscle involved cGMP-, cAMP- and K(+) channel-dependent signalling pathways, with a minor contribution from NO [Oger et al., 2010]. In combination with the α1-AR antagonist doxazosin, sildenafil reduced adrenergic tone of prostatic and cavernosal smooth muscle and their combination provided a significant benefit when targeting relaxation of both tissues [Oger et al., 2008].

In-vivo, several studies have indicated a role for PDE5-inhibitors in the regulation of micturition function. Systemic vardenafil reduced both non-voiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, spinal cord injury rats, indicating potential mechanisms by which PDE5-Is improve storage symptoms in SCI patients [Behr-Roussel et al., 2010]. The effect of vardenafil on OAB-symptoms could be related to a cGMP-dependent RhoA/ROCK signaling inhibition, as shown in spontaneously hypertensive rats (SHR) [Morelli et al., 2009a; Morelli et al., 2009b]. Using the same animal model, bladder hypoxia was significantly reduced by acute vardenafil treatment [Morelli et al., 2009b]. Thus, besides relaxing muscular wall, PDE5 inhibition may positively affect urinary bladder blood perfusion. In the same respect, tadalfil was shown to increase prostate tissue oxygenation in SHR and human vesicular-deferential artery is characterized by a high expression and activity of PDE5, which was inhibited by tadalafil in vitro; these results suggest another possible mechanism through which PDE5i exert beneficial effects on LUT symptoms [Morelli et al., 2011].

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [Andersson and Arner, 2004]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita et al. examined the effects of isoproterenol, prostaglandin E1 and E2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra [Morita et al., 1994]. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström et al.[2006] characterized the distribution of PDE 5, cGMP and PKG1 in female pig and human urethra,

and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NO-NO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations. Fibbi et al. [2009] confirmed that the highest expression and biological activity of PDE5 was found in bladder. However, a consistent PDE5 expression and activity was also found in prostatic urethra. In contrast, the prostate gland showed the lowest PDE5 abundance and cultures derived from this tissue were less sensitive to vardenafil. Using a different animal model associated with C-fibre afferent activation, it was shown that the NO/cGMP signalling pathway is involved in the regulation of the micturition reflex, with an action that seems more predominant on the sensory rather on the motor component of the micturition reflex [Caremel et al., 2010].

The observation that patients treated for erectile dysfunction with PDE5 inhibitors had an improvement of their LUTS, has sparked a new interest in using these drugs also for treatment of LUTS and OAB. After the report in an open study that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS [Sairam et al., 2002], this observation has been confirmed in several well designed and conducted RCTs.

To date, 12 RCTs are available comparing the effect of PDE5 inhibitors alone to placebo and the combination of alpha-blockers and PDE5 inhibitors vs alpha-blockers alone [Bechara et al., 2008; Gacci et al., 2011; Kaplan et al., 2007; Liguori et al., 2009; McVary et al., 2007a; b; Porst et al., 2009; 2011; Roehrborn et al., 2008; Stief et al., 2008; Tamimi et al., 2010; Tuncel et al., 2010]. In these studies, different PDE5 inhibitors and different doses were administered.

PDE5-inhibitors significantly improve IPSS and IIEF scores, but not Qmax when compared to placebo. According to a recent meta-analysis by Gacci and co-workers, differences in IPSS score were significantly lower in older and obese patients [Gacci et al., 2011]. The combination of PDE5-inhibitors and alpha-blockers lead to significant improvements of the IPSS and IIEF score as well as Qmax when compared to the use of alpha-blockers alone. Recently, Dmochowski showed that tadalafil once daily for LUTS had no significant effect on bladder function as measured by detrusor pressure at maximum urinary flow rate or such as maximum detrusor pressure and bladder outlet obstruction index while improving IPSS [Dmochowski et al., 2010]. PDE5-inhibitors were generally shown to be safe and well tolerated.

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In none of the trials referred to such an effect was found. (However, see Oelke et al.[2012]). On the other hand, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstital cells, and suburothelial afferent nerves). In general, it is believed that major mechanisms contributing to LUTS include reduced nitric oxide/cyclic guanosine monophosphate signaling pathway, increased RhoA kinase pathway activity, autonomic overactivity, increased bladder afferent activity and pelvic ischemia [Andersson et al., 2011].

In practical considerations it has to be mentioned that only tadalafil has been recently approved for the the treatment of LUTS due to benign prostatic obstruction; long-term experience with PDE5 inhibitors in patients with LUTS is still lacking [Oelke et al., 2011]. In addition, insufficient information is available on the combination of PDE5 inhibitors with other LUTS medications such as 5-alpha-reductase-inhibitors.

VI. ANTIDEPRESSANTS

Several antidepressants have been reported to have beneficial effects in patients with DO [Lose et al., 1989; Martin and Schiff, 1984]. The use of antidepressants was shown to be an independent risk factor for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men (Krimpen Study) [Kok et al., 2009].

1. IMIPRAMINE

Imipramine is the only drug that has been widely used clinically to treat this disorder. Imipramine has complex pharmacological effects, including marked systemic antimuscarinic actions [Baldessarini, 1985] and blockade of the reuptake of serotonin and noradrenaline [Maggi et al., 1989], but its mode of action in DO has not been established [Hunsballe and Djurhuus, 2001]. Even if it is generally considered that imipramine is a useful drug in the treatment of DO, no good quality RCTs that can document this have been retrieved. It has been known for a long time that imipramine can have favourable effects in the treatment of nocturnal enuresis in children with a success rate of 10-70 % in controlled trials [Glazener et al., 2003; Hun-

sballe and Djurhuus, 2001]. It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine [Bigger et al., 1977; Giardina et al., 1979]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [Baldessarini, 1985]. The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have have been performed during the last decade [Hunsballe and Djurhuus, 2001; Natalin et al., 2009]. No good quality RCTs have documented that the drug is effective in the treatment DO. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

A prospective (no controls) study the impact of the "three-drug therapy" (antimuscarinic, alpha-blocker and tricyclic antidepressants) on the treatment of refractory detrusor overactivity (DO) showed a significant increase on bladder capacity and decreases on urgency, urge-incontinence and frequency. Objective urodynamic data as well as symptom score improved significantly with triple therapy [Natalin et al., 2009].

Selective serotonin-reuptake-inhibitors (SSRIs) have been tested with regard to their effects on OAB symptoms. Milnacipran hydrochloride, a serotonin-norepinephrine reuptake inhibitor (SNRI), or paroxetine hydrochloride, a selective serotonin reuptake inhibitor, were analyzed in a prospective open trial in neurogenic OAB-patients. Milnacipran reduced daytime urinary frequency, improved the quality of life index and increased bladder capacity as shown in urodynamic studies. No such changes were noted in the other categories of the lower urinary tract symptoms questionnaire or urodynamic studies, or in the paroxetine group [Sakakibara et al., 2008].

2. DULOXETINE

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Katofiasc et al., 2002; Thor and Katofiasc, 1995]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [Fraser and Chancellor, 2003]. In a placebo-controlled study, the drug showed efficacy in patients with OAB [Steers et al., 2007]. The number of micturition episodes, the primary outcome, was reduced by 2 in the duloxetine arm and by 0.5 in the placebo arm. Episodes of urgency incontinence were also significantly reduced by duloxetine. These data have not been reproduced so far in another trial. However, the high withdrawal rate observed across all studies in which the drug was evaluated fou SUI, affecting 20-40% of the patients at short-term and up to 90% in long-term studies, do not predict clinical utility of duloxetine in OAB.

VII. CYCLOOXYGENASE (COX) INHIBITORS

Prostanoids (prostaglandins and thromboxanes) are synthesized by cyclooxygenase (COX) from a common precursor, arachidonic acid. Prostanoids may be involved in the control of bladder function under normal and pathological conditions, including DO and OAB. Human bladder mucosa has the ability to synthesize eicosanoids [Jeremy et al., 1987], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [Downie and Karmazyn, 1984; Leslie et al., 1984]. Even if prostaglandins cause contraction of human bladder muscle, it is still unclear whether prostaglandins contribute to the pathogenesis of unstable detrusor contractions. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Cardozo et al. performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg 3 times daily [Cardozo et al., 1980a]. The drug was shown to have favourable effects, although it did not completely abolish DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache and gastrointestinal symptoms. Palmer studied the effects of flurbiprofen 50 mg x 4 versus placebo in a double-blind, cross-over trial in 37 patients with idiopathic DO (27% of the patients did not complete the trial) [Palmer, 1983]. Active treatment significantly increased maximum contractile pressure, decreased the number of voids and decreased the number of urgent voids compared to baseline. Indomethacin 50 to 100 mg daily was reported to give symptomatic relief in patients with DO, compared with bromocriptine in a randomized, single-blind, cross-over study [Cardozo and Stanton, 1980b]. The incidence of side effects was high, occurring in 19 of 32 patients.

Although these early clinical studies with nonselective COX inhibitors showed some promise in the treatment of these disorders, the drugs were not further developed for this indication mainly due to side effects. The interest in the use of selective COX-2 inhibitors was hampered by concerns about long-term cardiovascular toxicity with these drugs.

VIII. TOXINS

Intravesical pharmacological therapy for LUTS stems from the fact that circumventing systemic administration of active compounds offers two potential advantages. First, high concentrations of pharmacological agents can be given to the bladder tissue producing enhanced local effects. Second, drugs inappropriate for systemic administration due to off target effects can be safely used. Attractive as it may be, intravesical pharmacological therapy should still be considered as a second line treatment in patients refractory to oral therapy or patients who do not tolerate its systemic side effects. However, this statement is based on the assumption that intervention therapy should follow oral medication. Research aiming at defining if patients subgroups will benefit of intravesical therapy as first line is clearly necessary. An ongoing trial to define tolerability and cost effectiveness of daily antimuscarinic therapy versus a single intra-detrusor injection of 100U of BoNT/A for treatment of urgency urinary incontinence is at this moment under way [Visco et al., 2012].

1. BOTULINUM TOXIN

a) Mechanism of action of BONT

Botulinum toxin (BonT) is a neurotoxin produced by *Clostridium botulinum*, Of the seven subtypes of BONT, sub-type A (BONT-A) has the longest duration of action, making it is the most relevant clinically. BoNT/A is available in three different commercial forms, with the proprietary names of Botox®, Dysport®, Xeomin®, and Prosigne. Although the toxin is the same, it is wrapped by different proteins which modify the relative potency of each brand. This was the basis for the introduction of the non-proprietary names onabotulinum toxin A (onabotA), abobotulinum toxin A (abobotA) and incobotulinum toxin A (incobotA) for Botox®, Dysport® and Xeomin®, respectively. Prosigne is the proprietary name of a BoNT/A produced in China, which currently does not have a known non-proprietary name. Although potency of each one is usually expressed in units (U) the doses are not inter-changeable. Clinical dose conversion studies for the lower urinary tract do not exist. Available information indicates that onabotA is roughly three times more potent than abobotA and equivalent to incobotA. Nevertheless these equivalences should be approached with caution. Comprehensive reviews have been produced during the last few years. [Chapple and Patel., 2006; Nitti, 2006; Patel et al., 2006; Dinis et al., 2007; Karsenty et al., 2008; Apostolidis et al., 2009; Silva and Cruz, 2009; Dowson et al., 2010; Duthie et al., 2011; Mangera et al., 2011].

Most of the information available about intravesical application of BoNT/A derives from the use of onabotA (Botox®). However, in addition to sub-type A, some studies have investigated the effect of detrusor injection sub-type B, rimabotulinumtoxinB (proprietary names being Miobloc™ or Neurobloc™ according to countries). For further details see section 9.1.13 below.

BoNT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 [Dong et al., 2006] by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles (**Figure 16**). The two chains are then

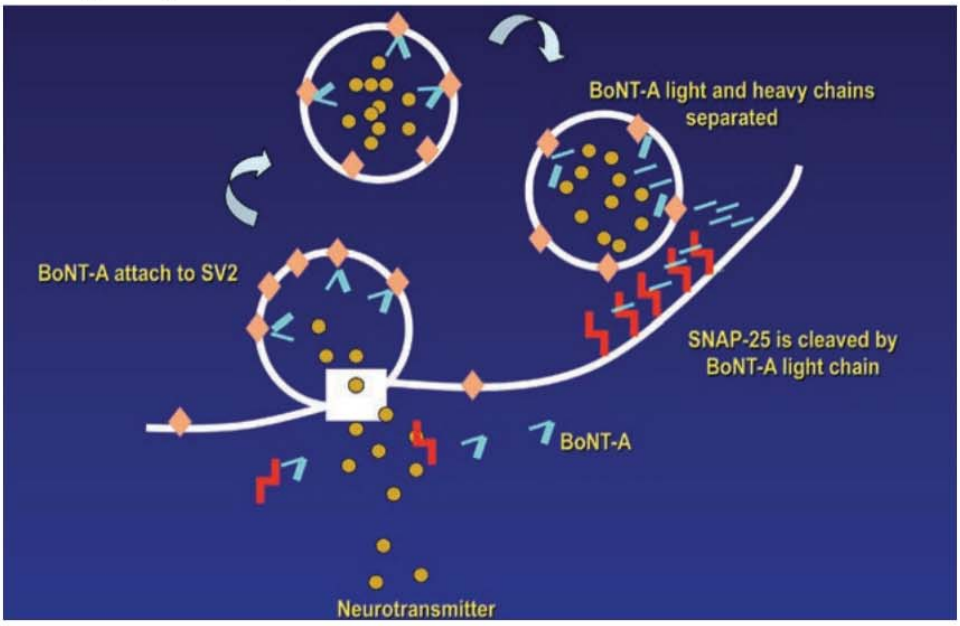

Figure 16 : Mechanism of action of botulinum toxin (BoNT). BoNT consists of a heavy and a light chain linked by a disulphide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles. The two chains are then cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble N-ethylmaleimidesensitive fusion attachment protein receptor) include synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein -VAMP) and syntaxin.

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BonT/A application was extensively evaluated in striated muscle. In this tissue paralysis occurs by prevention of acetycholine (ACh) release from cholinergic motor nerve endings [Humeau et al., 2000]. Accumulation of neurotransmitter containing synaptic vesicles is followed by terminal axonal degeneration. Striated muscle paralysis recovers within 2 to 4 months time. During this time axons develope lateral sprouts and eventually regenerate completely [de Paiva et al., 1999].

In the human bladder SV2 and SNAP-25 expression has been demonstrated in parasympathetic, sympathetic and sensory fibers [Coelho et al., 2011]. Almost all parasympathetic nerves express the two proteins [Coelho et al., 2011]. As these nerves play a fundamental role for detrusor contraction during voiding, the blockade of ACh release is believed to play an essential role in detrusor hypo- or acontractility that follows BoNT/A injection in the bladder. In accordance with this view, it was shown that in normal or SCI animals BoNTA treatment decreased the bladder contractions evoked by electrical stimulation of spinal nerves without altering intrinsic contractions [Ikeda et al., 2012]. However cholinergic axon sprouting concomitant with clinical remission could not been documented in the detrusor [Haferkamp et al., 2004].

Bladder sensory impairment is also expected to play an important role in the final effect of BoNT/A bladder injection. About half of the peptidergic sensory fibers express SV2 and SNAP25 [Coelho et al, 2011]. BoNT/A inhibits the spinal cord release of glutamate, substance P (SP) and CGRP from sensory nerves [Purkiss et al., 2000; Aoki et al., 2005; Meng et al., 2007] as well as the release of neuropeptides at the peripheral extremities [Rapp et al., 2006; Lucioni et al, BJU Int, 2008]. BoNT/A has also been shown to reduce the suburothelial immunoreactivity for TRPV1 or P2X3 [Apostolidis et al., 2005]. Morenilla Palao et al. [2004] have shown that BonT/A impedes TRPV1 trafficking from intracellular vesicles to the neuronal membrane, a process that is also dependent on SNARE proteins. All these mechanisms may contribute to the recent observation that BoNT/A reduces afferent firing from bladder afferents and antidromic release of neuropeptides [Ikeda et al., 2012]. Although SV2 and SNAP-25 immunoreactivity has not been detected in urothelial cells [Coelho et al., 2011], urothelial function seems also compromised after BoNT/A administration. BonT/A has been shown to inhibit ATP release from urothelium in animal models of spinal cord injury [Khera et al.,2004; Smith et al., 2008]. Therefore, it is not surprising that administration of BoNT/A to inflamed rat bladders reduces spinal c-fos counts at the L6 and S1 spinal cord segments [Vemulakonda et al., 2005].

Cleaved, inactive SNAP-25 appears rapidly after BoNT/A injection. In the guinea-pig a robust expression of cleaved SNAP 25 could be detected already at 12 hours and maximum intensity could be detected at 24 hours with little changes afterwards. In guinea-pigs cleaved SNAP-25 expression was restricted to nerve fibers. Almost all parasympathetic fibers, either preganglionic and postganglionic were affected while less than half of the sensory fibers express the cleaved protein [Coelho et al., 2012a; b]. In the human urinary bladder cleaved SNAP 25 could be detected in NDO patients up to 11 months after BoNT/A injection. [Schulte-Baukloh et al., 2007]. The longer duration of cleaved SNAP 25 in the detrusor smooth muscle than in striated muscles, has no firm explanation at the moment. However the longer persistence of the inactive form of SNAP-25 plus the involvement of pre and postganglionicparasympathetic neurons may contribute to persistence of the BoNT/A effect in the bladder.

Interstitial cells (ICs) in the suburothelium form a syncytium through extensive coupling via the gap-junction protein connexin 43 and have close contacts with sensory nerves. These facts led to the hypothesis that ICs act as modulators of bladder behaviour [Wiseman et al., Apostolidis et al., 2006]. However, the expression of connexin 43 is not altered by BoNT/A [Roosen et al, 2009]. Hence, at the moment a firm evidence for the action of BoNT/A on ICs is scant.

BonT/A may decrease the levels of neurotrophic agents in the bladder tissue. Levels of Nerve Growth Factor (NGF) [Giannantoni et al.,; Liu et al., 2009] and Brain-derived Neurotrophic Factor (BDNF) [Pinto et al., 2010] have been shown to decrease in the bladder and/or urine following BoNT/A injections. As both neurotrophins have paramount roles for growth, maintenance and plasticity of peptidergic sensory nerves, these findings may point toward another mechanism whereby BonT/A acts upon the bladder.

b) BoNT/A effects on bladder histology

There is no evidence that repeated injections of onabotA into the detrusor muscle cause inflammatory infiltrates, fibrotic activity or apoptosis within the bladder wall [Comperat et al., 2006, Apostolidis et al., 2008, Kessler et al.]. Rather the reverse, one study demonstrated that NDO patients treated with BonT/A had less fibrosis than nontreated patients [Compérat et al., 2006]. The presence of eosinophilic infiltrate was shown to increase in specimens of patients receiving multiple treatments, a finding that could not be fully explained [Apostolidis et al., 2008].

c) BoNT/A injection protocol

When the treatment was first described in 1999 for NDO patients, onabotA was diluted in normal saline in order to obtain a concentration of 10 units/ml [Schurch et al., 2000]. Under visual control through a rigid cystoscope and a flexible 6 Fr injection needle, 30 injections of 1 ml (10 units of onabotA) were done in 30 different bladder wall locations above the trigone to prevent vesico-urethral reflux. Additional refinements have been added to this technique along the following years, including the use of a local anaesthetic agent (4% lidocaine) and a flexible cystoscope [Harper et al., 2003]. The recent demonstration that onabotA 200 U applied in 30 injections sites (1ml saline each) above the trigone is preferable to 300 U in NDO patients (200 U in 30 injections sites is the approved protocol by medical authorities) reduces the amount of onabotA per injection site to 6.66 U/ml. For abobotA larger studies used a similar technique albeit the number of injections was only 20 [del Popolo et al., 2008; Grise et al., 2010]. The number of units per injection site is obviously different taking in consideration that 500-1000 U are used [del Popolo et al., 2008]. The volume of saline at each injection site is commonly 1 ml but volumes so low as 0.25 ml per site were also used [Grise et al., 2010].

The effect of BONT/A after increasing the dose per injection site and decreasing the number of injected sites was investigated in one study. Patients were randomized to receive 300 U either in 10 or 30 sites [Karsenty et al., NAU, 2005]. The authors reported that 10 site injection was quicker and less painful and that no differences in efficacy between the two procedures could be detected up to 24 weeks. In accordance, it was found that patients receiving 300 U of onabotA distributed over 30 injection sites (30 ml of fluid in total) or the same dose of toxin distributed over 10 injection sites (10 ml of fluid in total) had a similar distribution of the fluid, as determined by MRI. About 1/3 to 1/4 of the total detrusor volume was covered by the two protocols, respectively [Mehnert et al, 2009].

When considering IDO or BPS/IC patients the most relevant aspects in the injection protocol is the smaller amount of toxin at each site, as most studies used onabotA 100 or 200 U or abobotA 500 U [see Mangera et al., 2011, Giannantoni et al., 2012 for reviews]. Another variable at stake is the trigone injection. The suggested risks of injecting bladder trigone were never demonstrated, whether onabotA or abobotA was used [Karsenty et al., 2007; Citeri et al., 2008; Mascarenhas et al., 2008; Pinto et al, 2010). A few studies have, therefore, compared trigonal vesus trigonal sparing protocols in IDO patients. A recent trial randomised 22 IDO patients to receive abobotA 500 U administration in 20 injections (1ml each) sparing the trigone against 15 off the trigone plus 5 injections in the trigone [Manecksha et al., 2011]. Mean postvoid residual volumes and clean intermittent self-catheterisation rates between the two groups were similar. However the change from baseline of the OABSS score was greater in the trigone injected group.

Another study compared 10 trigonal injections versus 40 detrusor or suburothelial injections of 100 U of onabotA in IDO patients [Kuo, 2007]. The most effective protocol was the 40 detrusor injections because it brought more robust symptomatic improvement which lasted longer. The trigone injection only protocol was the less effective and durable of the three, although the risk of urinary retention was null [Kuo, 2007].The suburothelial protocol brought intermediate results, worse than the detrusor but better than the trigone only technique [Kuo, 2007]. Pinto et al. [2010] injected 100 U distributed by 10 sites only in the trigone in 26 women with BPS/IC: No cases of voiding dysfunction were observed. PVR remained normal and bladder contractility index was not changed by onabotA.

Another variable of the injection technique is the volume of the saline used to reconstitute the toxin. Most studies used 1.0 mL per injection, although a few used 0.5 mL [Grosse et al., 2005; Schulte-Baukloh et al., 2005], 0.2 mL [Kuo et al., 2004], 0.25 ml [Grise et al., 2010] or even 0.1 mL per injection site [Rapp et al, Urology, 2004]. In a recent experimental study the amount of cleaved SNAP-25 induced by a fixed amount of onabotA was directly related with the volume of the injection [Coelho et al., 2012]. Thus more controlled studies designed to compare different number and locals of injection and the volume od each injection are necessary.

BoNT/A does not cross the urothelium if instilled in the bladder [Coelho et al., 2012]. Onabot/A instillation in the bladder encapsulated in liposomes may eventually overcome the urothelial barrier and induced distinctive bladder effects [Chuang et al., 2009]. However this technology has not yet been tested in humans. In contrast, electromotive administration seems to overtake this problem, at least in children. In 15 children with NDO due to myelomeningocele, a 10F indwelling catheter containing a silver spiral electrode was placed in the bladder, after providing a local transurethral anaesthesia with 2% lidocaine. The bladder was filled with saline and 10 U/kg of abobotA was added. A maximal current of 10 mA (100 mA increment/s) for 15 minutes was applied using abdominal pads [Kajbafzadeh et al., 2010]. The urodynamic and symptomatic results were excellent (see below). Skin erythema and burning sensation were de only side effects reported with this method. If this technique can be applied to adults it is not known. However, it would certainly simplify BoNT/A administration.

d) Effect of Bont/A on NDO adult patients

OnabotA 200 U is by now approved by FDA and by several European countries to treat NDO in SCI and MS patients. This was in part the consequence of the

findings of two large pivotal phase 3 studies where efficacy and safety of onabot A in about 700 patients with NDO was compared against placebo in patients with NDO and incontinence caused by multiple sclerosis (EDSS ≤ 6.5) or spinal cord injury below T1 [Cruz et al., 2011; Ginsberg et al., 2012]. About 60% of the patients were taking antimuscarinics and maintained the same dose throughout the study. Two doses, 200 and 300 U of onabotA were compared against placebo. Primary outcome measure was the change from baseline in week episodes of urinary incontinence at week 6 after treatment. Secondary outcome measures included the change from baseline in maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction and quality of life using the I-QOL total score. Both studies yielded similar findings. In the first study [Cruz et al., 2011] onabotA significantly reduced UI and improved QOL in both MS and SCI patients, with no clinically relevant differences between the two doses. At week 6 mean change from baseline in weekly incontinence episodes was -21.8 in onabotA 200U, -19.4 with 300U and -13.2 with placebo ($p < 0.01$). At the same time point 7.6%, 38.0%, and 39.6% of patients in the placebo, 200U, and 300U onabotutA groups, respectively, were fully continent. The proportion of patients with no IDC was around 60% after onabotA 200 and 300 groups but only 17.4% after placebo. In the second study [Ginsberg et al., 2012], onabotA resulted in a 23,0%, 26,7% and 27,4% change from baseline in the incontinence episodes in the placebo, and 200 and 300 groups, respectively. Furthermore, 36% and 41% of patients in the 200 and 300 U groups, respectively, achieved dry status, contrasting with 10% in the placebo arm. In both studies, detrusor pressure and cystometric capacity increased significantly in the two onabotA groups, without clinically relevant differences between the two doses [Cruz et al., 2011; Ginsberg et al., 2012]. Patients could request a retreatment 12 weeks after initial treatment. Median time for saline treated patients was about 90 days days and 250 to 300 days for those treated with 200 or 300 onabotA, without differences between the two doses [Cruz et al., 2011; Ginsberg et al., 2012]. No diferences were found between patients with SCI or MS in terms of clinical response to onabotA [Cruz et al., 2011; Ginsberg et al., 2012].

The most common adverse event was UTI [Cruz et al., 2011; Ginsberg et al., 2012]. In the SCI population, the majority of which was performing CIC at baseline, the incidence was similar across all treatment groups (around 50%). In the MS population, it was highest in the onabotA 300 U arm (saline 32%, 200U: 58.5%, 300U: 70%) in the study by Cruz et al. [2011] whereas the incidence of UTI was similar, around 50%, after 200 and 300 onabotA doses in the study by Ginsberg et al., [2012]. This was related with dose dependent incidence of de novo CIC in MS patients (12.2% after saline, 29.5 after 200U, 42.2 after 300U [Cruz et al., 2011]. Ginsberg et al. [2012] observed that the incidence of CIC in patients not catheterizing at baseline was dose dependent, 10% on placebo, 35% on 200 U and 42% on 300 U, and mainly affected MS patients. The higher incidence of adverse events and the lack of clinically advantages of 300 U led to the approval of 200 U dose in NDO.

These pivotal phase 3 trials confirms observations coming from smaller trials. Schurch et al., [2005] randomized 59 NDO patients due to spinal cord injury to received onabotA 200 U, 300 U or placebo. OnabotA treated patients had a significant reduction in incontinence episodes and amelioration of urodynamic parameters versus placebo, that were still sustained 6 month post-treatment. In an additional subanalysis, onabotA also improved quality of life over placebo [Schurch et al., 2007]. No differences between onabotA 200 and 300 U were detected [Schurch et al., 2005]. A Canadian multicenter double-blind study [Herschorn et al., 2011] randomised 57 patients with NDO secondary to spinal cord injury or multiple sclerosis and urinary incontinence despite current antimuscarinic treatment to onabotA 300 U (28) or placebo (29). The mean daily number of incontinence episodes was significantly lower for onabotA than for placebo at week 6 (1.31 vs 4.76, $p<0.0001$). This effect was sustained at weeks 24 and 36. onabotA induced improvements were also seen in urodynamic and quality of life parameters and were maintained up to week 36.

Although not officially approved for NDO, abobotA has been the object of investigation in a few comparative clinical trials. A small study randomized a total of 31 NDO patients due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis to intravesical injections of abobotA 500 U or placebo [Ehren et al., 2007]. Patients in the abobotA arm had a significantly higher cystometric capacity at 6 and 12 weeks, lower maximum detrusor pressure and episodes of urinary incontinence and less consumption of antimuscarinic drugs. Efficacy and safety of abotoA were, additionally, investigated in NDO patients that had abandoned antimuscarinic therapy. Two doses, 500 U (n = 39) or 750 U (n = 38) were compared. Complete continence at day 30 was observed in 22 patients (56.4%) and 28 patients (73.7%) receiving 500Uor 750U. The median delay in the reappearance of leakages was 168 days. Although there was a trend towards a greater improvement with 750 U, no statistically significant differences in terms of clinical and urodynamic variables and QoL were found between the treatment groups. Tolerability was excellent and equivalent for both doses.

The symptomatic improvement brought by BoNT/A injection in the bladder does not coincide with the moment of injection. The onset of BoNT/A effect was evaluated in a small open-label prospective study that specifically investigated the chronology of the symptomatic changes. Some improvement in urgency, nocturia and frequency could already be demonstrated as soon as 2 days after neurotoxin

injection in NDO patients [Kalsi et al., 2008]. In SCI and MS patients treated with onabotA, 200 or 300U, significant decrease in the number of incontinence episodes over placebo was first detected at week 2 after injection [Cruz et al., 2011].

A recent subanalysis of a phase 3 study showed that similar reductions in urinary incontinence episodes and proportion of patients fully dry were achieved, regardless of antimuscarinic use. Moreover, increment of maximal cystometric, decrease in detrusor pressure, improvement in quality of and median time to patient request for re-treatment were similar in anticholinergic users and non-users [Sievert et al., 2012] These observations go along with those made Reitz et al. [2004] and Grosse et al. [2005] who concluded that a substantial proportion of SCI patients could reduce or interrupt anti-muscarinic medication after BoNT/A injection.

Multiple Sclerosis patients represent a particular subgroup of patients in whom a careful analysis of the efficacy and safety of BoNT/A additional attention if voluntary voiding is present before treatment. Cohort studies clearly suggest that using onabotA 300 U reduces markedly episodes of urinary incontinence. Highly significant improvements in urgency, incontinence episodes, frequency, nocturia and urodynamic parameters (bladder capacity, volume to detrusor overactivity and maximal detrusor pressure) were observed. However, most of the patients required CIC to empty the bladder after receiving onabotA 300 U [Kalsi et al., 2007; Khan et al., 2011] In spite of this drawback, improvement in quality of life was quite remarkable indicating that patients may prefer CIC to incontinence [Kalsi et al., 2007; Khan et al., 2011]. A subanalysis of the large pivotal phase 3 study for 154 MS patients was recently reported [Cruz et al., 2011]. Fifty received saline injections, 51 onabotA 200U and 53 onabtA 300U. Weekly episodes of urinary incontinence decreased 18.1, 24.4 and 25.9 at week 6 after saline, 200 U and 300 U, respectively. About 40% of onabotA treated patients were dry at that visit, without relevant differences between the two doses. Quality of life and urodynamic parameters improved in both onabtA groups, also without relevant differences between 200 and 300 U. However, there was a dose dependent increase in post-void residual that led to CIC 2.6%, 24.3% and 37.5% of the patients after saline, 200U or 300U, respectively [Cruz et al., 2011]. Urinary infections were also higher after 200 U (58.5%) than after 300 U (70%). Therefore this subanalysis indicates that 200 U should be preferred to 300 U in for MS patients.

Whether lower that 200 U onabotA can still be effective in controlling urinary incontinence in MS patients without impairing pretreatment voluntary voiding, it is yet unclear. A pilot study with 12 MS patients with a mean EDSS of 5.0 (3.0-7.5) treated with onabotA 100 U seems to indicate that this is a valid alternative [Mehnert et al., 2010]. Daytime and night-time frequency, urgency and pad use significantly decreased while maximum bladder capacity increased. Post-void residual volume increased moderately during the initial 12 weeks but no patients required CIC. Median time to re-injection was 8 months. So, additional studies specifically designed to evaluated onabotA 100 U seems warranted in MS patients with voluntary voiding.

e) BONT/A and UTI in adult NDO patients

UTI are one of the most frequent adverse event of BoNT/A injection. In a phase 3 trial in SCI patients performing CIC, the incidence after saline or onabotA 200 and 300 U was similar, around 50%, reflecting the fact that most patients were on CIC across the three groups before treatment. In the MS population, the incidence of UTI was highest in the onabotA 300 U arm (saline 32%, 200U: 58.5%, 300U: 70%). This was eventually related with a dose dependent increase in post void residual and incidence of de novo CIC in MS patients receiving onabotA (12.2% after saline, 29.5 after 200U, 42.2 after 300U) [Cruz et al., 2011]. In a similar phase 3 trial, Ginsberg et al. [2012] found a similar incidence of UTI, of about 50%, in SCI and MS patients whether 200U or 300U were used. Although most of these infections were non-complicated, a careful exclusion of active UTI at the moment of injection and a cautious UTI screening after each BoNT/A bladder treatment seems justifiable.

A consequence of BONT/A treatment only recently noticed is a decrease in the incidence of severe urinary tract infections in NDO patients. In 30 SCI patients Gamé et al. [2008] observed that the number of pyelonephritis, orchitis and prostatitis in the 6 month before onabotA 300U, 1.75±1.87 per patient, decreased to 0.2±0.41 in the first 6 month after treatment. In 17 SCI patients that received onabotA injections for a period of 6 years, the number of urinary tract infection at the sixth year was 1.8±0.5 per year, significantly lower than at baseline, 6.7±2.1 [Giannantoni et al., 2008]. In a multicentre, cross-sectional retrospective cohort study, data from 214 NDO patients treated in 7 German centers were collected. The rate of urinary tract infections in 12 months proceeding and in the 12 months following onabotA was 68% and 28%, respectively [Boy et al., 2008]. The reason for these findings is unclear but may lie in a decreased maximum detrusor pressure resulting in less bladder wall ischemia and vesico-ureteral reflux [Wefer et al., 2009].

f) BONT/A in IDO patients

The enthusiasm of investigators rapidly produced a reasonable number of pilot studies investigating BoNT/A in patients with IDO refractory to antimuscarics. Although proper dose-escalating studies capable of defining ideal doses were lacking, investigators opted for the administration of BoNT/A in doses smaller than those initially used in NDO. That is the reason why most pilot studies used either onabot 200 U or abobot 500 U ([see list at the end, see also Mangera et al,, 2011] and 4 RCT trials compared

onabotA 200 U against placebo [Sahai et al., 2007; Brubaker et al., 2008; Flynn et al., 2009; Tincello et al., 2012]. Due to high incidence of voiding dysfunction associated with the use of onabotA 200U in IDO patients one large cohort, 100 patients, investigated the effect of onabot 100 U. Two dose escalating placebo controlled studies [Dmochowski et al., 2010; Rovner et al.,2011; Denys et al.,, 2012] investigated the ideal dose of onabotA. That dose seems to be 100 U. However, data from pivotal phase 3 studies with this dose are not yet available.

The largest placebo controlled RCT carried out until the moment was conducted in 8 centers in UK (the RELAX study) and randomised a total of 240 women with refractory DO to receive onabotA 200 U or placebo distributed by 20 bladder wall sites above the trigone (10 U/1ml) [Tincello et al., 2012]. Primary outcome was voiding frequency per 24 h at 6 months. Secondary outcomes included urgency and incontinence episodes and quality-of-life data. A total of 122 women received onabotA and 118 received placebo. Median leakage episodes were already significantly reduced by week 6 and at 6 months were 1.67 in onabotA vs 6.0 in the placebo group. Continence was more common after onabotA (31% vs 12%). Significant decreases also occurred in voiding frequency (8.3 vs 9.67) and in daily urgency episodes (3.83 vs 6.33). Quality of life scores were better in the toxin group. Urinary tract infections (31% vs 11%) and voiding difficulty requiring CIC (16% vs 4%) were more common after onabotA [Tincello et al., 2012].

Only one placebo controlled RCT on IDO [Sahai et al., 2007] included male patients (onabotA 200 U: 9 females and 7 males; Placebo 11 females and 8 males). Maximum cystometric capacity was the primary outcome measure and changes in overactive bladder symptoms, post-void residual, maximum detrusor pressure during filling cystometry, reflex detrusor volume and Quality of Life questionnaires were secondary outcome measures. Follow-up occurred at 4 and 12 weeks after injection, at which point the study was unblinded. Significant improvement in maximum cystometric capacity, urinary frequency and incontinence episodes were observed at 4 and 12 weeks in patients treated with BONT/A. Urgency was also significantly reduced over placebo only at 4 weeks. Post-void residual increased at 4 weeks but differences to placebo became insignificant by 12 weeks. Despite significant improvements in quality of life observed among patients treated with BONT/A, 37.5% of them required intermittent self-catheterization to empty the bladder. Two additional small RCT compared onabotA 200 U against placebo in women with IDO. Brubaker et al. [2008] randomized 28 women for onabotA 200 U and 15 for placebo. Approximately 60% of the women who received toxin had a clinical response based on the Patient Global Impression of Improvement. The median duration of their responses was 373 days, significantly longer than the 62 days for placebo. Post-void residual urine increased in 43% of the women in the BONT/A group (12 out of 26 women) and urinary tract infection developed in 75% of these women (9 of 12). These numbers exceeded by far the expected ranges and forced the suspension of the trial. Median duration of urinary retention after the first injection was approximately 2 month but increased to 5 months at a second injection [Brubaker et al., 2008].

Flynn et al. [2009] reported the preliminary results of a study comparing onabotA 200 or 300 U against placebo in patients with urinary incontinence. The primary outcome measure was the number of incontinence episodes per 24 hours whereas 24 hours pad weights, number of pads, voiding frequency, nocturia and urodynamic parameters at cystometry were secondary outcomes. Until the moment only 15 patients received onabot 200 or 300 U and 7 placebo, distributed by 10-12 sites above the trigone. Incontinence episodes were halved and pads per day were reduced by 2/3 in the onabotA group whereas no changes occurred in the placebo group. No changes were observed in nocturia, daily voiding frequency, peak flow or detrusor pressure in either group. Post-voiding residual over 200 ml was observed in the onabotA group. Four subjects experienced UTI, 2 in onabotA and 2 in the placebo group.

The obvious necessity of reducing micturition dysfunction in IDO patients treated with onabotA 200 U led to the investigation of the efficacy and safety of lower doses. Schmid et al. [2006] injected onabotA 100 U in 100 IDO patients refractory to antimuscarinic therapy. Treatment remained highly effective, incontinence and urgency sensation disappearing in 86% and 82% of patients, respectively, during an average period of 6 months. Temporary urinary retention only occurred in 4% of the cases, with additional 15% reporting moderate voiding difficulties.

The utterly necessary dose escalating studies were only recently accessible. Dmochowski et al. [2010] conducted a phase 2, multicenter, randomized, double-blind study were 288 females and 25 males with IDO experiencing ≥ 8 urgency incontinence episodes per week and ≥ 8 or more micturitions per day. They were randomized to receive 50, 100, 150, 200 or 300 U onabotA or placebo in 20 sites above the trigone (0.5 ml of fluid injected per site). A dose response was observed at week 12 for full continence (15.9%, 29.8%, 37.0%, 40.8%, 50.9% and 57.1% in the placebo, and 50, 100, 150, 200 and 300 U groups, respectively. However, during the full time course of the study, clear differentiation among doses of 100 to 300 U was not always apparent. MCC had small increases in placebo (49.5 ml), 50 U (50 ml) and 100 U (71 ml). At higher doses the increment become marked larger, 101 ml, 91 ml and 130 ml in 150 U, 200 U and 300 U groups [Dmochowski et al., 2010]. For other parameters like frequency and urgency, the magnitude of change was consistently less and a dose dependent response was not evident. A sustained response was absent in the placebo and 50 U

group compared to groups receiving 100 U or more. The proportion of patients with posttreatment PVR of 200 ml or greater was dose dependent and patients requiring CIC were 0%, 3,6%, 9,1% 12,7% 18,2% and 16,4 for placebo, and 50, 100, 150, 200 and 300 U groups, respectively. Another common adverse event were UTI, 16,3%, 33,9%, 44%, 48.1% and 34.5% for placebo, and 50, 100, 150, 200 and 300 U groups, respectively [Dmochowski et al., 2010]. The conclusions was that 100 U may be the dose that appropriately balances the symptom benefits with most common adverse events, in particular the risk of CIC due to increase post-void residual urine. Another dose-escalating study randomized 107 patients (87.9% women) for placebo or onabotA (50 U, 100 U or 150 U) applied through 15 injections of 1ml each above the trigone [Denys et al., 2011]. A >50% improvement in urgency and urgency incontinence versus baseline, the primary end point, was observed in 65% and 56% of patients who received 100 U and 150 U, the difference being only numerically superior to placebo. Complete continence was observed in 55% and 50% patients after 100 U and 150 U, respectively, Urodynamic improvements were consistent with 100 U and 150 U but not with 50U. The proportion of patients with a high PVR was low in all groups [Denys et al., 2011].

Two additional non-placebo controlled RCT also support onabotA 100 U as the ideal dose for IDO. Cohen et al [2009] randomized 44 OAB-dry and wet patients to receive 100 U or 150 U. No significant differences in clinical or urodynamic outcome measures were noted between the two doses. QOL was significantly improved in both groups with no difference between 100 U or 150 U. Altaweel et al. [2011]randomized 11 patients for onabotA 100U and 11 patients to onabotA 200U. No clinical or urodynamic differences were detected between the 2 groups at 3 months follow-up. Urinary retention occurred in 2 patients in the 200 U and in 1 patient in the 100 U arm.

Successful OAB treatment with onabotA does not appear to be related to the existence of DO. In a subanalysis of the dose finding study for onabotA, no differences in outcomes were found between those with and those without baseline DO [Rovner et al., 2011]. Likewise, in a cohort of 5 male and 27 female patients with OAB and without DO, improvement in frequency and urinary incontinence was observed after treatment with onabotA [Kanagarajah et al., 2011]. Two doses were tested, 100 and 150U, without no clinically relevant differences between them [Kanagarajah et al., 2011].

A small open-label prospective study specifically investigated the chronology of the onabot 200 U in IDO patients. Urgency, nocturia and frequency improved as soon as 4 days in IDO patients, therefore slightly later than in NDO cases [Kalsi et al., 2008].

These positive data must, nevertheless, be weighed against a recent negative trial for onabotA 100 U [Dowson et al., 2011]. The RCT enrolled 23 patients with a diagnosis of OAB without DO refractory to antimuscarinics to receive intradetrusor injections of either botn-A (100 U Botox) or saline (placebo). An interim analysis was performed and the trial halted as a result of poorly perceived patient benefit. Storage symptoms remained statistically unchanged following onabotA while 3 patients in the treatment arm initiated CIC [Dowson et al., 2011].

In IDO, BoNT/A is recommended for patients refractory to antimuscarinics, that is, patients that do not respond or do not tolerate the first line medication. In a retrospective analysis of the efficacy of 100-150 U of onabotA BTX-A injections in 85 patients, treatment was more successful in patients who did not tolerate anticholinergics than in those who abandoned the medication due to poor efficacy (86% vs. 60%, respectively) [Makovey et al., 2011].

g) BONT/A in children and elderly patients

In children, the dose of BONT/A should be calculated according to body weight. Doses of between 12 U/kg of weight up to a maximum dose of 300 U [Schulte-Baukloh et al., 2002] and 4 U/Kg [Corcos et al., 2002] have been used for onabotA. The maximum suggested for abobotA is 20 U/kg up to a maximum of 400 U [Altaweel et al., 2006; Akbar et al BJU Int 2007). BoNT/A has been essentially assayed in children with myelomeningocele [Schulte-Baukloh et al., 2002; 2003; Corcos et al., 2002; Riccabona et al., 2004; Kajbafzadeh et al., 2006; Altaweel et al., 2006]. Like in adults, the toxin increased bladder capacity and decreased maximal detrusor pressure. In 26 children with a mean age of 6,9 years, 19 of them (73%) became completely dry between clean intermittent catheterizations while 88% reported a global improvement in urine incontinence. Interestingly, in 11 (73%) out of the 15 children who had vesicoureteral reflux before injection, reflux either disappeared or decreased in grade. BONT/A also improved bowel function in 66% of the children with intestinal problems [Kajbafzadeh et al., 2006]. The success rate in terms of continence and cessation of antimuscarinic medication may, however, be substantially inferior to that seen in adults, potentially due to irreversible bladder wall changes associated with longstanding detrusor overactivity [Altaweel et al., 2006]. In a group of 20 children with myelomenigocele continence was achieved in only 13 children. At a second injection, this number also did not change appreciably [Altaweel et al., 2006].

Electromotive administration of BoNT/A may represent a substantial breakthrough among children. In 15 children with NDO due to myelomeningocele, electromotive administration of abobotA instilled in the bladder in a dose of 10 U/kg, proved very effective and safe. . The mean reflex volume (99 ± 35 ml to 216 ± 35 ml) and maximal bladder capacity (121 ±39 ml to 262 ± 41 ml) increased substantially while maximal detrusor pressure decreased

from 75 ± 16 cm H2O to 39 ± 10 cm H2O. Urinary incontinence improved in 12 patients (80%), [Kajbafzadeh et al., 2011].

To date, two case series have looked at the use of BoNT/A in children with non-neurogenic OAB refractory the anti-cholinergics. Both studies have shown an excellent response to treatment [Hoebeke et al., 2006; Marte et al., 2010]. Data have been updated recently [McDowell et al., 2011]. A total of 57 children of both gender received abobotA 12 U/kg up to a maximum dose of 480 U in multiple bladder sites. A total disappearance of OAB symptoms occurred in 66% and a partial improvement in 19% of the patients. About half of the cases had repeated injections after a mean time slightly exceeding 6 months No cases of voiding dysfunction or UTI were reported [McDowell et al., 2011].

Elderly patients represent, as well, a very special population where urgency and incontinence are not only very distressful but also particularly prevalent. Nevertheless, only 1 study specifically addressed efficacy and safety of BoNT/A in elderly patients. Twenty one patients with refractory IDO (18 females and 3 males) with a mean age of 81.2 years (range 75 to 92) received onabotA 200 U in 20 bladder sites [White et al , 2008]. A significant decrease in the number of daily voids, from 11.4 ± 1.67 to 5.19 ± 0.83 and incontinence pads per day, from 4.0 ± 0.89 to 1.3 ± 0.60, occurred. One month after treatment 16 of the 21 patients (76%) reported greater than 50% improvement in symptoms after 1 injection while only 3 did not show improvement after 2 injections [White et al., 2008]. Mean time to deterioration was 7.12 months. There were no treatment related complications.

h) Effect of BoNT/A on quality of life

Firm evidence that BoNT/A bladder injection in IDO patients increase quality of life can be extracted from several RCT in which QoL changes were in most cases secondary outcome parameters.

A multicenter, randomized, double blind placebo controlled trial by Schurch et al. [2007] which randomized 59 NDO patients with urinary incontinence for onabotA 200U or 300U or placebo. I-QOL scores improved significantly over placebo, at all time points whether 300U or 200U were used. A single center, double blind, placebo controlled study was performed by Ehren et al. [2007]. Thirty-one NDO patients with incontinence were randomized to abobotA 500 U or placebo. Patients in the abobotA group showed improved quality-of-life parameters compared to the placebo group. The Canadian multicenter double-blind study [Herschorn et al., 2011a] that randomised to onabotA 300 U or placebo 57 incontinent patients with NDO secondary to spinal cord injury or multiple sclerosis also found significant advantage of onabotA in terms of I-QoL score. One pivotal phase 3 study used the I-QoL questionnaire to evaluate quality of live changes in SCI and MS patients randomized to 200 and 300 U of onabotA or placebo. Change from baseline was 24 points for both onabotA doses ar 6 and 12 weeks but only 11 points at week 6 and 8 points at week 12 in the placebo group. The I-QoL questionnaires requires that a minimum change of 11 point occur in order to QoL to be detectable by patients, a barrier that was overcome by both onabotA doses [Cruz et al., 2011]. Improvements were present both in SCI and MS patients. In another large phase 3 trial these data were totally confirmed [Ginsberg et al., 2012]. Interestingly, a comparison in QoL in patients performing and non-performing CIC in the placebo, 200U and 300U arms did not show differences in patient perception, indicating that improvement in the continence condition was a more relevant outcome [Ginsberg et al., 2012].

Improvement in QoL was also found in a study that compared abobot 500 U versus /750 in a NDO population predominantly suffering from SCI. A disease- and organ-specific Qualiveen questionnaire with four domains (limitations, constraints, fears, and feelings) was used to assess the Specific Impact of Urinary Problems on QoL The initial evaluation was repeated at days 30, 90, 180, and 360. Identical improvements were detected for the two doses [Grise et al., 2010] The importance of continence for patients quality of life is also confirmed by the study of 43 MS patients treated with onabotA 300 U [Kalsi et al., 2007]. Although 98% of patients had to perform CIC after treatment, there were sustained improvements in all quality-of-life scores with a mean duration of effect was 9.7 months. Results were maintained with repeat treatments for 11.7 months. These results were confirmed in a larger MS cohort by Khan et al. [2011]. Urogenital Distress Inventory and Incontinence Impact Questionnaire 7 scores showed considerable improvement 4 weeks after onabotA 300 U treatment even when repeated 6 times. Again, the fact that 76% of the patients were dry seemed more relevant for QoL score than the necessity of CIC that was required by almost all patients [Khan et al., 2011].

Two RCT compared quality of life after BoNT/A administration to IDO patients. Sahai et al. [2009] used the King's Health Questionnaire (KHQ) at baseline and at 4 and 12 weeks, after injection of onabotA 200 U or saline in 16 and 18 patients of both genders. Overall QoL was significantly improved in the onabotA treated patients compared with placebo in the KHQ subdomains, 'Incontinence Impact', 'Emotions', 'Physical imitations', 'Social Limitations' and 'Severity Measures' at all time points. Other subdomains were improved only at some follow-up visits. The RELAX study that randomised a total of 240 women with refractory IDO to receive onabotA 200 U or placebo [Tincello et al., 2012] showed significant improvement in ICIQ-SF and I-QoL scores. However, none of the questionnaires were restored to the normal score (0 for ICIQ; 100 for IQOL)[Tincello et al. 2012]. The dose finding study by Dmochowski et al. [2010] in which placebo and onabtA 50, 100, 150, 200 and 300 U were compared showed a sustained improve-

ment in the King's Health Questionnaire score only in patients that received doses of 100 U or higher. In contrast, patients randomized to onabotA 50 U had changes similar to those observed after placebo [Dmochowski et al., 2010]. The dose finding study by Denys et al. [2011] showed an I-QoL improvement in patients receiving onabotA 100 U and 150 U, though at some time points scores were only numerically higher than in placebo or 50U groups. The general health status, as measured by the EQ-5D visual analogue scale also improved in patients that received 100 or 150 U [Denys et al., 2011].

i) Side effects of bladder wall injection of BoNT/A

The most frequent side effects reported after intradetrusor BonT/A injection are bladder pain and urinary infections [Karsenty et al., 2008; Del Popolo et al., 2008]. Hematuria may also occur, most of the times mild in nature. The most dangerous one, paralysis of the striated musculature due to circulatory leakage of the toxin has never been reported. Transient muscle weakness was, nevertheless, reported with abobotA application in several studies [Wyndaele and Van Dromme, 2002; Akbar et al., 2007; Del Popolo et al., 2008]. Among 199 NDO patients followed during 8 years, 5 developed hypostenia when injected with after abotbotA 1000 U [Del Popolo et al., 2008]. In another study with 44 patients, 3 adults also treated with 1000 units developed muscular weakness which subsided after 5 to 7 weeks [Akbar et al., 2007]. No such cases were reported with onabotA [Karsenty et al., 2008]. The reason for the lack of transient muscle weakness among Botox-treated patients is unclear but might be related with the larger size of its molecule which limits diffusion into the blood stream. Anyway, the risk of hyposthenia associated with abobotA might be avoided by using lower doses of the toxin, no more that 750 units for adults and 20 units/kg for children [Akbar et al., 2007, Del Popolo et al., 2008]. In addition, caution should be used in selecting high risk patients for botulism including children, patients with low pulmonary reserve or patients with myasthenia gravis. Aminoglycosides should be avoided during BoNT-A treatment since they might blockade motor plates and therefore enhance BoNT/A effect.

The risk of vesicoureteral reflux, which for long precluded trigonal injections [Schurch et al., 2000b, Reitz et al., 2004] seems unfounded [Karsenty et al, J Urol, 2007; Mascarenhas et al., 2008; Citeri et al., 2008; Eichel et al, 2008].

The most feared complication of BoNT/A application in patients with voluntary voiding is urinary retention and a transient necessity to perform CIC. It is, therefore, strongly recommended that in patients with spontaneous voiding BoNT/A administration is preceded by a complete information of this risk. Caregivers should ideally teach CIC to each patient before toxin injection.

In one cohort of 137 MS patients, 65% of whom relied on CISC to empty their bladder, repeated onabotA 300 U injections systematically increase that percentage to 95% [Khan et al., 2011]. In a subanalysis of MS patients with an EDSS around 5 included in the pivotal phase 3 RCT in which NDO patients were randomized for placebo, onabot 200 or 300 U the incidence of de novo CIC was dose dependent, 2.6%, 24.3% and 37.5%, respectively [Cruz et al., 2011]. A reduction of onabotA to 100 units might not be enough to solve the inconvenience. In a small cohort of 12 MS patients with a mean EDSS of 5, 25% of the patients required CIC or a suprapubic cathether to empty the bladder [Mehnert et al., 2010]. Future studies are needed in this area.

In IDO patients injected in the detrusor the rate of urinary retention or high post-voiding residuals requiring CIC is dose dependent [Dmochowski et al., 2010]. After injection of onabot 200 U 16-40% of the treated patients needed CIC [Kuo et al., 2004; 2005; Popat et al., 2005; Sahai et al., 2007; Brubaker et al., 2009; Dmochowski et al., 2010; Tincello et al., 2012). With onabotA 100 U the risk was substantially lower, from 4% to 13% [Schmid et al., 2006; Kuo, 2007; Dmochowski et al., 2010; Cohen et al., 2009]. Onabot 50 U was associated with the lower risk of increasing postvoid residuals and de novo CIC, 3,6%. [Dmochowski et al., 2010]. In contrast, detrusor injection of onabotA 100 U restricted to the trigone [Kuo et al., 2007; Kuo et al., 2010] were devoid of any risk of dysfunctional voiding. The same lack of dysfunctional voiding after trigonal injections of onabotA 100U was confirmed by Pinto et al. [2010] in BPS/IC women.

At this moment it is not possible to identify beforehand patients that will develop voiding difficulty after BoNT/A injection. The positive or negative status of the ice water test does not correlate with the risk of urinary retention after onabotA injection in NDO patients [Huwyler et al., WJU 2007]. A retrospective analysis of 217 patients receiving their first intravesical BoNTA injection for refractory IDO in a tertiary center concluded that risk factors for dysfunctional voiding and urinary retention included male gender ($p = 0.013$), baseline postvoid residual (PVR) > 100 ml ($p = 0.003$) and onabotA > 100 U ($p = 0.029$) [Kuo et al., 2010]. Also in a retrospective analysis of a cohort of 67 patients with IDO treated with onabotA 200 U CIC was necessary in 19 (28%). When compared to those not requiring CIC, those that started CIC had lower pretreatment maximum flow rate (15 vs 22 mL/s, P=0.003), lower projected isovolumetric pressure (43 vs 58, P=0.02) and lower bladder contractility índex (113 vs 180, P=0.001) [Sahai et al, BJU Int 2009].

Another common adverse event related with intradetrusor injection of BoNTA/ is UTI. In NDO patients due to SCI, almost all doing CIC at baseline, the risk of UTI in patients receiving onabotA, whether 200 U or 300 U was similar to those treated with placebo, slightly above 50% [Cruz et al., 2011]. The Canadian study randomised 57 NDO patients to placebo or

onabotA 300U. NDO was mostly due to SCI and the incidence of UTI was similar, 55% and 57%, respectively in the placebo and onabotA groups [Herschornet al., 2011]. However, in MS patients the risk was dose-dependent, 32%, 58.5% and 70%, respectively, eventually related with the increase in post-voiding urine residual volume and necessity of performing CIC in the MS population [Cruz et al., 2011]. In the cohort of 137 MS patients subjected to repeated injections of onabot 300 U and almost all emptying the bladder by CIC, after the 3-day prophylactic course further antibiotics for UTI were required in 9% of the total of 327 treatment sessions. Low dose long-term antibiotic prophylaxis was needed in additional 17% of the patients [Khan et al., 2011]. An word of caution shoukd however be left here. Most of these UTI were mild in nature. Severe infections like pyelonephritis, orquites or prostatitis seem to be substantially reduced after BoNT/A treatment of NDO [Game et al, 2008].

In IDO patients the risk of UTI is higher in males than in females [Kuo et al., 2010] and may well affect more than 1/3 of the patients. In RCT comparing placebo against onabot 200U the incidence of UTI was 0% vs 7% [Sahai et al., 2007], 22% vs 44% [Brubaker et al., 2009] or 11% vs 31% [Tincello et al., 2012], respectively. This adverse event seems to be dose related, eventually associated with the post-voiding urine volume increase. Domochowski et al. [2010] detected UTI in 16,3%, 33,9%, 44%, 48.1% and 34.5% of patients randomized for placebo, and 50, 100, 150, 200 and 300 U groups, respectively.

Although it is a concerned frequently rose by caregivers, at this moment there is no evidence that repeated BoNT/A injections cause detrusor atrophy or bladder wall fibrosis. Whether onabotA or abobotA were used, repeated injections in NDO patients in the short to medium term did not decrease bladder compliance which would presumably be the case if fibrosis were to develop [Reitz et al., 2007; Del Popolo et al., 2008]. Histological inspection of injected bladders did not show inflammatory changes, fibrosis, or dysplasia after repeated treatments and independently of the neurogenic or non-neurogenic origin of the detrusor overactivity [Haferkamp et al., 2004; Compérat et al., 2006; Apostolidis et al., 2008]. Rather the reverse, one study demonstrated that NDO patients treated with BonT/A had less fibrosis than nontreated patients [Compérat et al., 2006]. Curiously, the presence of eosinophilic infiltrate was shown to increase in specimens of patients receiving multiple treatments, a finding that could not be fully explained [Apostolidis et al., 2008].

j) Effectiveness of repeated injections in NDO and IDO patients

Median time for NOD patients due to SCI or MS to request a retreatment was around 300 days after onabotA 200 or 300 U but only 92 days after placebo [Cruz et al., 2011]. Therefore for patients that respond to BoNT/A a programme of reinjections is inevitable. The mean duration of the BoNT/A effect after repeated injections seems to remain stable, without any evidence of tachyphylaxis.

Three studies were identified that assessed the effect of repeated injections of onabotA and abobotA in NDO patients. A cohort of 199 patients with spinal cord lesions treated with abobotA 500 U to 1000 U was analyzed retrospectively, after 8 years of repeated injections. The intervals of between injections remained constant. Urodynamic improvements, patients satisfaction with treatment and number of pads or other protective devices was also constant after treatments [Del Popolo et al., 2008]. Intervals exceeded 12 months in 19.5% of the patients, ranged between 10-12 months in 40.2%, was < 10 months in 30.5% and < 6 months in only 10% of the patients [Del Popolo et al., 2088].

In another study, 20 consecutive NDO (SCI 18, MS 2) patients received at least five intradetrusor injections of onabotA 300 U in 30 sites above the trigone. Intervals between injections remained constant, between 193 and 199 days. Clinical continence improved significantly after the first injection and then remained constant after repeat injections. The median reflex volume increased from a 200 ml at baseline to values between 440 and 500 ml at follow-up studies. The presence of NDO decreased by 60–75%. Maximum cystometric capacity increased more than 2 folds and maximum detrusor pressure from a median of 70 cm H2O to values of about 20 cmH2O [Reitz et al., 2007].

In a MS cohort with137 patients who underwent detrusor onabot 300 U, 99 (72%) returned for a second treatment, and 47, 25, 14 and 5 returned for retreatments 3 to 6, respectively. The median interval for 1st, 2nd , 3rd, 4th, and 5th re-injections ranged between 12 and 13 months. The outcome in terms of continence did not differ among treatments [Khan et al., 2011].

Four studies were identified that analyzed repeated injections in IDO patients. In general, longer duration of BoNT/A effect and a relatively higher rate of treatment drop out is seen among IDO patients.

From a cohort of 34 IDO patients treated with onabotA 200 U, 58% received a 2nd injection and 26% received a 3rd and 4th injection. Significant improvements in OAB symptoms, QoL and urodynamic parameters were observed after each injection as compared with baseline, without differences in efficacy parameters between the 1st and last treatment. When analyzing the reasons why 20 out of the 34 patients abandoned the programme, the fear of CIC (25%) and poor response (20%) were the leading causes [Sahai et al., 2010].

This study was recently updated for 100 patients [Dowson et al., 2012]. A statistically significant reduction in frequency, urgency, and urge urinary

incontinence were seen following onabotA 200 U injection compared to baseline. Such improvement was again maintained after repeated injections. The mean inter-injection interval was 322 days. Interestingly, 37% of the patients stopped treatment after the first two injections, dropouts being rare thereafter. The most common reason for discontinuing treatment was poor efficacy (13%). CIC related issues was pointed out by 11% of patients in spite of the incidence of CIC after the first injection being 35% [Dowson et al., 2012].

In a prospective, observational study after 1 single onabotA 100 U injection, 26 patients were followed up for 2 years. One was a primary failure, 3 were lost to follow-up, and 11 patients had a repeated injection at 5–26 months. At 2 years 7 of the remaining 11 patients were recommended repeated injection or another treatment, and four required no other treatment.

Schmid et al. [2008] reported on 25 women and 5 men that received repeated [2] injections of onabotA for treatment of IDO. The interval between two subsequent treatments ranged between 4 and 26 months (mean 12 months). Improvement of OAB symptoms, quality of life and urodynamic parameters were observed after reinjection.

k) Cost-effectiveness of BoNT/A

Economic aspects of BonT/A are a concern due to the price of the drug and the need for repeated cystoscopies, very often performed under general anaesthesia and under close monitoring to detect and treat eventual episodes of autonomic dysreflexia. Nevertheless, In UK, in a cohort of 101 patients with detrusor overactivity, 63 of whom of neurogenic origin, BonT/A treatment was shown to be cost-effective in both NDO and IDO cases [Kalsi et al, 2006]. Costs were based on the resources used by typical patients in UK and in the cost-effectiveness of 200-300 U BoNT/A (Botox) compared with standard care [Kalsi et al., 2006]. In Germany a multicenter cost analysis showed that BonT/A (onabotA) treatment halved costs for incontinence aids and for urinary tract infection treatment in 214 NDO patients. In patients using incontinence aids, mean costs per patient decreased from €2 to €1 per day, whereas the mean cost of drugs to treat UTIs per patient decreased from €163 to €8 per year [Wefer et al., 2009].

Also in NDO patients, break-even point for BoNT/A and augmentation cystoplasty costs may be reached at five years. However BoNT/A may be substantially more cost-effective if the duration of effect of each injection is superior to 5 months or if the complications associated with augmentation cystoplasty overtake 40% of the patients [Padmanabhan et al., 2011].

For OAB/IDO, an assessment of costs, from a US payer perspective, extending up to 3 years, was made for 3 interventions, sacral neuromodulation, BoNTA, and augmentation cystoplasty in patients refractory to antimuscarinics. The initial treatment cost was $22,226, $1,313, and $10,252 for sacral neuromodulation, BoNTA, and augmentation cystoplasty respectively. Three years after initiating treatment, the cumulative cost was $26,269, $7651, and $14,337 respectively. Sensitivity analyses revealed that sacral neuromodulation persisted as the most costly intervention [Watanabe et al., 2010].

l) Comparisons between different BoNT/A brands

Systematic head-to-head comparisons between the different brands of BoNT/A are still lacking. Within each brand very few studies compared different doses for neurogenic or idiopathic DO. However, metanalysis and systematic reviews are already available which give some light on this important topic.

A recent metanalysis identified 19 randomised or quasi-randomised controlled trials for OAB/DO treatment in adults in which at least one management arm involved intravesical injection of botulinum toxin. Comparison interventions could include no intervention, placebo, lifestyle modification, bladder retraining, pharmacological treatments, surgery, bladder instillation techniques, neuromodulation, and different types, doses, and injection techniques of BoNT/A. Most patients in the studies had neurogenic DO, but some included patients with idiopathic DO. All studies demonstrated superiority of botulinum toxin to placebo. Lower doses of onabotA (100 to 150 U) appeared to have beneficial effects, but larger doses (300 U) may have been more effective and longer lasting, but with more side effects [Duthie et al., 2011].

Mangera et al. [2011] in a systematic review identified good-quality studies that evaluated onabotulinumtoxinA for all the indications in adults. However that was not the case with abobotA. Although this does not imply that onabotA is more effective than abobotA, it should be a consideration when counselling patients on the use of botulinum toxin in urologic applications. The two preparations should not be used interchangeably, either in terms of predicting outcomes or in determining doses to be used.

The only study available that compares two different brands used onabotA 200 or 300 U against the Chinese BoNT/A Presigne in the same dosage. Improvement in MCC was significantly greater with onabotA Botox versus Prosigne (+103.3% vs. +42.2%; P = 0.019). Continence was achieved by week 12 in 16 onabotA recipients (76.2%) and in 10 Presigne recipients (47.6%; P = 0.057) [Gomes et al., 2010]. Future studies seems, therefore, justified to assess the relative potencies of the different brands of BoNT/A.

m) BONT/B

Some humans repeatedly injected with BONT-A may develop resistance to the toxin, possibly due to antibody formation. Although this event seems very rare in the case of bladder injections, a minimum interval of 3 months between two BoNT/A injections is gener-

ally recommended to decrease its occurrence. If resistance appears, recent reports [Dykstra et al., 2003; Pistolesi et al., 2004; Reitz et al., 2004] investigated the replacement of BONT-A serotype by BONT-B. At this moment empiric doses of BoNT/B are being used as there is no clear potency equivalents for the two serotypes and between BoNT/B brands.

In 3 patients with spinal NDO, bladder injection of 5000 UI [Pistolesi et al., 2004] or 7500 UI [Reitz and Schurch, 2004) of BONT-B (Neurobloc ®) restored bladder function for 6 months [Reitz and Schurch, 2004]. Interestingly, 1 patient experienced dry mouth and dry eyes that resolved within 20 days. As this side effect was not reported after bladder BONT-A application, it is possible that different toxin serotypes have some different degrees of organ affinity. Dykstra et al. [2003] carried on a dose escalation study with BONT-B (rimabotB in 15 female patients with OAB. They used doses of 2500, 3750, 5000, 10,000, and 15,000 U injected at 10 sites. Only 1 patient failed to respond and a clear dose-dependent effect, was observed, with the longest response seen in those injected with 15,000 U. Two patients, both injected with 15,000 U, experienced dry mouth and general malaise. In another study involving IDO and NDO patients, in which rimabotB 5000 U were used, Hirst and coworkers [2007] observed a limited duration of action, with most of the symptomatic beneficial effects wearing off by 10 weeks in most of the patients. The short duration of action for BONT-B at safe doses may, therefore, limit the clinic usefulness of this serotype.

n) BONT/A in IC/PBS

BONT/A significantly inhibits the noxious sensory input from the bladder [Vemulakonda et al., 2005; Rapp et al., 2006; Lucione et al., 2008]. Therefore several pilot studies were carried out in the last few years. None is placebo controlled, a fact that limits the scientific value of the observations. On the other hand different techniques of administration have been assessed. These two facts may explain some heterogeneity of results.

The first pilot study with 13 females observed that, 9 (69%) had subjective improvement after onabotA 100 or 200 U injected in the trigone and above the trigone. Mean scores in the Interstitial Cystitis Symptom Index and the Interstitial Cystitis Problem Index improved by 71% and 69%, respectively. Daytime frequency, nocturia, and pain measured by a Visual Analogue Scale (VAS) decreased by 44%, 45%, and 79%, respectively. Symptom improvement lasted a mean of 3.7 months (range 1 to 8) [Smith and Chancellor, 2004]. In another pilot study with 15 patients, Giannantoni et al. [2006; 2008] reported similar obervations after bladder injection of onabotA 200 U (150U above the trigone, 50 U in the trigone). Subjective improvement at 1 and 3 month follow-up occurred in 86% of the patients but at 5-month only persisted in 26.6% . Importantly, 9 patients experienced moderate to severe voiding difficulties [Giannantoni et al., 2006; 2008] A third study could not demonstrate any effect of onabotA in 13 IC/PBS patients treated with onabotA 100–300 U in the bladder [Davies et al., 2006].

Three other studies, which added substantial modifications to the above protocol, reported, on the contrary, considerable improvement in clinical and urodynamic outcomes after BoNT/A adminitration.

A prospective, randomized study enrolled 67 patients with refractory IC/PBS Of these, 44 patients received suburothelial injection of onabotA 200 U [15] or 100 U [29] followed by cystoscopic hydrodistention 2 weeks later. The control group (23 patients) only received hydrodistention. The IC/PBS symptom score significantly decreased in all three groups, but VAS pain reduction and urodynamic improvement were only observed at 3 months in the arms that received onabotA, without any relevant differences between the two doses. A successful result at 12 and 24 months was reported in 55% and 30% of onabotA treated patients, respectively, compared with only 26% and 17% in the control group. The validity of these positive long-term results should however be interpreted with caution since all patients remained on baseline pentosan polysulphate throughout the study [Kuo and Chancellor, 2009].

Taking in consideration that most of the bladder nociceptors course in the trigone, Pinto et al. [2010] restricted 100 U onabotA injections to the trigone, in 10 sites (10 U/ 1 ml each. Twenty six women with positive findings at cystoscopy and biopsy were enrolled. All patients reported subjective improvement at 1- and 3-month follow-up in pain, daytime and nighttime voiding frequency, O'Leary-Sant score and QoL. Bladder volume to first pain and maximal cystometric capacity more than doubled. Treatment remained effective in >50% of the patients for 9 months. Retreatment was equally effective in all cases, with similar duration of the effect [Pinto et al., 2010]. No cases of dysfunctional voiding were reported after trigonal injections of onabotA 100U. Also PVR at urodynamics and bladder contractility index were not impaired [Pinto et al., 2010].

The third was a small placebo controlled trial comparing periurethral injections of onabotA 50U (n=9) versus saline (n=11). The rationale was to investigate the participation of periurethral somatic afferents to pain. The solution, 2 ml, was injected in the region of the bladder neck, at the 3 o'clock and 9 o'clock positions. Unfortunately, there was no differences between the onabotA and the at 3-month follow-up in terms of symptoms.

At this moment, without a well conducted placebo controlled RCT it is difficult to state how effective is BoNT/A in BPS/IC. However, taking in consideration the effects the toxin induces in nociceptors and in the urothelium and the favourable results of the two largest clinical trials, it is tempting to suggest that further assessments are warranted.

2. CAPSAICIN AND RESINIFERATOXIN (RTX)

a) Rationale for intravesical vanilloids

The rationale for intravesical vanilloid application in patients with detrusor overactivity (DO) was offered by the demonstration that capsaicin, following bladder C-fiber desensitization, suppresses involuntary detrusor contractions dependent upon a sacral micturition reflex [de Groat, 1997]. The C-fiber micturition reflex is usually inactive but it was shown that it is enhanced in patients with chronic spinal-cord lesions above sacral segments [de Groat, 1997] in those with chronic bladder outlet obstruction [Chai et al., 1998) and in those with IDO [Silva et al., 2002]. In the bladders of NDO patients, the enhancement of the micturition reflex is accompanied by an increase in the number of sub-urothelial C-fibers expressing TRPV1 [Brady et al., 2004]. Curiously, NDO patients who responded better to intravesical RTX exhibited a significant decrease in the density of TRPV1 immunoreactive fibers, whereas non-responders experience a non-significant variation [Brady et al., 2004]. A decrease in TRPV1 expression in urothelial cells of NDO patients was also demonstrated after intravesical application of RTX [Apostolidis et al., 2005; 2006].

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

b) Intravesical capsaicin

Intravesical capsacin for NDO was studied in 6 non-controlled [Fowler et al., 1992; Fowler et al., 1994; Geirsson et al., 1995; Das et al.,1996; Cruz et al., 1997, De Ridder et al., 1997] and 1 controlled clinical trial [de Seze et al., 1998]. Capsaicin was dissolved in 30% alcohol and 100-125 ml (or half of the bladder capacity if lower than that volume) of 1-2 mM solutions were instilled into the bladder and left in contact with the mucosa for 30 minutes. Best clinical results were found among patients with incomplete spinal cord lesions, in whom clinical improvement could be observed in up to 70-90% the patients [Fowler et al., 1994, Cruz et al., 1997; De Ridder et al., 1997]. In patients with complete spinal cord lesions the success rate was much lower [Geirsson et al., 1995].

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

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

c) RTX in NDO

Resiniferatoxin (RTX) has the advantage over capsaicin in being much less pungent [Cruz et al., 1997]. Intravesical RTX application in NDO patients was evaluated in five small open-label studies (Cruz et al., 1997; Lazzeri et al., 1997; 1998; Silva et al., 2000; Kuo 2003). Different RTX concentrations, 10 nM, 50 nM, 100 nM and 10 μM were tested. RTX brought a rapid improvement or disappearance of urinary incontinence in up to 80% of the selected patients and a 30% decrease in their daily urinary frequency. Furthermore, RTX also increased the volume to first detrusor contraction and maximal cystometric capacity. In general, in patients receiving 50-100 nM RTX the effect was long-lasting, with a duration of more than 6 month being reported. In patients treated with 10 μM doses, transient urinary retention may occur [Lazzeri et al., 1998].

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

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

d) RTX in IDO

The first study with intravesical RTX in IDO patients was designed as a proof-of-concept study and involved 13 patients. Intravesical RTX 50 nmol/L was associated with an improvement in volume to FDC from 170 ± 109 mL to 440 ± 153 mL at 30 days, and to 391 ± 165 mL at 90 days. An increase in mean MCC from 291 ± 160 mL to 472 ± 139 mL at 30 days and to 413 ± 153 mL at 90 days was also observed.

These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency [Silva et al., 2002]. Subsequent small open label studies confirmed these observations using either a single high (50-100 nM) or multiple low (10 nM) dose approaches [Kuo, 2003; Dinis et al, 2004; Kuo et al., 2005].

The effect of RTX on refractory IDO was evaluated in two randomized clinical trials [Kuo et al., 2006; Rios et al., 2007]. Kuo et al. [2006] randomised 54 patients to receive 4 weekly instillations of a low concentration RTX solutions (10 nmol/L) or the vehicle solution, 10% ethanol in saline [Kuo et al., 2006] Three months after completing the 4 intravesical treatments, the RTX treated group had 42.3% and 19.2% of patients feeling much better or improved, respectively. This was significantly more than in the placebo group, 14.2% and 7.1% respectively. At 6 months treatment remained effective in 50% patients in the RTX group but only in 11% in the placebo group [Kuo et al., 2006]. Such clinical and urodynamic findings could not be reproduced in another study in which patients were randomly assigned to receive a single intravesical dose of 100 ml of either RTX 50 nM or placebo. Patients were followed-up only for 4 weeks. During this period a single 50 nM intravesical dose of RTX was not better than placebo for the treatment of women with IDO and urgency incontinence [Rios et al., 2007].

e) RTX and urgency

The involvement of bladder C-fibers in IDO has led some investigators to explore the role of these sensory afferents to the genesis of urgency. In a non-controlled study involving 12 male patients with LUTS associated with BPH, mean IPSS halved following intravesical administration of RTX (50 nmol/L). The decrease in IPSS was largely due to improvements in scores related to urgency, in addition to improvement in nocturia and frequency [Dinis et al., 2005]. In another open-label study 15 patients with intractable urgency and frequency, with or without urgency incontinence or bladder pain/discomfort, and without urodynamic evidence of DO received one single 50 nM RTX solution. A trend towards an improvement of urgency was noticed [Apostolidis et al., 2006].

In a quasi-randomised study, 23 OAB patients with refractory urgency entered a 30 day run-in period in which medications influencing the bladder function were interrupted. At the end of this period patients filled a 7-day bladder diary. Then, patients were instilled with 100 ml of 10% ethanol in saline (vehicle solution) and 30 days later a second 7-day diary was collected. Finally, patients were instilled with 100 ml of 50 nM RTX in 10% ethanol in saline and additional bladder diaries were collected at 1 and 3 months. After vehicle instillation, the mean number of episodes of urgency per week was 56 ± 11. At 1 and 3 months after RTX instillation the number of episodes of urgency decreased to 39 ± 9 ($p = 0.002$) and 37 ± 6 ($p = 0.02$), respectively [Silva et al., 2007].

f) Intravesical RTX and IC/PBS

TRPV1 involvement in pain has stimulated the investigation of RTX as a treatment for bladder pain in IC/PBS. After desensitization of bladder C-fibers, RTX reduces the spinal expression of c-fos, a pain evoked gene, in animal models of cystitis [Dinis et al., 2004]. TRPV1 knock-out mice, which do not express the receptor in the bladder, do not experience an increase in the frequency of bladder reflex contractions or in the expression of c-fos in the spinal cord during cystitis [Charrua et al., 2007]. Patients with IC/PBS have more TRPV1 expressing sensory fibers in their bladder mucosa than normal individuals [Mukerji et al., 2006].

In a placebo-controlled study of 18 patients with IC/PBS, Lazzeri et al. [2000] reported an improvement in pain and urinary frequency after administration of intravesical RTX in 10 nmol/L concentration. This effect was short-lasting, eventually due to the use of a low dose of RTX. Chen and co-workers conducted a dose-escalating study and concluded that the most commonly reported adverse event with RTX was pain during instillation. However, at 10 or 5 nM RTX was safe and could improve bladder pain [Chen et al., 2005]. Additionally, 3 non-controlled studies have also reported bladder pain improvement after intravesical RTX [Lazzeri et al., 2004; Apostolidis et al., 2006; Peng and Kuo, 2007]. A randomized, double-blind study in 163 patients with IC/PBS, in which several doses of intravesical RTX (10 nmol/L, 50 nmol/L, and 100 nmol/L) were compared with placebo, failed, however, to show any advantage for the neurotoxin over placebo in terms of overall symptoms, pain, urgency, frequency, nocturia, or average voided volume during 12 weeks of follow up [Payne et al., 2005].

IX. OTHER DRUGS

1. BACLOFEN

Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex at several points along its central pathway [de Groat, 1997; Pehrson et al., 2002]. Experimental data suggest the GABAergic system as an interesting target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of GABA(B) receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium [Pehrson et al, 2002]. In spinal intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes whereas intrathecal application of baclofen induced urethral relaxation during isovolumetric bladder contractions [Miyazato et al., 2009]. After spinal cord injury (SCI), Miyazato et al.

[2009] found signs of hypofunction of the GABAergic system (glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased), and showed that activation of GABA(A) and GABA(B) receptors in the spinal cord inhibited DO as evidenced by a reduction in non-voiding contractions. GABA(B) receptor activation preferentially reduced DO prior to inhibiting voiding contractions while GABA(A) receptor activation inhibited DO and voiding contraction at the same concentration.

As a GABA agonist on GABA(B) receptors, baclofen was used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier [Taylor and Bates, 1979]. Baclofen is one of the most effective drugs for the treatment of spasticity following spinal cord injury, traumatic or hypoxic brain injury, and cerebral palsy [Ochs, 1993], and intrathecal baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [Bushman et al., 1993]. Baldo et al. [2000] found a rapid (24 hours) and persistent increment in the volume to first detrusor contraction and of the maximal cystometric whereas maximal detrusor pressure decreased. At ten days the volume to first detrusor contraction had increased from 143 ml to 486 ml. In selected patients with spasticity and bladder dysfunction, intrathecal baclofen seems to be an effective therapy.

X. COMBINATIONS

1. α_1-AR ANTAGONISTS WITH ANTIMUSCARINICS

Traditionally, male lower urinary tract symptoms (LUTS) were thought to result from benign prostatic obstruction (BPO) secondary to benign prostatic enlargement (BPE). However, male LUTS may arise from prostatic pathology, bladder dysfunction, or both. Thus, diagnosis and appropriate treatment of men with OAB symptoms are complex and difficult. α1-AR antagonists remain the most widely used pharmacologic agents for relief of bladder outflow resistance, as they relax prostatic and urethral smooth muscle tone, the dynamic component of BPO [Andersson and Gratzke, 2010; Lepor et al., 2012]. In contrast, antimuscarinics, which function by competitively blocking the muscarinic receptors, are the first-line pharmacologic treatment for OAB [Andersson et al., 2009]. Given the prevalence of combined voiding and OAB symptoms as well as the finding that the QoL of these patients is affected primarily by the symptoms of OAB, it might be logical for this category of patients to be given antimuscarinic drugs [Ruggieri et al., 2005].

A variety of such combinations have been evaluated. Several randomized, controlled trials demonstrated that the combination treatment of antimuscarinic drugs and α1-AR antagonist was more effective at reducing male LUTS than α1-AR antagonists alone in men with OAB and coexisting BPO [Saito et al., 1999; Athanasopoulos et al., 2003; Lee et al., 2004; 2005; Kaplan et al., 2006; 2008]. Therapeutic benefit of combining an antimuscarinic agent (propiverine) with α1-AR antagonists (tamsulosin), as compared to α1-AR antagonists alone, was reported by Saito and colleagues [Saito et al., 1999]. The rates of improvement in daytime frequency, incontinence, and urgency were greater in the combination group than the α1-AR antagonist-alone group. The postvoid residual (PVR) was unchanged in both groups, and there was only one case (1.5%) of acute urinary retention (AUR) with the combined treatment.

Subsequently, Lee et al. [2005] compared the efficacy and safety of combination therapy with propiverine and doxazosin in 211 men with urodynamically confirmed bladder outlet obstruction (BOO) and OAB symptoms for 8 weeks. Compared with the doxazosin arm, the patients in the combination therapy group showed greater improvement in urinary frequency, average micturition volume, and storage and urgency scores of international prostate symptom score (IPSS). Patient satisfaction was significantly higher in the combination group. There was also a significant increase in PVR (+20.7 mL) in the combination group, but no case of urinary retention was reported.

A large-scale, multicenter, randomized, double-blind, placebo-controlled trial (the TIMES study) demonstrated the efficacy and safety of tolterodine extended release (ER) alone, tamsulosin alone, and the combination of both in 879 men with OAB and BPO [Kaplan et al., 2006]. In the primary efficacy analysis, 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefits by week 12 ($p<0.001$ vs. placebo; $p=0.001$ vs. tolterodine ER; $p=0.03$ vs. tamsulosin). In the secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin compared with placebo experienced small but significant reductions in urgency incontinence, urgency episodes, daytime frequency, and nocturia. However, there were no significant differences between tamsulosin monotherapy and placebo for any diary variables at week 12. Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements in total IPSS (−8.02 vs. placebo, −6.19, $p=0.003$) and QoL (−1.61 vs. −1.17, $p=0.003$). Although there were significant improvements in the total IPSS among patients who received tamsulosin alone, the differences in total IPSS among patients that received tolterodine ER versus placebo were not significant. The combination of antimuscarinics and α1-AR antagonists may be the most effective therapy in men with OAB symptoms in the presence of BPO.

A subanalysis [Rovner et al., 2008] of data from the TIMES study focused on the urgency perception scale and concluded that the group of 217 men who received tolterodine plus tamsulosin showed

significantly improved urgency variables and patient-reported outcomes. Moreover, this group of patients reported increased satisfaction with the treatment as well as willingness to continue the treatment. Another subanalysis [Kaplan et al. 2008] of data from the TIMES study examined the effects of the drugs on urinary symptoms as assessed by the IPSS. Based on this subanalysis, the authors concluded that tolterodine ER plus tamsulosin was significantly more effective than placebo in treating storage LUTS, including OAB symptoms. However, these results should be considered with caution, as they were derived from post-hoc analysis of the TIMES data.

Maruyama et al. [2006] reported different results in their prospective, randomized, controlled study in which naftopidil (25-75 mg/day), an α1d-AR antagonist, alone or in combination with propiverine hydrochloride (10-20 mg/day) or oxybutynin hydrochloride (2-6 mg/day), was administered for 12 weeks to 101 BPH patients. In the study, the IPSS and QoL index improved significantly in both groups, with no marked differences between groups. Maximum flow rate (Qmax) and PVR tended to improve in both groups, again with no differences between groups. However, median post-therapeutic PVR was significantly larger in the combination group (45.0 mL) than in the monotherapy group (13.5 mL, $p = 0.021$). There were significantly more patients with increased residual urine volume relative to unchanged residuals in the combination therapy (22.9%) group versus the monotherapy group (5.0%, $p = 0.038$). The authors of this study concluded that combination therapy with a low-dose antimuscarinic agent was not more effective than monotherapy. Moreover, although they did not encounter any cases of urinary retention, the percentage of patients with increased residual urine volume was significantly greater in the combination therapy group than the monotherapy group.

The results of another study using low-dose antimuscarinic therapy was published by Kang et al. [2009]. They evaluated the efficacy and safety of combined treatment with tamsulosin 0.2 mg and propiverine hydrochloride 10 mg compared with tamsulosin monotherapy. After 3 months, both groups showed significant improvements in IPSS, QoL, voided volume, Qmax, and PVR, but only the QoL index was significantly different between groups in favor of the combination group. No cases of AUR were recorded in this low-dose study.

Medical therapy to reduce detrusor overactivity in a neurogenic bladder has focused on antimuscarinic therapy, which increases bladder capacity, decreases bladder filling pressure, and improves compliance [Goessl et al., 1998; Stohrer et al., 2007]. Although antimuscarinics combined with clean intermittent catheterization is the most commonly recommended medical therapy for neurogenic bladder, the results are sometimes unsatisfactory, and many patients continue to have poor bladder compliance and remain incontinent [Razdan et al., 2003]. MacGuire reported that α-AR antagonists decreased bladder pressure with filling and increased capacity, and that the addition of an antimuscarinic enhanced these effects, indicating that α-AR antagonists and the antimuscarinic had a synergistic effect on detrusor tone in the decentralized bladder [McGuire and Savastano, 1985]. This finding led to the widespread use of α1-AR antagonists in the treatment of neurogenic bladder [Chancellor et al., 1994; Swierzewski, Gormley et al. 1994; Abrams et al., 2003). Swierzewski treated 12 patients with spinal cord injury who had poor bladder compliance, despite therapy with clean intermittent catheterization and an antimuscarinic, with 5 mg terazosin for bladder management (Swierzewski et al., 1994). After 4 weeks, compliance increased by 73%, bladder pressure decreased by 36 cmH2O, and capacity increased by 157 mL. These results support the theory that α-AR antagonists and antimuscarinics have a synergistic effect on the bladder in the neurogenic population.

In a retrospective chart review, combination therapy with an antimuscarinic agent, an α1-AR antagonist, and imipramine produced superior results to those obtained using a single agent in patients with neurogenic bladder dysfunction [Cameron et al. 2009]. These patients showed significant improvement in clinical parameters and compliance, and decreased bladder pressures at capacity. It has been shown that in the decentralized human detrusor, there may be an increase in α-1-AR sites sites and a switch to α-1-AR mediated contractile function from the typical ß-AR mediated relaxation function during bladder filling [Sundin et al. 1977]. The tricyclic antidepressant imipramine is a muscarinic receptor agonist and a direct smooth muscle inhibitor that decreases bladder overactivity by blocking the reuptake of serotonin. Other effects include the peripheral blockade of noradrenaline, stimulating the ß ARs at the dome of the bladder, and decreasing bladder contractility [Hoebeke and Vande Walle, 2000]. These results suggest that targeting multiple receptors may maximize the effectiveness of pharmacological treatment of neurogenic bladder and should be considered in patients in whom treatment with antimuscarinics alone fails.

2. COMBINED ANTIMUSCARINICS

Although antimuscarinic agents are the first choice of treatment for patients with OAB symptoms, these drugs do not always lead to the desired effect of detrusor stability and continence, especially for patients with spinal cord injury or neurologic diseases such as multiple sclerosis or meningomyelocele. In these patients, the goal of urological therapy is to maintain continence and to reduce intravesical pressure. When antimuscarinic treatment fails,

however, invasive procedures such as the injection of botulinum toxin, intravesical application of drugs, or surgery are necessary.

A combined antimuscarinic regimen was evaluated as a non-invasive alternative by Amend and colleagues [Amend et al., 2008] for patients who had neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure. They added secondary antimuscarinics to the existing double-dosed antimuscarinics for patients who previously demonstrated unsatisfactory outcomes with double-dosed antimuscarinic monotherapy. The study drugs were tolterodine, oxybutynin, and trospium. After a 4-week combined regimen, incontinence episodes decreased and reflex volume, maximal bladder capacity, and detrusor compliance increased. Side-effects were comparable to those seen with normal-dosed antimuscarinics. Those positive findings were speculated to be due to: 1) synergistic activation of different muscarinic receptors or interactions of receptors on different parts of the bladder wall, 2) undiscovered faster metabolism of antimuscarinics requiring an increased dosage of different antimuscarinic drugs, and/or 3) down-regulation of subdivisions of antimuscarinic receptors under monotherapy that may lead to better susceptibility of other subdivisions when treated by the second drug. The combined regimen needs further investigation to verify its efficacy as a non-invasive alternative for patients in whom antimuscarinic monotherapy fails.

3. ANTIMUSCARINICS AND 5α-REDUCTASE INHIBITORS

The standard first-line medical therapy for men with moderate-to-severe LUTS is an α1-AR antagonist, a 5α-reductase inhibitor, or combination therapy with both. Both α1-AR antagonist and 5α-reductase inhibitors alleviate LUTS in men by reducing bladder outlet resistance. Alpha1-AR antagonists decrease smooth muscle tone in the prostate and bladder neck, while 5α-reductase inhibitors reduce prostate volume. As mentioned, several trials have demonstrated the efficacy and safety of the combination therapy of antimuscarinics and α1-AR antagonist for patients with OAB and coexisting BPO. However, post hoc analyses of the TIMES study [Kaplan et al., 2006] suggested that men with smaller prostates benefit more from antimuscarinic therapy than those with larger prostates [Roehrborn et al., 2008; Roehrborn, Kaplan et al., 2009]. Chung and coworkers conducted an open-label, fixed-dose study to assess the efficacy and safety of tolterodine ER in combination with dutasteride in men with a large prostate (≥30 g) and persistent OAB symptoms after α1-AR antagonist therapy who had been unsuccessfully treated with dutasteride alone [Chung et al. 2010]. At the start of the study, all patients had been on dutasteride 0.5 mg daily for at least 6 months and α1-AR antagonist therapy had failed. All patients were given 4 mg tolterodine ER daily for 12 weeks and had discontinued α1-AR antagonist before the start of the study. At 12 weeks, the frequency (-3.2/24hrs, $p < 0.02$), urgency (19.2%, $p < 0.03$), number of severe OAB episodes (71.4%, $p < 0.05$), and incidence of nighttime voiding (-0.9, $p < 0.003$) were found to have decreased significantly from baseline. The IPSS decreased with dutasteride treatment (from 19.3 to 14.3) and further decreased with the addition of tolterodine to 7.1 ($p < 0.001$). Storage symptoms decreased from 9.8 to 4.5 ($p < 0.001$). Dry mouth occurred in four (7.5%) subjects, constipation in one (2%), and decreased sexual function in two (3.9%). Post-void residual increased by 4.2 mL, Qmax decreased by 0.2 mL/s, and no patients went into retention. The authors concluded that the combination of tolterodine and dutasteride was effective, safe, and well-tolerated in men with large prostates with persistent OAB symptoms and LUTS secondary to BPO.

The results of this study indicate that antimuscarinics are safe and effective in selected patients with OAB and BPO when used in combination with 5α-reductase inhibitors. Further studies are required to verify the efficacy of antimuscarinics combined with 5α-reductase inhibitors in these patients.

4. α_1-AR ANTAGONISTS WITH 5A-REDUCTASE INHIBITORS

It has been well established that the combinations of α1-AR antagonists with 5-α reductase inhibitors (doxazosin finasteride: MTOPS; dutasteride+ tamsulosin: CombAT) can improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery [McConnell et al., 2003, Roehrborn et al., 2010].

XI. FUTURE POSSIBILITIES

1.PERIPHERALLY ACTING DRUGS

a) Vitamin D_3 receptor analogues

It is well known that vitamin D affects skeletal muscle strength and functional efficiency, and vitamin D insufficiency has been associated with notable muscle weakness. The levator ani and coccygeus skeletal muscles are critical components of the pelvic floor and may be affected by vitamin D nutritional status.Weakened pelvic floor musculature is thought to be associated with the development of urinary incontinence and fecal incontinence symptoms. Aging women are at increased risk for both pelvic floor dysfunction and vitamin D insufficiency. However, to date, only small case reports and observational studies have shown an association between insufficient vitamin D and pelvic floor dysfunction symptom severity (Parker-Autry et al., 2012). Rat and human bladders were shown to express receptors for vitamin D [Crescioli et al., 2005],

which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D3 have also been shown to inhibit benign prostatic hyperplasia (BPH) cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [Crescioli et al., 2002; 2003; 2004]. Experiments in rats with bladder outflow obstruction [Schröder et al., 2006] showed that one of the analogues, BXL-628, at non-hypercalcemic doses, did not prevent bladder hypertrophy, but reduced the decrease in contractility of the bladder smooth muscle which occurred with increasing bladder weight [Schröder et al., 2006]. The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [Morelli et al., 2007]. Upregulation of his pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO [Peters et al., 2006; Christ and Andersson, 2007]. In rats with outflow obstruction, previous elocalcitol-treatment improved the effects of tolterodine on bladder compliance [Streng at al., 2012]. It was suggested that in rats elocalcitol exerted additional beneficial actions on outflow obstruction-induced functional changes during the filling phase of micturition. This supports combined therapy in BPH-related LUTS. If the results are valid in humans, combined therapy with the drug would be of value.

The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that BXL628 was able to arrest prostate growth within 12 weeks in men aged>or=50 years with prostatic volume > or = 40 ml [Colli et al., 2006]. In an RCT enrolling 120 female patients with OAB, where the primary endpoint was an increase in the mean volume voided, a significant increase vs placebo (22% vs 11%) was demonstrated [Colli et al., 2007]. Whether or not vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB, requires further RCTs. However, currently, the development of the drug seems to be stopped [Tiwari, 2009].

b) TRP channel antagonists

The transient receptor potential (TRP) channel superfamily has been shown to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder, and may act as sensors of stretch and/or chemical irritation [Araki et al., 2008; Everaerts et al., 2008; Andersson et al., 2010; Araki, 2011]. TRPV1 and TRPV4 channels have been found to be expressed in the urinary bladder [Tominaga et al., 1998; Birder et al., 2001; Gevaert et al., 2007]. TRPV1 is present and active both in the urothelium and in the nerve fibers of several species including humans [Ji et al., 2002; Charrua et al., 2009a]. TRPV4 was initially described in the urothelium of rodents and humans [Janssen et al., 2011]. Co-expression of the two receptors was observed in 20% of rat urothelial cells [Kullmann et al., 2009]. Recent observations indicate, however, that TRPV4 may also be expressed in bladder afferents. In fact, about 30% of L6 dorsal root ganglia neurons that project to the urinary bladder co-express TRPV1 and TRPV4 [Cao et al., 2009; Charrua et al., 2012a]. The physiological meaning of this observation is unclear.

TRPV1 KO mice have a normal or quasi-normal phenotype. In awake animals, the only change detected in TRPV1 KO mice was a smaller volume per void when compared with wild type (WT) controls [Birder et al., 2001]. In cystometries performed under anaesthesia, the TRPV1 KO mice phenotype seems also very benign. Some studies reported that this animals have totally normal cystometric traces [Charrua et al., 2007]. However, other studies showed that TRPV1 KO mice develop a few non-voiding contractions preceding the voiding contraction [Birder et al., 2001; Frias et al., 2012]. Accordingly, TRPV1 antagonists (GRC 6211) did not show any relevant effect on bladder activity of intact rodents [Charrua et al, 2009b]. In contrast with TRPV1 KO mice, the micturition phenotype of TRPV4 KO animals is clearly abnormal. TRPV4 KO mice are incontinent, most probably due to incomplete bladder emptying [Gevaert et al., 2007] Cystometric studies carried out under physiological conditions revealed that TRPV4 KO mice have an marked increase in the inter-contraction interval when compared to wild-type (WT) littermates. [Gevaert et al., 2007; Birder et al. 2002]. Likewise, TRPV4 antagonists (HC-067047) decreased the frequency of bladder contractions and increased the inter-contraction interval [Everaerts et al, 2010]. These observations indicated that TRPV4 has a role in the control of normal micturition reflex.

Indisputably, TRPV1 or TRPV4 have a role in the increase of micturition frequency associated with cystitis [Charrua et al., 2007; Everaerts et al., 2010]. While inflamed WT mice exhibit bladder hyperactivity and intense spinal Fos expression after different forms of bladder inflammation, including acetic acid or bacterial extracts, TRPV1 KO mice have normal cystometries and normal spinal c-fos expression [Charrua et al., 2007]). The The same holds true for TRPV4. In fact, TRPV4 KO mice exhibit significantly lower voiding frequencies and larger voided volumes than WT after inflammation with cyclophosphamide [Everaerts et al, 2010].

The blockade of TRPV1 and TRPV4 with specific antagonist confirm the observations carried out in knock-out animals. As a matter of fact, the TRPV1 antagonist GRC 6211 or the TRPV4 antagonist HC-067047 both abolish the increase of micturition frequency associated with chemical cystitis [Everaerts et al. 2010; Charrua et al., 2009b]. Recently,

it was shown that the systemic co-administration of TRPV1 and TRPV4 antagonist was more effective in treating the cystitis-induced increase of micturition frequency than the individual application of each antagonist [Charrua et al., 2012b]. In particular, the effect could be observed at very low doses of the TRPV1 and TRPV4 antagonists, which had no effect when given isolated. This observed effect might be the answer to overcome the eventual adverse events related with the application of some of these antagonists [Planells-Cases et al., 2011]. Just to mention a few, TRPV1 antagonists are associated with hyperthermia and increased risk of cardiac ischemia [Avelino et al., 2012] while TRPV4 antagonists may eventually precipitate urinary retention and overflow incontinence [Gevaert et al., 2007].

It is known for long that TRPV1 is involved in the emergence of neurogenic detrusor overactivity following spinal cord transaction [Avelino & Cruz, 2006]. Quite recently a TRPV1 antagonist GRC 6211 has been shown to decrease reflex detrusor overactivity in rats after chronic spinal cord transaction. With increasing doses it was possible to obtain a total suppression of bladder activity [Santos-Silva et al., 2012]. The clinical relevance of this finding will certainly be further investigated in the future.

There seem to be several links between activation of different members of the TRP superfamily and LUTS/DO/OAB, and further exploration of the involvement these channels in LUT function, normally and in dysfunction, may be rewarding. However, proof of concept studies in humans are still lacking.

c) Prostanoid receptor agonists/antagonists

Recent developments in the field of prostanoid receptors may open new possibilities to use selective prostanoid receptor antagonists for DO/OAB treatment [Aoki et al., 2009; Jones et al., 2009]. There is evidence suggesting that PGE2 contributes to the pathophysiology of DO/OAB: PGE2 infused into the bladder induces DO in humans and animals, increases PGE2 production in DO models and there are high concentrations of PGE2 in the urine of patients with OAB [McCafferty et al., 2008]. PGE2 is an agonist at EP receptors 1 to 4, all G-protein coupled, which mediate its physiological effects. Based on studies using knockout (KO) mice and EP1 receptor antagonists, it was suggested that the effects of PGE2 on bladder function were mediated through EP1 receptors [Schroder et al., 2004]. EP receptors can be found on urothelium/urothelium, in detrusor smooth muscle and in intramural ganglia [Wang et al., 2008; Rahnama'i et al., 2010; Rahnama'i et al., 2011]. Functionally, it has been proposed that modulation of bladder activity exerted via EP1 receptors occurs via an afferent mechanism. Schröder et al. [2004] found no difference in urodynamic parameters between unobstructed EP1 receptor KO and WT mice. However, EP1 receptor KO mice did not respond to intravesical PGE2 instillation, while WT mice developed DO. The lack of EP1 receptor did not prevent bladder hypertrophy due to partial bladder outflow obstruction but after obstruction WT mice had pronounced DO, while this was negligible in EP1 receptor KO mice.

Lee et al. [2008] found that in normal rats a selective EP receptor antagonist significantly increased bladder capacity, micturition volume and micturition intervals. The antagonist significantly decreased the stimulatory effects of PGE2, and decreased the frequency and amplitude of non-voiding contractions in animals with BOO. More recently it has been shown that also EP3 receptor KO mice have a diminished response to bladder infusion of PGE2, and demonstrate an enhanced bladder capacity under basal conditions [Jones et al., 2009]. This findings suggest an important contribution for EP3 receptors in the modulation of bladder function under physiological conditions as well as under conditions of enhanced PGE2 production evoking DO. Thus, EP1 and EP3 receptors may have a role in PGE2 mediated DO.

Interestingly, activation of EP3 receptors evoked diuresis and EP3 receptor antagonism was found to induce an antidiuretic effect [Jugus et al., 2009]. Thus, to modulate bladder activity, it appears that the EP3 receptor has a role in regulating urine production. Both effects may be useful for treatment of DO/OAB. It cannot be denied that EP1/EP3 receptors constitute interesting and promising targets for drugs aimed at DO/OAB treatment. However, a randomised, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of the EP-1 receptor antagonist, ONO-8539, in patients with the overactive bladder syndrome suggests that the role of EP1 receptor antagonism in the management of OAB syndrome is minimal [Chapple et al., 2011].

d) Intraprostatic Injections of drugs

Intraprostatic injection therapy is probably the oldest minimally invasive surgical therapy for BPH and has been investigated for over 100 years with renewed interest recently. There are different injectables and various routes of administration, transperineal, transrectal and transurethral.

1. Ethanol

Ethanol injection is one of the most investigated intra-prostatic therapies and have been investigated for more than a decade [Goya et al., 1999]. However, the mechanism of action, patient selection and application of ethanol (the number of injection sites and the injection volume) have not been well investigated and long-term results are scarce. It seems that ethanol causes inflammation, coagulative necrosis with protein denaturation and cell membrane lysis, and, finally, sloughing of prostatic tissue resulting in cavity

formation [Plante et al., 2003]. The majority of trials demonstrated a significant reduction in symptoms and post-void residual volume as well as a significant improvement in Qmax and QoL and prostate volume also decreased significantly in the majority of studies [Goya et al., 2004; Grise et al., 2004; Plante et al., 2007; Sakr et al., 2009]. The durability of clinical effects beyond 1 year seems poor. One trial with a mean follow-up of 3 years showed a retreatment rate of 41% [Goya et al., 2004].

2. BoNT-A

BoNT-A investigation for the treatment of benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH) started in 2003 [Maria et al., 2003] after the experimental study by Doggweiler et al. [1998] demonstrating prostatic atrophy in the rat after intraprostatic injection of the neurotoxin. In an exploratory study, which involved injection of 200 U of onabotA in moderate to large prostate glands, a rapid prostate volume decrease was induced and still present at 12 months [Maria et al., 2003]. Following this study, Kuo [2005] reported similar findings when injecting prostate glands of 50 ml or larger. BoNT-A injection in smaller prostate glands caused a much lesser reduction in prostate volume, but a 15% reduction was still observed [Chuang et al., 2005; Chuang et al., 2006c). Independent of the extent of prostate volume reduction, improvement of LUTS and flow were consistently reported [Maria et al., 2003; Kuo, 2005; Chuang et al., 2005; Chuang et al., 2006c], while a decrease in total serum PSA were observed only in some studies [Maria et al., 2003; Guercini et al., 2005]. In a multicenter, double-blind, randomized phase II clinical trial of 100 and 300 unit doses of onabotA to treat the lower urinary tract symptoms of BPH, Crawford and coworkers concluded that intraprostatic injection of 100 or 300 units of onabotA passed predetermined criteria for treatment efficacy and safety (30% improvement from baseline to 3 months in American Urological Association symptom index and/or maximum urinary flow rate and safety). The ideal dose was not found, but it seemed that 100 unit dose may be preferable due to similar efficacy with reduced costs and adverse effects [Crawford et al., 2011]. Some serious adverse events were reported, including 3 cases of urosepsis related to the onabotA injection. Other minor adverse events reported were urinary tract infection, pelvic pain, urinary retention, macroscopic hematuria and hematospermia [Crawford ED et al., 2011].

Silva et al. [2008], selected a particular group of patients with high co-morbidity in which more invasive treatments were contraindicated. Intraprostatic BoNT-A injection was carried out transrectally, under ultrasound guidance. Twenty-one men with large BPE, 70±10 ml, on chronic indwelling catheter for at least 3 mo who were not candidates for surgery because of poor general condition received 200 U BoNT-A in the transition zone. Baseline prostate volume of decreased to 57±10 ml at 1mo and to 47±7ml at 3 months. At 1 month, 16 patients (76%) could resume voiding with a mean Qmax of 9.0±1.2 ml/s. At 3 months, 17 patients (81%) voided with a mean Qmax of 10.3±1.4 ml/s. Residual urine was not significant and mean serum total PSA showed a slight decrease [Silva et al. 2008]. The analysis of 11 patients of the initial cohort showed that the duration of prostate atrophy after the single injection of 200U of BoNT-A was found to be about 18 months [Silva et al., 2009b].

Intraprostatic injection of BoNT/A seems devoid of sexual adverse events. Sixteen sexually active men aged > 60 years with BPH/benign prostatic enlargement (BPE) refractory to standard medical therapy received 200U of BoNT/A by transrectal route. Erectile function was evaluated using the International Index of Erectile Function – Short Form (IIEF-5) questionnaire. Orgasmic/ejaculatory function and libido were evaluated using questions 9, 10, 11 and 12 of the IIEF – Long Form. Intraprostatic injection of BoNT-A did not cause deterioration of any domain of sexual function [Silva et al., 2011].

Although necrosis of the gland at the places of BoNT-A injection could explain the rapid volume reduction, transrectal ultrasound examination of the glands, performed in these or in previous studies [Maria et al., 2003; Kuo , 2005; Chuang et al., 2005; Silva et al., 2008, was unable to detect signs of cavitation that indirectly could suggest the presence of necrosis. Therefore, the reason for the decreased prostate volume should be more appropriately related to the widespread apoptosis detected in the gland after BoNT-A administration. Apoptosis was reported in rats, dogs, and humans, and affected both the epithelial and stromal components [Doggweiler et al., 1998; Chuang et al., 2005; Chuang et al., 2006b; Chuang et al., 2006d, Silva et al., 2009a].

Although until now, no important side-effects have been reported after intraprostatic injection of the neurotoxin in doses ranging between 100 and 300 U, a multicenter, double-blind, randomized phase II clinical trial of 100 and 300 unit doses of onabotA to treat the lower urinary tract symptoms of benign prostatic hyperplasia, was recently published [Crawford et al., 2011]. onabotA prostatic injection met the two safety criteria proposed, (a dose failed if: 1- a life threatening, disabling or fatal event was determined to be related to the onabotA injection, or 2- 40% or more of the participants reported a moderate or severe side effect related to the botulinum toxin injection). Nonetheless, some serious AEs were reported, including 3 cases of urosepsis related to the onabotA injection and the remaining events were judged not related to the injection. Other minor AEs reported were urinary tract infection,

pelvic pain, urinary retention, macroscopic hematuria and hematospermia [Crawford et al., 2011].

3. NX-1207

NX-1207 is a new drug under investigation for the treatment of LUTS associated with BPH. It is a new therapeutic protein of proprietary composition with selective pro-apoptotic properties [Shore , 2011]. The drug is injected directly into the directly into the transitional zone of the prostate as a single administration to induce focal cell loss in prostate tissue through apoptosis, leading to non-regressive prostate shrinkage and both short- and long-term symptomatic improvement. Information about the drugs is scarce and mostly published in abstract form and not yet in the peer-reviewed literature. Two US Phase II trials have been performed [Shore , 2011]. One of them was a multicenter, randomized, non-inferiority study involving 32 clinical sites with 85 subjects and two dose ranges (2.5 and 0.125 mg) and an active open-label comparator (finasteride). Subjects and investigators on NX-1207 were double-blind as to dosage. The primary endpoint was change in AUASI at 90 and 180 days for a single injection of NX-1207 as compared to finasteride on a non-inferiority basis. Inclusion criteria included an AUA Symptom Score ‡ 15, diminished peak urine flow (< 15 ml/s) and a prostate size of > 30 and < 70 mg. The mean AUA Symptom Score improvement after 90 days in the intent to- treat group was 9.71 points for 2.5 mg NX-1207 (n = 48) versus 4.13 points for finasteride (n = 24) (p = 0.001) and 4.29 for 0.125 mg NX-1207 (n = 7) (p = 0.034). The 180-day results also were positive (NX-1207 2.5 mg non-inferior to open-label finasteride).

No significant changes in serum testosterone or serum PSA levels in the NX-1207 cohorts. There were no reported adverse effects on sexual function. Two US multicenter, double-blind, placebo-controlled Phase III studies are currently underway. The results of such studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

4. PRX302

PRX302 is a modified form of proaerolysin, a highly toxic bacterial pore-forming protoxin that requires proteolytic processing by prostate-specific antigen (PSA) [Sing et al., 2007]. The safety and efficacy of PRX302 was evaluated in men with moderate to severe BPH [Denmeade et al.,2010]. The patients were refractory, intolerant, or unwilling to undergo medical therapies for BPH and had an IPSS >12, a quality of life (QoL) score >3, and prostate volumes between 30 and 80 g. Fifteen patients were enrolled in phase 1 studies, and 18 patients entered phase 2 studies. Subjects received intraprostatic injection of PRX302 into the right and left transition zone via a transperineal approach in an office-based setting. Phase 1 subjects received increasing concentrations of PRX302 at a fixed volume; phase 2 subjects received increasing volumes per deposit at a fixed concentration. IPSS, QoL, prostate volume, Qmax), IIEF, serum PSA levels, pharmacokinetics, and adverse events were recorded at 30, 60, 90, 180, 270, and 360 days after treatment. Sixty percent of men in the phase 1 study and 64% of men in the phase 2 study treated with PRX302 had >30% improvement compared to baseline in IPSS out to day 360. Patients also experienced improvement in QoL and reduction in prostate volume out to day 360. Patients receiving >1 ml of PRX302 per deposit had the best response overall. There were no deleterious effect on erectile function. Adverse eventswere mild tomoderate and transient in nature. The major study limitation was the small sample size.The promising safety profile and evidence of efficacy in the majority of treated subjects in these phase 1 and 2 studies supports further development of PRX302 as a minimally invasive, targeted treatment for BPH. However, no further studies, verifying the initial data, seem to have been published.

e) Cannabinoids

There is increasing evidence that cannabinoids can influence micturition in animals as well as in humans, both normally and in bladder dysfunction [Ruggieri, 2011]. The effects of the cannabinoids are exerted via two types of well defined receptors, CB1 and CB2, distributed widely in the body. However, additional receptor subtypes cannot be excluded [Pertwee et al., 2010; Ruggieri 2011]. Both in the CNS and in peripheral tissues, CB1 and CB2 receptors have been identified; centrally CB1 and peripherally CB2 receptors seem to be predominant [Pertwee et al., 2010; Ruggieri, 2012] (**figure 17**). CBI as well as CB2 receptors have been identified in all layers of the human bladder [Merriam et al., 2008; Gratzke et al., 2009; Tyagi et al., 2009; Walczak et al., 2009]; their expression in the urothelium was found to be significantly higher than in the detrusor, and the expression of CB1 was higher than that of CB2 [Tyagi et al., 2009]. Gratzke et al. [2009] found higher expression of CB2 receptors, but not CB1 receptors, in the mucosa than in the detrusor. Compared to the detrusor, larger amounts of CB2receptor containing nerves that also expressed TRPV1 or CGRP were observed in the suburothelium. Nerve fibers containing CB2 receptors and VAChT (cholinergic neurons) were located in the detrusor. In general, activation of CB1 peripherally has been associated with vasodilation and motility changes via suppression of release of neurotransmitters, whereas activation of CB2 appears to induce anti-inflammatory, antinociceptive, and immunosuppressive actions [Pertwee et al., 2010; Ruggieri, 2011]. Several animal studies have suggested a modulatory role of CB2 receptors in both afferent signalling and cholinergic nerve activity [Gratzke et al., 2009; 2010; 2011]. Thus, in vivo the selective CB2 receptor agonist, cannabinor, increased micturition intervals and volumes, and

increased threshold and flow pressures, suggesting that peripheral CB2 receptors may be involved in sensory functions. In rats with partial urethral obstruction treated daily for 14 days with cannabinor, bladder weight was lower, the ability to empty the bladder was preserved and nonvoiding contraction frequency was low compared to those in controls.

The key enzyme for the degradation of anandamide and other endogenous cannabinoids, is fatty acid amide hydrolase (FAAH, **Figure 18**). FAAH was found to be expressed in rat and human urothelium and was coexpressed with CB2 receptors. In rats, a FAAH inhibitor altered urodynamic parameters that reflect sensory functions, suggesting a role for the endocannabinoid system in bladder mechanoafferent functions [Strittmatter et al., 2011].

It has not been established whether the effects of the cannabinoids are exerted in the CNS (brain, spinal cord) or peripherally. In a preliminay report Blywert et al. [2003] demonstrated an effect of combined CB1/CB2 receptor activation on detrusor overactivity in rats with spinal cord transection, which seemed to exclude the brain as a main site of action.

The clinical experiences the cannabinoid treatment of micturition disturbances inclung LUTS are limited [Ruggieri, 2011], but both open-label and placebo-controlled studies have demonstrated that orally administered cannabinoid modulators may alleviate neurogenic overactive bladder (OAB) symptoms refractory to first-line treatment [Brady et al., 2004; Freeman et al., 2006; Kavia et al., 2010]. Brady et al. [2004] evaluated the efficacy of 2 whole plant extracts (δ9-tetrahydrocannabinol and cannabidiol) of Cannabis sativa in patients with advanced MS and refractory LUTS. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia decreased significantly following treatment. Freeman et al. [2006] tested in a subanalysis of a multicenter trial (the CAMS study) whether cannabinoids could decrease urge incontinence episodes without affecting voiding in patients with MS. The CAMS study randomized 630 patients to receive oral administration of the cannabis extract δ9-tetrahydrocannabinol or matched placebo. Based on incontinence diaries a significant decrease in incontinence episodes was demonstrated.

Kavia et al. [2010] assessed the efficacy, tolerability and safety of Sativex(®) (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS. They performed a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial on 135 randomized subjects with MS and overactive bladder (OAB). The primary endpoint, reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks), showed little difference between Sativex and placebo. However, four out of seven secondary endpoints were significantly in favour of Sativex, including number of episodes of nocturia, number of voids/day, and number of daytime voids. The improvement in I-QOL was in favour of Sativex, but did not reach statistical significance.

Systemic cannabinoids have effects on the lower urinary tract that may have a therapeutic potential; local delivery (intravesical, spinal) may be possible, but more information is needed. The mechanisms of cannabinoid receptors in control of the human LUT

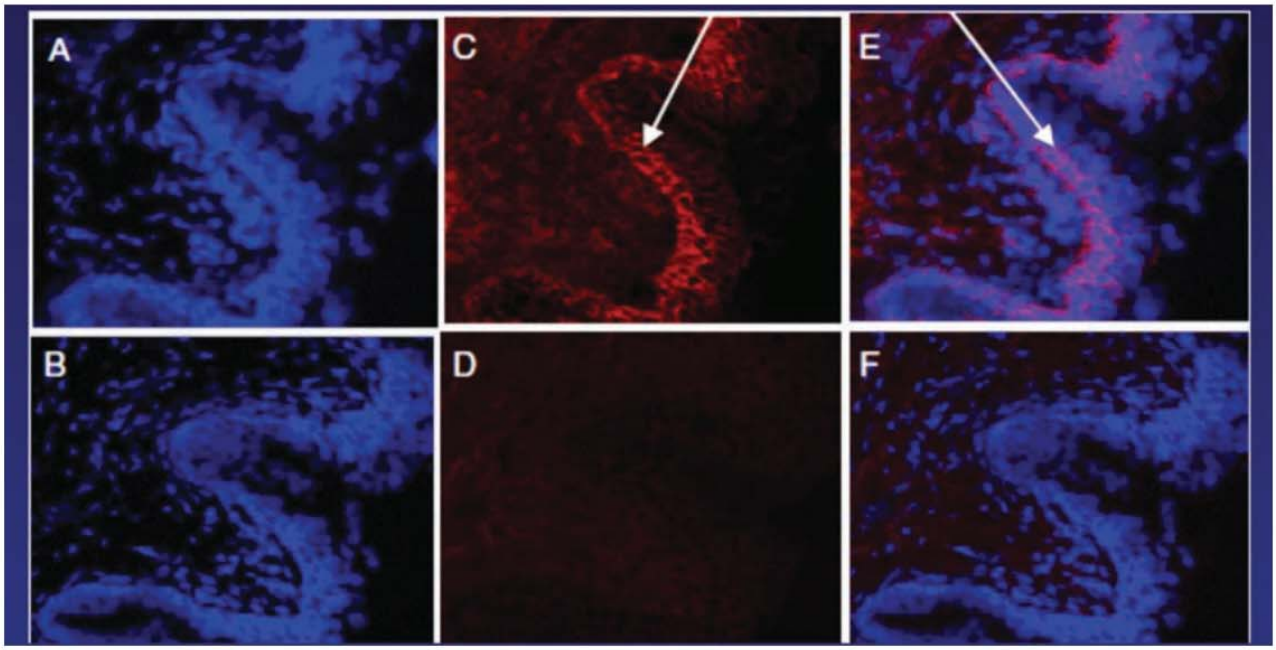

Figure 17 : CB2 receptors in the urothelium/lamina propria. The effects of the cannabinoids are exerted via two types of well defined receptors, CB1 and CB2, distributed widely in the body. Both in the CNS and in peripheral tissues, CB1 and CB2 receptors have been identified; centrally CB1 and peripherally CB2 receptors seem to be predominant.

is incompletely known, and further research is necessary for the development of novel cannabinoid drugs for treatment of LUT disorders.

2. CENTRALLY ACTING DRUGS

Many parts of the brain seem to be activated during storage and voiding [see, Griffiths 2007; Fowler et al., 2008; Griffiths and Tadic, 2008], and there is increasing interest in drugs modulating the micturition reflex by a central action [Andersson and Pehrson, 2003]. Several drugs used for pain treatment also affect micturition; morphine and some antiepileptic drugs being a few examples (**Figure 19**). However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OAB, since selective actions may be difficult to obtain. Holstege [2005], reviewing some of the central mechnisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that "the problem in OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level."

a) Gonadotropin-releasing hormone antagonists

The beneficial effects of the 5α-reductase inhibitors, finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example, antiandrogens or gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone: LHRH) agonists is either poor or at the expense of unacceptable side effects such as medical castration associated with hot flushes, decrease of potency and libido, and negative effects on bone density following long-term androgen ablation [Schroeder et al., 1986; Peters et al., 1987; Bosch et al., 1989; Eri and Tveter, 1993]. With GnRH antagonists submaximal, non-castrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus avoiding medical castration. Several GnRH antagonists – such as cetrorelix, ozarelix and teverelix - have been tested in Phase IIA/IIB clinical trials for their ability to improve LUTS in patients with BPH [Colli and Tanko, 2011].

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

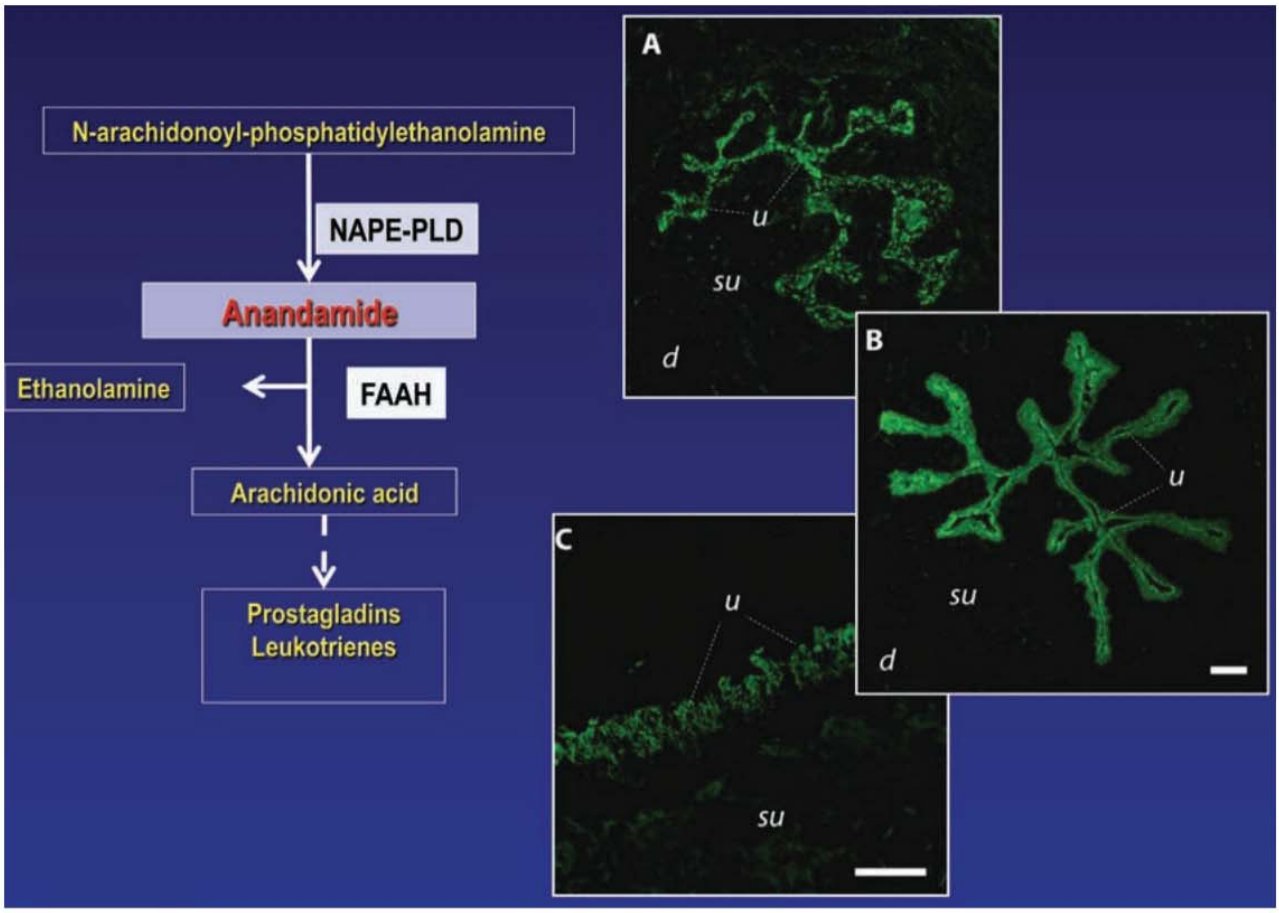

Figure 18: Metabolism of and distribution of fatty acid amide hydrolase (FAAH; cannabinoid degrading enzyme) immunoreactivity in the rat urothelium

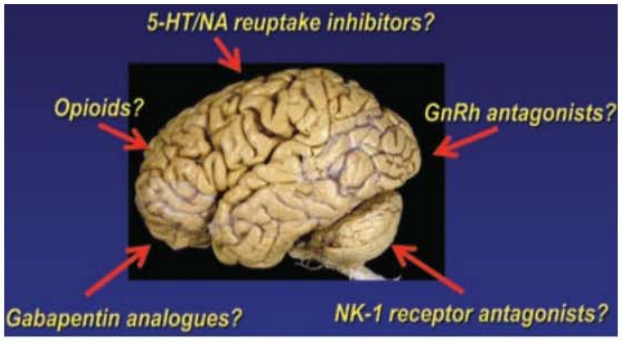

Figure 19 : OAB drugs with a central mode of action. Several principles seem to work, but currently used drugs have low efficacy and/or unacceptable side effects. However, there is great potential for further developments

Due to these results, two phase III studies were conducted in the United States and Europe [AEterna Zentaris] ; in the US study, 637 men were randomized to receive either two doses of placebo or cetrorelix on weeks 2 and 26. The drug showed no statistically significant benefit in improving IPSS. In addition, cetrorelix did not have a significant effect on peak flow rate or prostate volume versus placebo. It is difficult to reconcile this lack of efficacy given favorable prior results. A subsequent multicenter European trial also failed to show any treatment-related efficacy of cetrorelix. The experience with cetrorelix highlights the importance of randomized, placebo-controlled trials that are appropriately powered to show clinical benefit and safety.

b) Gabapentin

Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders [Striano and Striano 2008]. It was originally designed as an anticonvulsant GABA (y-aminobutyric acid) mimetic capable of crossing the blood-brain barrier [Maneuf et al., 2003]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [Maneuf et al., 2003]. It has been suggested that it acts by binding to a subunit of the α2δ unit of voltage dependent calcium channels [Gee et al., 1996; Striano and Striano, 2008]. Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone et al. [2006] reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim et al. [2004] studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other α2δ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives, but convincing RTC are still lacking.

c) Tramadol

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

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

d) NK1-receptor antagonists

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

receptor-expressing neurons in the spinal cord, using intrathecally administered substance P-saponin conjugate [Seki et al., 2002]. Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (L-DOPA) stimulation [Ishizuka et al., 1995a].

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

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting [Massaro and Lenz, 2005], significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), as shown in a well designed pilot RCT [Green et al., 2006]. The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total urinary incontinence and urgency incontinence episodes, and urgency episodes. Aprepitant significantly ($p<0.003$) decreased the average daily number of micturitions (-1.3+/-1.9) compared with placebo (-0.4+/-1.7) at 8 weeks. The average daily number of urgency episodes was also significantly ($p<0.047$) reduced (-23.2+/- 32%) compared to placebo (-9.3+/-40%), and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. Since this initial proof of concept study suggested that NK-1 receptor antagonism hold promise as a potential treatment approach for OAB symptoms, a randomized, double-blind, multicenter trial enrolled 557 adults with overactive bladder (8 or more average daily micturitions and 1 or more daily urge incontinence episodes) [Frenkl et al., 2010]. After a 1-week placebo run-in the patients were randomized to treatment with 8 weeks of daily 0.25, 1 or 4 mg serlopitant, 4 mg tolterodine extended release or placebo. Patients kept 7-day voiding diaries. The primary end point was change from baseline in micturitions per day. Secondary end points included urgency, total incontinence, urge incontinence episodes and incidence of dry mouth. Of the 557 patients randomized, 476 completed the trial and had valid efficacy data for analysis. Mean change from baseline in daily micturitions was significantly greater for 0.25 (-1.1) and 4 mg (-1.1) serlopitant, and for tolterodine (-1.5) than for placebo (-0.5), but not for 1 mg serlopitant (-0.8). No serlopitant dose response was demonstrated. Tolterodine was numerically superior to all doses of serlopitant in mean micturitions per day and secondary end points. The incidence of dry mouth on serlopitant (3.3%) was comparable to placebo (4.6%) and lower than tolterodine (8.8%). Serlopitant was generally well tolerated.

NK-1 receptor antagonists may have a role in the treatment of overactive bladder but at least the componds tested so far does not offer advantages in efficacy compared to tolterodine.

A different approach, modulation of neuropeptide release rather than NK receptor blockade, was tested in a pilot study with cizolirtine, which is a substance-P and CGRP release modulator at the spinal cord level. The modulation of substance-P and CGRP is probably related to the increase of extracellular levels of noradrenaline and serotonin. Cizolirtine 200 and 400 mg were compared to placebo in 79 OAB patients. Although the decrease in key OAB symptoms was significantly higher in the active arms, adverse events were reported in 68% and 81% of the patients on cizorlitine 200 and 400mg. More commonly reported side effects were gastro-intestinal in nature, including dry mouth and vomiting [Martınez-Garcıa et al., 2008]. No further developments of this compound have been reported.

C. Drugs used for treatment of stress incontinence in women

Many factors seem to be involved in the pathogenesis of stress urinary incontinence (SUI) in women: urethral support and function, bladder neck support and function of the nerves and musculature of the bladder, urethra, and pelvic floor [Delancey, 1997; Mostwin et al, 2005, Koelbl, Nitti et al, 2009; Chapple and Milsom, 2012]. Pure structural factors cannot be treated pharmacologically. However, SUI in women is generally thought to be characterized by decreases in urethral transmission pressure and, in most cases, resting urethral closure pressure [Henriksson et al, 1979; Hilton et al, 1983, Koelbl and Nitti, 2009]. It, therefore, seems logical that increasing urethral pressure should improve the condition.

Factors which may contribute to urethral closure include the tone of the urethral smooth and striated muscle (the rhabdosphincter) and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacological evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by released noradrenaline [Andersson, 1993; Andersson and Wein, 2004; Andersson and Wein, 2012]. A contributing factor to SUI, mainly in elderly

women with lack of estrogen, may be lack of mucosal function. The pharmacological treatment of SUI (**Table 3**) aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated musculature, either directly or through increased motorneuron activity. Several drugs may contribute to such an increase [Andersson and Wein, 2012], but relative lack of efficacy or/and side effects have limited their clinical use.

I. α-ADRENOCEPTOR AGONISTS

Several drugs with agonistic effects on peripheral α-ARs have been used in the treatment of SUI. Relatively recently, a central role of noradrenaline (NA) in increasing the excitability of urethral rhabdosphincter motorneurons in the rat analogue of Onuf's nucleus, an effect due at least in part to α1-AR receptor dependent depolarization. This could contribute to the mechanism by which NA reuptake inhibitors improve SUI [Yashiro et al, 2010]. Ephedrine and norephedrine (phenylpropanolamine; PPA) seem to have been the most widely used [Andersson and Wein, 2012]. The original United States Agency for Healthcare Policy and Research Guidelines [Agency for Healthcare Policy and Research, 1992] reported 8 randomized controlled trials with PPA, 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) were listed as 0% to 14%, percent reduction in continence as 19% to 60%, and percent side effects and percent dropouts as 5% to 33% and 0% to 4.3% respectively. The most recent Cochrane review on the subject [Alhasso et al, 2005, reprinted virtually unchanged in 2008] assessed randomized or quasi-randomized controlled trials in adults with stress urinary incontinence which included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in 2, norepinephrine in 3, clenbuterol in 3, terbutaline in 1, eskornade in 1 and RO 115-1240 in 1). The authors concluded, "there was weak evidence to suggest that use of an adrenergic agonist was better than placebo in reducing the number of pad changes and incontinence episodes, as well as, improving subjective symptoms". There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination. Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25% of subjects reported such effects, but when these consisted of effects due to adrenergic stimulation, they caused discontinuation in only 4% of the total.

Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [Andersson and Wein, 2012]. Kernan et al. [2000] reported the risk of hemorrhagic stroke to be 16 times higher in women less than 50 years of age who had been taking PPA as an appetite suppressant (statistically significant) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (not statistically significant). There was no increased risk in men. PPA has been removed from the market in the United States. It is still allowed as a treatment for SUI in a few countries. Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some [Bent et al., 2003) had suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003, the Food and Drug Administration of the US decreed such a ban, a move which has survived legal appeal.

Midodrine and methoxamine stimulate α1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate at best, and the clinical usefulness seems to be limited by adverse effects [Alhasso et al., 2003; Radley et al., 2001; Weil et al., 1998].

Attempts continue to develop agonists with relative selectivity for the human urethra. Musselman et al. [2004] reported on a phase 2 randomized crossover study with RO 115-1240, a peripheral active selective α1A/1L-AR partial agonist [Blue et al., 2004] in 37 women with mild to moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug. PF-3774076, a CNS penetrating partial α1A-AR agonist, increased peak urethral pressure in dogs and was selective with respect to α1B and α1D receptors,

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

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

but heart rate and blood pressure changes caused significant concern (Conlon et al., 2009). Furuta et al. [2009] reported that the α2-AR can inhibit the release of glutamate presynaptically in the spinal cord and proposed that α2-AR antagonists would be useful as a treatment for SUI. This hypothesis awaits testing.

II. β-ADRENOCEPTOR AGONISTS

Clenbuterol. β-AR stimulation is generally conceded to decrease urethral pressure [Andersson, 1993], but β2-AR agonists have been reported to increase the contractility of some fast contracting striated muscle fibers and suppress that of slow contracting fibers of others [Fellenius et al.,1980]. Some β-AR agonists also stimulate skeletal muscle hypertrophy – in fast twitch more so than slow twitch fibers [Kim et al., 1992]. Clenbuterol has been reported to potentiate the field stimulation induced contraction in rabbit isolated periurethral muscle preparations, an action which is suppressed by propanolol and greater than that produced by isoprotererol [Kishimoto et al, 1991]. These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yaminishi et al. [1994] reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs, abolished by β-AR blockade.

Yasuda et al. [1993] described the results of a double blind placebo controlled trial with this agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad usage per day, and overall global assessment. Pad weight decreased from 11.7± 17.9g to 6.0± 12.3g for drug and from 18.3± 29.0g to 12.6± 24.7g for placebo, raising questions about the comparability of the 2 groups. The "significant" increase in MUCP was from 46.0± 18.2 cm H2O to 49.3± 19.1 cm H2O, versus a change of -1.5 cm H2O in the placebo group. 56/77 patients in the clenbuterol group reported some degree of improvement versus 48/88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko et al. [2000] investigated the effects of Clenbuterol on 61 female patients with stress incontinence in a 12-week randomized study, comparing drug therapy to pelvic floor exercises. The frequency and volume of stress incontinence and the patient's own impression were used as the basis for the assessment of efficacy. The improvement of incontinence was 76.9%, 52.6%, and 89.5% in the respective groups. In an open study, Noguchi et al [1997] reported positive results with clenbuterol (20 mg b.i.d. for 1 month) in 9 of 14 patients with mild to moderate stress incontinence after radical prostatectomy. No subsequent published reports have appeared. Further well-designed RTCs investigating effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence.

There have been no recent reports of clinical trials with α1- or β-AR agonists or antagonists for SUI.

III. β –ADRENOCEPTOR ANTAGONISTS

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

IV. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS

1. IMIPRAMINE

Imipramine, among several other pharmacological effects has classically been reported to inhibit the reuptake of noradrenaline and serotonin in adrenergic nerve endings. In the urethra this could be expected to enhance the contractile effects of noradrenaline on urethral smooth muscle. Gilja et al. [1984] reported in an open study on 30 women with stress incontinence that imipramine, 75 mg daily, produced subjective continence in 21 patients and increased mean maximal urethral closure pressure (MUCP) from 34 to 48 mm Hg. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement. Lin et al. [1999] assessed the efficacy of imipramine (25 mg imipramine three times a day for three months) as a treatment of genuine stress incontinence in 40 women with genuine stress incontinence. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of "successful treatment" was 60% (95% CI 11.8-75.2). There are no RCTs on the effects of imipramine on SUI. No subsequent published reports have appeared.

Interestingly, Gillman [2007] reported that clomipramine had far greater 5HT reuptake inhibition than imipramine and roughly similar NA reuptake inhibition. Desipramine and reboxetine had greater NA reuptake inhibition (desipramine superior), with less effects than imipramine on 5HT uptake (desipramine superior).

2. DULOXETINE

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor, which has been

shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function [Thor et al., 1995; Katofiasc et al., 2002]. Bladder capacity was also increased in this model, both effects mediated centrally through both motor efferent and sensory afferent modulation [Fraser et al., 2003]. The sphincteric effects were reversed by α1 adrenergic (praxosin) and 5HT2 serotonergic (LY 53857) antagonism, while the bladder effects were mediated by temporal prolongation of the actions of serotonin and norepinephrine in the synaptic cleft [Fraser et al., 2003]. Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 h [Sharma et al., 2000].

Thor et al. [2007] described the mechanisms of action and the physiologic effects of duloxetine. 5HT (serotonin) and NA terminals are dense in spinal areas associated with lower urinary tract functioning especially around the pudendal nerve neurons in Onuf's nucleus. These are projections from separate areas in the brain stem. Glutamate is the primary excitatory neurotransmitter in the spinal cord, activating the pudendal neurons in Onuf's nucleus causing contraction of the urethral rhabdosphincter (**Figure 20**). The rhabdosphincter innervation is proposed as distinct from that of the levator ani [Thor and de Groat, 2010]. The responsiveness of the rhabdosphincter motor neurons to glutamate is modulated (facilitated) by 5HT (through 5HT2 receptors) and NA (through α1 -ARs). 5HT and NA, however, only modulate, and, when micturition occurs, glutamate excitation and the rhabdosphincter contraction cease. Excitatory effects on urethral sphincter activity are shared to a lesser extent by receptors for 5HT1A (indirect through a supraspinal stimulation), TRH, Vasopressin, NMDA and AMPA; inhibitory effects are similarly mediated by κ2 opioid, α1 ARs, GABA-A, GABA-B and glycine receptors [Thor and de Groat, 2010]. Some CNS penetrant selective 5HT2C agonists have been found to increase urethral muscle tone and inhibit micturition reflexes in animal models, and these are additional candidates for clinical development for the treatment of SUI [Brennan et al., 2009, Andrews et al., 2011].

Sevral RTCs have documented the effect of duloxetine i SUI [Norton et al., 2002; Dmochowski et al, 2003; Millard et al., 2004]. A Cochrane review of the effects of duloxetine for stress urinary incontinence in women is available, the last substantive amendment listed as 25 May 2005 [Mariappan et al., 2005]. Fifteen reports were deemed eligible for analysis, 9 primary studies and 6 additional reports related to 1 or 2 of the primary references. An additional analysis "performed under the auspices of the Cochrane Incontinence Group" was performed on just the 9 primary trials comparing duloxetine and placebo, and published separately [Mariappan et al., 2007]. The results can be summarized as follows. Subjective "cure" in the duloxetine 80 mg daily (40 mg b.i.d.) was higher than in the placebo group (10.8%

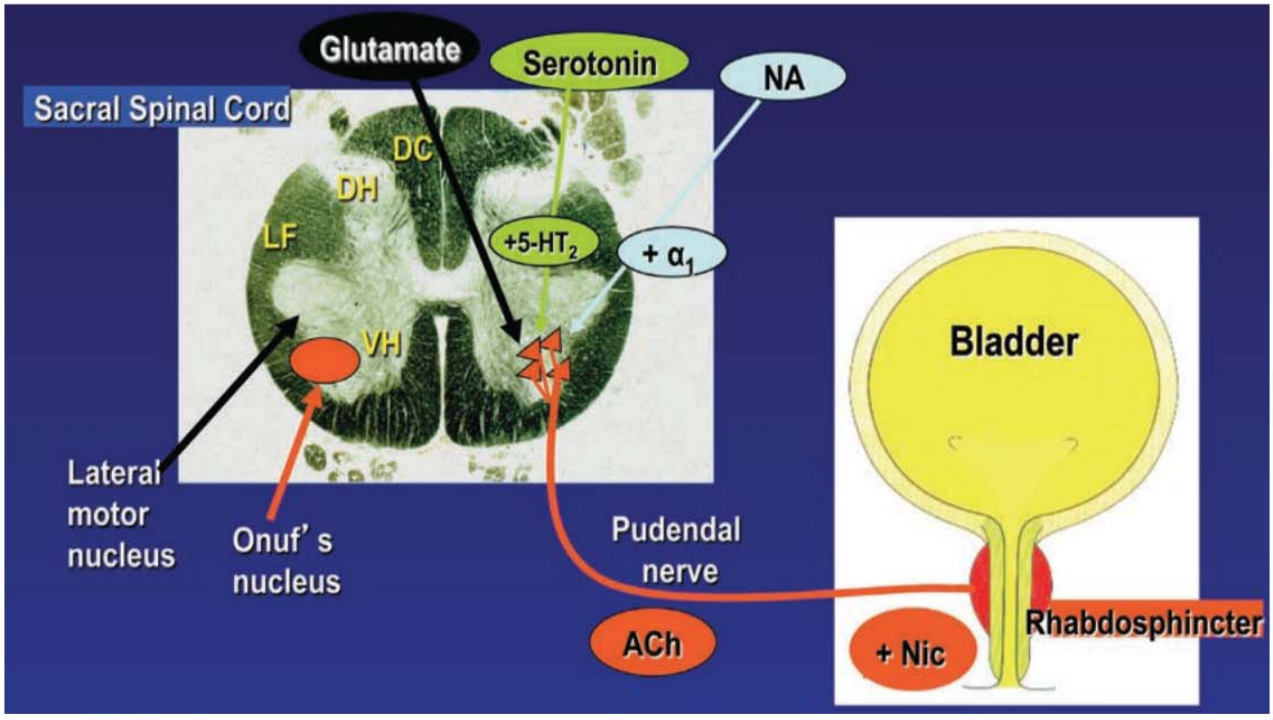

Figure 20: The striated urethral sphincter is innervated by the pudendal nerve, which contains the axons of motor neurons whose cell bodies are located in Onuf's nucleus. Glutamate exerts a tonic excitatory effects on these motor neurons, and this effect is enhanced by noradrenaline (NA) and serotonin (5-HT), acting on α1- adrenoceptors and 5-HT2-receptors, respectively. By inhibition of the reuptake of noradrenaline and serotonin, duloxetine increases the contractile activity in the striated sphincter (nicotinic receptors: + Nic). DC = dorsal commissure; DH = dorsal horn; VH = ventral horn; LF = lateral funiculus; ACh = acetylcholine

vs 7.7%, overall RR = 1.42; 95% CI, 1.02-1.98; p = 0.04). The estimated absolute size of effect was about 3 more patients cured of every 100 treated. Objective cure data, available from only 1 trial, showed no clear drug/placebo difference. Duloxetine showed greater improvement in I-QOL (WMD for 80 mg: 4.5; 95% CI 2.83-6.18, p<0.00001). Adverse effects in 6 trials were analyzed. These were reported by 71% of drug subjects and 59% of those allocated to placebo. Nausea was the most common adverse event and the incidence ranged from 23-25% and was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness and insomnia, overall RR 1.30 (95% CI, 1.23-1.37). Across these 6 trials 17% in the drug group withdrew, 4% in the placebo arm. In the 2007 article, the authors conclude by saying that further research is needed as to whether management policies incorporating duloxetine are clinically effective and cost effective compared to other current minimally invasive and more invasive approaches in patients with varying severity of SUI, and that "longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications".

Hurley et al. [2006] characterized the safety of duloxetine for treatment of SUI in women, using an integrated database generated from four published placebo-controlled clinical trials. The database included 1913 women randomized to duloxetine (N=958) or placebo (N=955), examining adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiograms, and laboratory analytes. AEs occurring initially or worsening during the double-blind treatment period were considered treatment-emergent (TEAE). Differences between duloxetine-treated and placebo-treated groups were compared statistically. Common TEAEs included: nausea (23.2%), dry mouth (13.4%), fatigue (12.7%), insomnia (12.6%), constipation (11.0%), headache (9.7%), dizziness (9.5%), somnolence (6.8%), and diarrhea (5.1%). Most TEAEs that emerged early were mild to moderate, rarely worsened, and resolved quickly. Overall AE discontinuation rates were 20.5% for duloxetine and 3.9% for placebo (P<.001). Most discontinuations (83%) occurred within the first month of treatment. SAEs were uncommon and did not differ between treatments. Statistically significant, but clinically unimportant mean increases in heart rate (2.4 bpm) and systolic and diastolic blood pressure (<or=2 mmHg) occurred. No arrhythmogenic potential was observed and any rare, transient, asymptomatic increases in hepatocellular enzymes normalized. The authors concluded that duloxetine was safe and tolerable, although transient AEs were not uncommon. Hashim and Abrams [2006] suggested, to reduce the risk of nausea, to begin with a dose of 20 mg twice daily for 2 weeks, then to increase to the recommended 40 mg b.i.d. dosage.

Ghoniem et al. [2005] randomized women with SUI to 1 of 4 treatment combinations: duloxetine alone (40 mg b.i.d.), pelvic floor muscle training, combination and placebo. Overall, drug with or without PFMT was superior to PFMT alone or placebo, while pad results and QOL data favored combination therapy to single treatment. Cardozo et al. [2004] reported that 20% of women awaiting continence surgery changed their minds while taking duloxetine. Duckett et al. [2006], offered a 4-week course to women awaiting a TVT operation. Thirty-seven percent (of 73) declined. Excluding women for whom concomitant prolapse surgery was planned, 8/33 (24%) scheduled for incontinence surgery alone came off the list. Sixteen (48%) discontinued duloxetine because of AEs, 9 (27%) found the drug ineffective.

Bent et al. [2008], reported on the effects of 12 weeks of duloxetine (40 mg b.i.d.) vs placebo in a large group of women with MUI. For SUI episodes, the mean IEF (incontinence episode frequency) per week decreased 58.9% with drug [7.69 to 3.93] vs 43.3% for placebo [8.93 to 6.05]. Interestingly, corresponding decreased for UUI episodes were 57.7% vs 39.6%. Both sets of values are statistically significant, but the baselines are different and the absolute change for SUI amounted to -3.76 episodes per week for drug, -2.87 for placebo. Nausea was reported by 18% of patients on drug, 4.5% on placebo. Corresponding percents for other AEs include, dry mouth (12 vs 2.8), dizziness (9.7 vs 2.4), constipation (8.3 vs 4.2), fatigue (6.7 vs 2.8). Nausea and dizziness were less common in a subgroup taking concurrent antidepressants. Women 65 years and older with SUI or stress predominant MUI (S-MUI) were given duloxetine (40 mg b.i.d. after a 2-week start on 20 mg b.i.d.) or placebo for 12 weeks by van Leeuwen et al [2008]. They conclude, "this study supports the use of duloxetine in elderly women with SUI or S-MUI". The data show an absolute change in SUI + S-MUI episodes of -11.7 and -6.9 IEF/week (drug and placebo) and median percent changes of -52.5% vs -36.7% from 24h diaries, both significant at p<0.001. However, the changes for SUI alone were -53% vs -42% (NS) while for S-MUI alone they were -51.6% vs -32.7% (p<0.001). Nausea was less than in other trials (7.5% vs 3.1%), perhaps due to the lower starting dose. Other AEs included fatigue (14.2% vs 5.4), constipation (10.4 vs 0.8), dizziness (9.0 vs 4.6), excess sweating (5.2 vs 0).

Schagen van Leeuwen et al. [2008] investigated efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Duloxetine-treated patients had a significantly greater decrease from baseline to endpoint in mean incontinence episode frequency/week than placebo-treated patients (-52.47% vs. -36.70%). The

responder rate (> or =50% reduction in incontinence episode frequency/week) was 57.1% in the duloxetine group and 35.2% in the placebo group (P<0.001). Significant benefits of duloxetine were also demonstrated for weekly continence pad usage, mean time between voids, incontinence quality of life questionnaire scores (P<0.001), and global impression of improvement ratings (P<0.001). Patients with depressive symptoms and cognitive impairments were few and changes were insignificant.

Persistence on duloxetine was studied by Vella et al. [2008] who found that only 31% of an original cohort of 228 were still taking drug beyond 4 weeks, 12% at 4 months, 10% at 6 months, and 9% at 1 year. Fifty-six percent of the discontinuations were attributed to side effects, 33% to lack of efficacy, Bump et al. [2008], however, reported that the positive effects of duloxetine were maintained in patients who continued treatment up to 30 months, but admitted that this subgroup was likely to include predominantly patients who had favorable responses. The number decreased from 1424 in this cohort at 3 months to 368 at 30 months Shaban et al. [2010] concluded that duloxetine is “optional second line for women not willing or unfit for surgery after warning against side effects as recommended by NICE guidelines in the UK”. Similar sentiments are expressed by Robinson and Cardozo [2010].

Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in the European Union [European Medicines Agency, Scientific Discussion, 2005] in women with moderate to severe incontinence (defined as 15 or more episodes per week). It was withdrawn from the FDA consideration process in the United States for the treatment of SUI, but is approved for the treatment of major depressive disorder (20-30 mg b.i.d. initially, 60 mg once daily maintenance), diabetic peripheral neuropathic pain (60 mg once daily), generalized anxiety disorder (60 mg once daily, fibromyalgia (c0 mg once daily initially, 60b mg once daily maintenance) and chronic musculoskeletal pain (30 mg once daily initially,60 mg once daily as maintenance. The product information contains a “black box” warning of “increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders”, noting also that “depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide” [Prescribing Information, revised September 2011, Eli Lilly and Company, Indianapolis, Indiana 46285]. Other warnings and precautions in the U.S. in the United States Product Information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease), orthostatic hypotension, serotonin syndrome (general statement regarding SSRIs and SNRIs), abrupt discontinuation (may result in dizziness, paresthesias, irritability and headache), inhibitors of CYP1A2 (such as ciprofloxacin), thioridaxine (do not administer concomitantly) potent inhibitors of CYP2D6 (may increase concentration), and others. Adverse events for 6801 drug and 4487 placebo treated patients reported in the US Product Information (treatment for the indications mentioned) are nausea (24% vs 8%), dry mouth (13 vs 5), fatigue (10 vs 5), somnolence (10 vs 3), insomnia (10 vs 6), constipation (10 vs 4), dizziness (10 vs 5).

D. Stress urinary incontinence in men

Although a problem of significant magnitude, especially after radical prostatectomy (RP) for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention.

Intrinsic sphincter function is the most important outlet factor maintaining continence in men. Urethral support is less important, and there is no entity similar to the hypermobility phenomenon in women. The proximal urethral sphincter extends from the bladder neck through the prostatic urethra. Its function is removed by radical prostatectomy. The distal urethral sphincter includes the rhabdosphincter, urethral smooth muscle and extrinsic paraurethral skeletal muscle, extending from the prostatic urethra below the verumontanum through the membranous urethra [Koelbl, Nitti et al, 2009]. Tsakiris et al [2008] searched for articles on drug treatment of male SUI published between 1966 and June 2007 and did a generalized database search in addition. Nine trials were identified using alpha adrenergic agonists, beta-2 antagonists or SNRSs. Only one of these included a comparison arm [Filocamo et al, 2007], 40 mg b.i.d. duloxetine plus pelvic floor exercise (PFE) vs PFE with placebo. The results suggested a positive effect of drug, but were a bit confusing. Of those patients completing the 4 month trial [92/112] 78% of the drug treated patients vs 52% of those in the placebo group were “dry”. However, one month after the end of the study, the corresponding figures were 46% vs 73%, a shift still observed 2 months later. The authors of the review article suggested further larger and well designed studies on duloxetine for this potential usage.

Cornu et al. [2011] reported a series of post RP men with SUI or MUI (stress predominant) randomized to duloxetine [I5] and placebo [16] after a 2-week placebo run in. Dosage was 20 mg b.i.d. for 7d, 40 mg b.i.d. for 67d, 20 mg for 14d. Subjects were at least 1 year post surgery. Outcome measures included percent decrease in IEF, 1h pad test and various QOL measures. Statistical significance for IEF percent decrease occurred only at week 8 & 12 [(-) 52.2 ± 38.6% vs (+)19 ± 43.5%] but there was clearly a trend at 4 weeks. There was no statistical difference in 1h pad test weights but there was in various QOL scores. A 50-100% decrease in IEF was seen at 12

weeks in over half of the patients. Adverse events for drug and placebo included fatigue (50 vs 13%), insomnia (25 vs 7), libido loss (19 vs 7), constipation (13 vs 7), nausea (13 vs 7), diarrhea (13 vs 7), dry mouth (6 vs 0), anorexia (6 vs 0), and sweating (25 vs 20). Drawbacks and concerns are the small number (the original proposed sample size was 90) and the lack of any placebo effect on IEF and QOL. There were 4 men with MUI in the drug group, 5 in the placebo group. Results for SUI and UUI were not separated. One would logically not expect improvement to continue after drug withdrawal unless a permanent change occurred in behavior, anatomy or neuromuscular function. In an uncontrolled usage study on men with post RP SUI, Serra et al [2011] reported that the benefit remained in 85% after the drug was stopped. In that series, 25% of patients withdrew because of AEs and 33% because of lack of effect.

Usage of duloxetine for SUI in the male is universally off label. A drug for this indication would be welcome. Larger controlled and better designed studies are necessary to provide conclusive positive or negative data on this subject.

E. Drugs to treat overflow incontinence/acute urinary retention

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

Based upon theoretical reasoning, animal studies [Kamo et al., 2005; Gu et al., 2004], and reports of drugs that can cause overflow incontinence [Anders et al., 1985], a variety of medical approaches to the treatment of overflow incontinence have been proposed [Chutka and Takahashi, 1998; Diokno AC, 2004; Hampel et al., 2005]. Treatment may aim to increase bladder contractility, decrease bladder outlet resistance, or both. Theoretically, all drugs that improve decreased sensation (and increase afferent activity) or drugs that increase detrusor contractile force could be useful. Alternatively, agents that decrease outflow resistance, thereby restoring an appropriate balance between detrusor strength and urethral resistance, could be used.

These drugs include direct or indirect muscarinic receptor agonists, α1-AR antagonists, choline esterase inhibitors, prostaglandins (PG), and skeletal muscle relaxants [Diokno AC, 2004]. The use of muscarinic receptor agonists, such as bethanechol, to stimulate detrusor muscarinic receptors, or choline esterase inhibitors, such as distigmine, to reduce the degradation of acetylcholine, is based upon the idea that stimulation of muscarinic receptors may overcome a hypocontractile detrusor [Barendrecht et al., 2007]. However, a recent systematic review of controlled clinical studies that used direct and indirect parasympathetic agonists in patients with an underactive detrusor reported that these drugs do not provide consistent benefits and may even be harmful. The available information indicates that muscarinic receptor agonists and choline esterase inhibitors have little, if any, beneficial effects on preventing and treating detrusor underactivity. While there is a theoretical basis for the use of β-agonists to relax the sphincter, no definite improvements in symptoms have yet been demonstrated [Riedl et al., 2000; Dasgupta et al., 2003; Barendrecht et al., 2007; Ahmad et al. 2009]. As bethanechol exerts its effect on intact smooth muscle cells only, it is of limited use for the treatment of bladder atony. Idiopathic detrusor atony is poorly responsive to medical treatment [Noel et al. 2010].

The use of α1-AR antagonists has repeatedly been shown to be beneficial in patients with acute urinary retention due to benign prostatic enlargement[McNeill et al., 2004; 2005; Fitzpatrick et al., 2012]. These drugs are believed to facilitate bladder emptying by relaxing tone at the bladder neck. Administration of alfuzosin 10 mg daily almost doubles the likelihood of a successful trial without a catheter, even in patients who are elderly with a PVR > 100 mL. Continued use of alfuzosin significantly reduced the risk of BPH surgery in the first 3 months; however, this effect was not significant after 6 months [Fitzpatrick and Kirby, 2006; Emberton et al., 2008; Kalejaiye et al., 2009]. Thus, α1-AR antagonists provide rapid symptom relief from outlet obstruction caused by benign prostatic enlargement and delay the time to acute urinary retention; however, they do not decrease the overall risk of acute urinary retention or surgery [Emberton et al., 2008; Edwards, 2008; Fitzpatrick et al., 2012].

Acute urinary retention may ocur after surgery. Buckley and Lapitan [2010] reviewed drugs used for treatment of post-operative urinary retention either alone or in combination, assessing cholinergic agents, α1-AR blockers, sedatives and prostaglandins. A statistically significant association between intravesically administered prostaglandins and successful voiding was detected, but no such association was found for the other drugs investigated. When cholinergic agents were combined with sedative there was an improved likelyhood of spontaneous voiding compared with placebo.

There are some potential new agents for the treatment of an underactive bladder. Misoprostol, a cholinesterase inhibitor, and cholinergic agents are potential candidates for the treatment of the under-

active bladder, but their safety and lack of benefit is of concern. Novel muscarinic receptor manipulation using the presynaptic M2 receptor antagonist or postsynaptic allosteric receptor enhancement is promising. The prokinetics used in gastroenterology and the smooth muscle ionotropics used in cardiology warrant consideration. The use of trophic factors such as insulin-like growth factor and nerve growth factor may improve muscle and nerve function in the lower urinary tract. Furthermore, the use of stem cells, regenerative medicine, and gene therapy might facilitate improved contractility in a weak detrusor [Chancellor et al., 2008].

However, these agents have never been tested systematically in patients with overflow incontinence; there have been no randomized controlled trials to demonstrate the effectiveness and safety of these agents. Therefore, there is no empirical basis to select medical treatments for overflow incontinence and all previously recommended treatments must be rated as “expert opinion” at best. Better systemic studies are required to determine the best medical treatment for overflow incontinence. Any medical treatment for overflow incontinence should be compared to catherization or surgery.

F. Hormonal treatment of urinary incontinence

I. OESTROGENS

1. OESTROGENS AND THE CONTINENCE MECHANISM

The oestrogen sensitive tissues of the bladder, urethra and pelvic floor all play an important role in the continence mechanism. For women to remain continent the urethral pressure must exceed the intra-vesical pressure at all times except during micturition. The urethra has four oestrogen sensitive functional layers all of which have a role in the maintenance of a positive urethral pressure 1) epithelium, 2) vasculature, 3) connective tissue, 4) muscle.

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

2. OESTROGENS FOR STRESS URINARY INCONTINENCE

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

Fantl et al.[1996] treated 83 hypo-oestrogenic women with urodynamic stress incontinence and/or detrusor overactivity with conjugated equine oestrogens 0.625 mg and medroxyprogesterone 10 mg cyclically for three months. Controls received placebo tablets. At the end of the study period the clinical and quality of life variables had not changed significantly in either group. Jackson et al. [1996] treated 57 post menopausal women with urodynamic stress or mixed incontinence with Oestradiol 2 mg or placebo daily for six months. There was no significant change in objective outcome measures although both the active and placebo groups reported subjective benefit.

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

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

Several studies have shown that oestrogen may have a role in combination with other therapies e.g. α-adrenoceptor agonists. However, phenylpropa-

malamine (the most widely used α-adrenoceptor agonist in clinical practice) has now been restricted or banned by the US Food and Drug Administration (FDA).

In a randomised trial Ishiko et al. [2001] compared the effects of the combination of pelvic floor exercise and oestriol (1 mg per day) in 66 patients with post menopausal stress urinary incontinence. Efficacy was evaluated every three months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate stress incontinent patients in both groups three months after the start of therapy and concluded that combination therapy with oestriol plus pelvic floor exercise was effective and could be used as first line treatment for mild stress urinary incontinence. Unfortunately this has not been reproduced in other clinical trials.

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

3. OESTROGENS FOR URGENCY URINARY INCONTINENCE AND OVERACTIVE BLADDER SYMPTOMS

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

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

Symptoms of an overactive bladder increase in prevalence with increasing age and lower urinary tract symptoms and recurrent urinary tract infections are commonly associated with urogenital atrophy. Whilst 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, pruritis and dyspareunia, greater improvement in cytological findings and higher serum oestradiol levels [Cardozo et al 1998]. Overall vaginal oestradiol has been found to be the most effective in reducing patient symptoms although conjugated oestrogens produced the most cytological change and the greatest increase in serum oestradiol and oestrone. The most recent meta anlysis of intravaginal oestrogen treatment in the management of urogenital atrophy was reported by the Cochrane group in 2003 [Suckling et al 2003]. Overall 16 trials including 2129 women were included and intravaginal oestrogen was found to be superior to placebo in terms of efficacy although there were no differences between types of formulation. 14 trials compared safety between the different vaginal preparations and found a higher risk of endometrial stimulation with conjugated equine oestrogens as compared to oestradiol.

Thus theoretically there could be a role for combination treatment with an anti muscarinic agent and vaginal oestrogen in post menopausal women. However, the two clinical trials which have been reported to date differ in their outcome. Tseng et al.[2009] showed superior efficacy in terms of symptom improvement for the overactive bladder when Tolterodine was used with vaginal oestrogen cream as opposed to Tolterodine alone. However, Serati et al. [2009] found no difference between Tolterodine with or without topical oestrogen in women with symptomatic detrusor overactivity.

4. EVIDENCE REGARDING OESTROGENS AND INCONTINENCE FROM LARGE CLINICAL TRIALS

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

average of 0.7 in the hormone group and decreased by 0.1 in the placebo group ($p< 0.001$). The authors concluded that daily oral oestrogen plus progestogen therapy was associated with worsening urinary incontinence in older post menopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.

The Women's Health Initiative (WHI) was a multi centre double blind placebo controlled randomised clinical trial of menopausal hormone therapy in 27347 postmenopausal women age 50-79 years enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23296 participants at baseline and one year [Hendrix et al., 2005]. The women were randomised based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg per day of conjugated equine oestrogen (CEE) plus 2.5 mg per day of medroxyprogesterone Acetate (CEE+MPA), whereas those who had undergone hysterectomy received oestrogen alone (CEE). At one year hormone therapy was shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline. The risk was highest for stress urinary incontinence CEE+MPA: RR, 1.7 95% continence interval) CI (1.61-2.18); CEE alone RR 2.15 mg, 95% CI, 1.77-2.62, followed by mixed urinary incontinence CEE+MPA: RR 1.49 95% CI 1.10-2.01. On CEE alone RR was 1.79 95% CI, 1.26-2.53. The combination of CEE and MPA had no significant effect on developing urge urinary incontinence RR, 1.15; 95% CI, 0.99-1.34 but CEE alone increased the risk RR 1.32; 95% CI, 1.10-1.58. For those women experiencing urinary incontinence at baseline frequency worsened in both active groups CEE+MPA; RR, 1.38 95% CI 1.28-1.49; CEE alone: RR, 1.47 95% CI, 1.35-1.61. Quantity of urinary incontinence worsened at one year in both active groups, CEE+MPA: RR, 1.20 95% CI, 1.06-1.76; CEE alone: RR, 1.59 95% CI, 1.39-1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities CEE+MPA: RR 1.18 95% CI, 1.06-1.32. CEE alone: RR 1.29 95% CI, 1.15-1.45 at one year. Thus based on this secondary analysis of data from a huge study conjugated equine oestrogen alone or in combination with Medroxyprogesterone Acetate was shown to increase the risk of urinary incontinence amongst continent women and worsen urinary incontinence amongst asymptomatic women after one year of therapy.

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

The most recent meta analysis of the effect of oestrogen therapy on the lower urinary tract has been performed by the Cochrane Group [Cody et al., 2009] and is notable as the conclusions are starkly different from those drawn from the previous review [Moehrer et al., 2003]. Overall 33 trials were identified including 19313 incontinent women (1262 involved in trials of local administration) of which 9417 received oestrogen therapy.

Systemic administration (of unopposed oral oestrogens – synthetic and conjugated equine oestrogens) resulted in worse incontinence than placebo (RR1.32; 95% CI: 1.17-1.48). Although this is heavily influenced by the size of the WHI study [Hendrix et al 2005]. When considering combination therapy there was a similar worsening effect on incontinence when compared to placebo (RR1.11; 95% CO: 1.04-1.08). There was some evidence suggesting that the use of local oestrogen therapy may improve incontinence (RR0.74; 95% CI: 0.64-0.86) and overall there were 1-2 fewer voids in 24 hours and less frequency and urgency.

The authors conclude that local oestorgen therapy for incontinence may be beneficial although there was little evidence of long term effect. The evidence would suggest that systemic hormone replacement using conjugated equine oestrogens may make incontinence worse. In addition they report that there are too few data to comment reliably on the dose type of oestrogen and route of administration.

II. OTHER HORMONES

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

Selective oestrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both oestrogenic and anti oestrogenic effects. In the clinical trials of levormeloxifene there was a fourfold increase in the incidence of incontinence leading to cessation of the clinical trial [Hendrix et al., 2001]. However raloxifene has not been shown to have any effect at all on urinary incontinence [Waetjen et al., 2004].There are no reported clinical trials evaluating the effect of androgens, and in particular Testosterone, on urinary incontinence in women.

Assessments, hormone treatment

Oestrogen has an important physiological effect on the female lower urinary tract and its deficiency is an aetiological factor in the pathogenesis of a number of conditions. However the use of oestrogen either alone or in combination with progestogen has yielded poor results. The current level 1 evidence against the use of oestrogen for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events and therefore the secondary analyses have only been based on self reported symptoms of urinary leakage without any objective data. Despite this all of these large randomised controlled trials show a worsening of pre-existing urinary incontinence both stress and urgency and an increased new incidence of urinary incontinence with both oestrogen and oestrogen plus progestogen. However, the majority of subjects in all of these studies were taking combined equine oestrogen and this may not be representative of all oestrogens taken by all routes of administration.

In a systematic review of the effects of oestrogens for symptoms suggestive of an overactive bladder the conclusion was that oestrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration [Cardozo et al., 2004]. It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency and urge incontinence may be a manifestation of urogenital atrophy in older post menopausal women rather than a direct effect on the lower urinary tract [Robinson and Cardozo, 2003]. Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal oestrogen therapy there is currently no evidence that oestrogens with or without progestogens should be used in the treatment of urinary incontinence.

III. DESMOPRESSIN

The endogenous hormone vasopressin (also known as anti-diuretic hormone) has two main functions: it causes contraction of vascular smooth muscle and stimulates water reabsorption in the renal medulla. These functions are mediated by two specific vasopressin receptors of which there are two major subtypes, namely the V1 and V2 receptors. The V2 subtype is particularly important for the anti-diuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to central diabetes insipidus, and genetic defects in the gene encoding the V2 receptor can cause nephrogenic diabetes insipidus [Insel et al., 2007]. Accordingly, decreased vasopressin levels are believed to be important in the pathophysiology of polyuria, specifically nocturnal polyuria, which can lead to symptoms such as nocturia [Matthiesen et al., 1996; Weiss et al., 2011a]. Nocturia is currently defined by the International Continence Society (ICS) as the complaint that an individual has to wake at night one or more times to void. It is, however, “an underreported, understudied, and infrequently recognized problem in adults” [Weiss et al., 2011b]. Nocturia leads to decreased quality of life [Kupelian et al., 2011], and has been associated with both increased morbidity and mortality [Nakagawa et al., 2010; Kupelian et al., 2012]. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioural factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist. While it remains largely unknown in what fraction of patients nocturia is explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioral factors that can explain it (e.g. excessive fluid intake) is usually considered to indicate decreased vasopressin levels [Bosch and Weiss., 2011, Weiss et al., 2011b]. Based upon these considerations, vasopressin receptor agonists have been used to treat nocturia, both in children and in adults. Desmopressin is the most common vasopressin analogue used to treat nocturia. Desmopressin shows selectivity for anti-diuretic over vasopressor effects. It has a more powerful and longer-lasting antidiuretic action than vasopressin. It is available in formulations for oral, parenteral, and nasal administration. It has a fast onset of action, with urine production decreasing within 30 minutes of oral administration [Rittig et al., 1998]. Because of symptomatic hyponatremia with water intoxication which is the only serious adverse event reported in children, occurred after intranasal or intravenous administration of desmopressin [Thumfart et al. 2005; Robson et al. 2007; Van de Walle et al. 2010], the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) removed the indication for the treatment of primary nocturnal enuresis from all intranasal preparations of desmopressin. An oral lyophilisate (MELT) formulation requiring no concomitant fluid intake is currently available. In a recent open-label, randomized, cross-over study, desmopressin MELT was shown to have similar levels of efficacy and safety at lower doses than the tablet formulation of desmopressin in children]. A recent study confirmed the superior pharmacodynamic charac-

teristics of desmopressin MELT to desmopressin tablets [De Guchtenaere et al., 2011].

The use of desmopressin in children with nocturnal enuresis was comprehensively reviewed by the Cochrane Collaboration in 2002 [Glazener et al. 2002]. These authors evaluated 47 randomized controlled trials involving 3448 children, of whom 2210 received desmopressin. According to their analysis, desmopressin was effective relative to placebo in reducing bed-wetting (e.g. a dose of 20 µg resulted in a reduction of 1.34 wets/night (95% CI 1.11; 1.57), and children were more likely to become dry with desmopressin (98%) than with placebo (81%). However, there was no difference between desmopressin and placebo after discontinuation of treatment, indicating that desmopressin suppresses symptom enuresis but does not cure the underlying cause. Additionally, not all children responded sufficiently to desmopressin monotherapy. The combination of desmopressin and an enuresis alarm resulted in a greatly improved short-term success rate and decreased relapse rates [Alloussi et al. 2011]. The combination of desmopressin and antimuscarinics resulted in better short- and long-term success rates as well as a lower relapse rate than desmopressin alone [Austin et al., 2008; Alloussi et al., 2009). For non-responders to desmopressin, replacement of desmopressin with other medications such as tricyclic antidepressants or loop diuretics could be of benefit, whereas muscarinic receptor antagonists may be ineffective in such children (De Guchtenaere et al., 2007; Neveus and Tullus, 2008).

Other studies have explored a possible treatment role for desmopressin in the treatment of nocturia in adults. A search for these studies in Medline using the terms “desmopressin” and “nocturia” was performed and limited to clinical studies of de novo nocturia, i.e. those that excluded subjects in whom childhood enuresis persisted into adulthood. Several previous studies investigated the use of desmopressin for the treatment of nocturia in the context of multiple sclerosis [Eckford et al., 1994;1995]. One study with single dose administration reported a reduction in nocturnal polyuria, but by design did not assess nocturia [Eckford et al., 1995]. Three placebo-controlled double-blind studies with a small patient number (16-33 patients total per study) reported a significant reduction in nocturia [Hilton et al., 1983; Eckford et al., 1994; Valiquette et al., 1996]. Other controlled studies of similar size, most with a crossover design, used micturition frequency within the first 6 h after desmopressin administration rather than nocturia as their primary endpoint. These studies consistently reported that desmopressin treatment for up to 2 weeks was efficacious [Kinn and Larsson, 1990; Fredrikson, 1996; Hoverd and Fowler, 1998]. While desmopressin treatment was generally well tolerated, 4 of 17 patients in one study discontinued treatment due to asymptomatic or minimally symptomatic hyponatremia [Valiquette et al., 1996]. Accordingly, desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients [Cvetkovic and Plosker, 2005]. In a small open-label study, desmopressin was also reported to reduce nocturnal polyuria in spinal cord injury patients [Zahariou, Karagiannis et al. 2007].

Further studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurological damage. The recruited patient populations were based upon different criteria, including having at least two nocturia episodes per night or having nocturnal polyuria. Earlier studies mostly used a desmopressin dose of 20 µg given either orally [Asplund et al., 1999] or intranasally [Hilton and Stanton, 1982; Cannon et al., 1999], and tended to be very small (≤25 patients). Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1003 screened patients, and higher oral doses (0.1-0.4 mg) were administered for a period of 3 weeks of double-blind treatment in adults [Mattiasson et al., 2002; Lose et al., 2004; van Kerrebroeck et al., 2007]. A total of 632 patients entered the dose-titration phase and 422 patients entering the double-blind phase of the three NOCTUPUS trials. To counter the argument that the study was performed in desmopressin responders after the dose titration phase, all patients in the NOCTUPUS trials were washed-out following the dose-titration phase and in order to be randomized, it was a requirement that the patients returned to baseline nocturnal diuresis before inclusion in the double-blind phase. The trials showed that oral desmopressin (0.1, 0.2 or 0.4 mg) is effective in both men and women aged ≥ 18 years with nocturia. The number of nocturnal voids decreased from 3 to 1.7 in the desmopressin group compared to 3.2 to 2.7 in the placebo group. In women, the number of nocturnal voids in the desmopressin group decreased from 2.92 to 1.61, whereas that in the placebo group decreased from 2.91 to 2.36. When clinical response was defined as ≥ 50% reduction in nocturnal voids from baseline, 34% of men experienced clinical response with desmopressin, compared with 3% of men who received placebo. In women, 46% of desmopressin-treated patients experienced a clinical response, compared with 7% of patients on placebo.

The efficacy of desmopressin for the treatment of nocturia was confirmed in a long-term (10-12 months) open-label study involving 249 patients, which was an extension of the randomized studies in known desmopressin responders. However, a rebound effect was seen when treatment was withdrawn, confirming the association between continued treatment and response (Lose et al. 2004). An open-label pilot study in a nursing home setting also reported that desmopressin had beneficial effects [Johnson et al. 2006].

Around 75% of community-dwelling men and women with nocturia (≥2 voids/night) have nocturnal

polyuria (NP) [Rembratt et al., 2003; Swithinbank et al. 2004]. The key urological factors most relevant to nocturia are NP and OAB in women [Irwin, Abrams et al., 2008], and NP and benign prostatic hyperplasia (BPH) in men. About 74% of women with OAB have nocturia and 62% of patients with OAB and nocturia have NP. Among men with nocturia, 83% have NP; 20% have NP alone, and 63% have NP in combination with another factor such as a small nocturnal bladder capacity or bladder outlet obstruction [Chang et al., 2006]. Therefore, desmopressin combination therapy with α1-AR antagonists and/or antimuscarinics should be considered for patients with treatment–resistant nocturia. Seventy-three percent of α1-AR antagonist-resistant BPH patients experienced a ≥50% reduction in nocturnal voids with oral desmopressin [Rembratt et al., 2003; Yoong et al., 2005]. A randomized, double-blind, placebo-controlled study evaluating the long-term (1, 3, 6, and 12 months) efficacy and safety of low dose (0.1 mg) oral desmopressin in elderly (≥ 65 years) patients reported that low dose oral desmopressin led to a significant reduction in the number of nocturnal voids and nocturnal urine volume in patients with BPH [Wang, Lin et al. 2011].

Because nocturia can be caused by different factors, several studies have investigated whether desmopressin may be beneficial in patients with other symptoms in addition to nocturia. In a small, non-randomized pilot study of men believed to have BPH, desmopressin was reported to improve not only nocturia, but also to reduce the overall international prostate symptom score (IPSS) [Chancellor et al., 1999]. An exploratory, placebo-controlled double-blind study in women with daytime urinary incontinence reported that intranasal administration of 40 µg desmopressin increased the number of leakage-free episodes 4 hours after drug administration (Robinson et al., 2004). One double-blind, placebo-controlled pilot study in patients with OAB treated with 0.2 mg oral desmopressin reported a reduction in voids along with an improvement in quality of life (QoL) [Hashim et al., 2009]. While these data indicate that desmopressin may be effective in treating voiding dysfunction not limited to nocturia, they are too sparse to allow treatment recommendations.

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL. However, one of the main clinically important side-effects of demopressin usage is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death. Hyponatremia usually occurs soon after treatment is initiated. The risk of hyponatremia appears to increase with age, cardiac disease, and increasing 24-hour urine volume [Rembratt et al. 2003]. Based on a meta-analysis, the incidence is around 7.6% [Weatherall; 2004]. Increased age and female gender are well-known risk factors for the development of desmopressin-induced hyponatremia. Bae et al. [2007] assessed the effects of long-term oral desmopressin on serum sodium and baseline antidiuretic hormone secretion in 15 elderly male patients with severe nocturia (greater than 3 voids nightly), who did not show hyponatremia within 7 days of administration of 0.2 mg desmopressin. Desmopressin (0.2 mg) was administered orally nightly for 1 year. Before and 1 month after the 1-year medication 24-hour circadian studies were performed to monitor changes in antidiuretic hormone. Every 3 months during the 1-year medication, serum changes and timed urine chemistry were monitored. The results showed that long-term desmopressin administration gradually decreased serum sodium and induced statistically, but not clinically significant, hyponatremia after 6 months of treatment Administration of desmopressin for 1 year did not affect baseline antidiuretic hormone secretion. The authors recommended that for long-term desmopressin administration serum sodium should be assessed regularly, at least every 6 months.

Little focus has been on exploring gender differences in the antidiuretic response to desmopressin. Juul et al. [2011] found an increasing incidence of hyponatremia with increasing dose, and at the highest dose level of 100 µg decreases in serum sodium were approximately twofold greater in women over 50 yr of age than in men. A new dose recommendation stratified by gender was suggested in the treatment of nocturia: for men, 50- to 100 µg melt was suggested to be an efficacious and safe dose, while for women a dose of 25 µg melt was recommended as efficacious with no observed incidences of hyponatremia. Initiation of desmopressin is currently not indicated for patients aged ≥65 years. The mechanisms behind desmopressin-induced hyponatraemia are well understood, and serum sodium monitoring at baseline and early during treatment of older patients for whom treatment with desmopressin is indicated can greatly reduce their risk of developing the condition. Other advice regarding treatment administration, such as restriction of evening fluid intake and adherence to recommended dosing, should be followed to minimize the risk of hyponatremia [Vande Walle et al., 2007].

Desmopressin is useful for patients with nocturia as well as for children with nocturnal enuresis. The drug has been proven to be well-tolerated and effective by several randomized, placebo-controlled trials and is recommended as a first-line treatment (either as monotherapy or in combination with other agents) for patients who have been appropriately evaluated and whose nocturia is related to NP, whether or not this is accompanied by BPH or OAB. For assessment, see **Table 2**.

G. Considerations in the Elderly

I. ANTIMUSCARINIC AGENTS

1. EFFICACY AND TOLERABILITY

The efficacy of antimuscarinic agents for treating symptoms of overactive bladder and urge urinary incontinence in older people is similar to that observed in younger and middle-aged adults. Age-related pooled results or sub-analyses from randomized controlled trials of tolterodine [Malone-Lee et al., 2001, Zinner et al., 2002], solifenacin (Wagg et al., 2006), darifenacin [Foote et al., 2007], fesoterodine [Kraus et al., 2010, Sand et al., 2012], and trospium chloride [Sand et al., 2011] indicate that reductions of 25-75% in urgency urinary incontinence episodes can be expected with use of these agents in older (65+) adults. Higher doses may be needed in those over age 75 [Kraus et al., 2010]. In a post-marketing surveillance study of darifenacin, Michel et al. [2010] found that increasing age was negatively associated with improvements in urgency episodes and incontinence, with a statistically significant, but non-clinically relevant effect (0.01 more urgency episodes per year of age). Older adults may derive greater benefit from use of a combined drug and behavioural therapy regime as compared to treatment with drug therapy alone [Burgio et al., 2000]. Dry mouth is the most frequently reported treatment-related adverse event, however overall tolerance has been reported as good to excellent with fewer treatment-motivated withdrawals in recent trials of older patients persisting on antimuscarinic therapy [Sand et al., 2012, Sand et al., 2011]. Constipation is also common and may be particularly bothersome for older adults already suffering from chronic bowel dismotility [Meek et al., 2011, Gallegos-Orozco et al., 2012].

However, the therapeutic effectiveness and tolerability of antimuscarinic agents in the elderly in the real world practice setting may differ from the results obtained in randomized controlled trials for several reasons. First, research trials generally exclude individuals with concomitant consumption of other antimuscarinic agents. In practice, older adults are a heterogeneous group, often consuming many medications that may augment, desensitize or alter the response to antimuscarinic therapy. As well, there is a higher prevalence of comorbidity among the elderly, which can further reduce treatment efficacy and heighten the potential for side effects to occur (see the Section on Incontinence in the Frail Elderly). Failure to acknowledge the multifactorial nature of urinary incontinence in the elderly often leads to suboptimal treatment. Urgency symptoms may be exacerbated by consumption of caffeinated beverages, pelvic floor muscle weakness, diuretics or other functional and systemic dysfunctions. Treatment should therefore address all possible etiologies, and not be limited to a solitary intervention.

2. COGNITIVE SAFETY

A growing body of literature has emerged to address the concern that antimuscarinic agents used to treat symptoms of overactive bladder may cross the blood-brain barrier and provoke subtle or not so subtle cognitive impairment [Callegari et al, 2011; Jakobsen SM et al., 2011; Wagg et al., 2010; Pagoria et al., 2011]. Large randomized controlled trials were not designed to adequately measure central nervous system adverse events [Paquette et al, 2011]. As a result, evidence on the relative risk of different antimuscarinic agents for crossing the blood brain barrier and inducing changes in cognitive comes primarily from in-vitro studies and experimental studies using detailed neuropsychological testing.

Early studies suggested that administration of antimuscarinic agents such as scopolamine could impair memory and attention in older adults, and possibly induce hallucinations and confusion [Flicker et al., 1992; Sperling et al., 2002]. Oxybutynin in particular, due to its small molecular size and increased propensity to cross the blood-brain barrier, has consistently shown potential to elicit cognitive impairment in new users after a single high dose of this agent or at steady state, and should be avoided in the elderly [Donellan et al., 1997; Katz et al., 1998; Kay et al., 2008, Wesnes et al., 2009]. Katz et al. [1998] used a double-blind, placebo-controlled cross-over design to test a convenience sample of 12 healthy continent older adults, and revealed cognitive decrements on seven of fifteen cognitive measures resulting from oxybutynin use. Impairments were observed in verbal learning, memory, reaction time, attention, concentration and psychomotor speed. In a sleep study, oxybutynin was found to significantly alter EEG patterns compared to placebo [Todorova et al., 2001]. Oxybutynin was compared to darifenacin and placebo in a 3-week randomized multicentre double-blind parallel-group study in 150 healthy volunteers aged 60-83 [Kay et al., 2006]. Darifenacin produced no impairments compared to placebo at 3-weeks, but oxybutynin caused significant memory deterioration in delayed recall compared to the other two groups. Darifenacin was associated with significantly slower reaction times than placebo in the Divided Attention Test, but not in other tests of information processing speed. Oxybutynin also reduced accuracy scores for immediate recall in one of three tests. Wesnes et al. [2009] showed in a single-dose crossover study with 12 healthy older volunteers that oxybutynin IR 10 mg induced significant deficits in attention and memory compared to placebo, whereas solifenacin 10 mg did not.

Studies with the antimuscarinic agents solifenacin, trospium chloride ER and darifenacin suggest that these agents confer significantly lower cognitive risk than oxybutynin. Administration of trospium chloride ER to 12 cognitively intact adults with overactive bladder aged 65-75 was found to have no effect on memory testing with the Hopkins Verbal Learning