# Urethral function in overactive bladder syndrome

Kummeling, M.T.M.

# CHAPTER 1

## GENERAL INTRODUCTION

1

# GENERAL INTRODUCTION AND OUTLINE THESIS

Overactive bladder syndrome (OAB) is a common lower urinary tract disorder with a prevalence increasing with age[1]. OAB was defined in 2002 by the International Continence Society (ICS) as the urgency to void, usually accompanying frequency and nocturia, with or without urge urinary incontinence (UUI)[2]. If infection, urolithiasis, neoplasm or neurological bladder dysfunction as the cause for the symptoms are excluded, the condition is yet idiopathic.

According to investigation of Dutch central statistical agency (CBS) in 2004, about 16% of the Dutch population above the age of forty years old suffers from OAB syndrome. This indicates that at least one million people may be affected[3], however not all seek medical attention[4]. The college for health insurances (CVZ) estimated costs for urinary incontinence material in 2011 at 148 million euro. The total costs for treatment of urinary incontinence were estimated at 256 million euro. OAB syndrome has a negative impact on health-related quality of life (QoL)[5, 6] and the worse the symptoms, the greater the negative effect[7]. Prevalence of OAB increase with age and increase up to 30% in the population older than 75 years[3]. With the increasing average life span of the population, the socioeconomic burden of OAB will rise in the future[8].

Currently there a several treatment options for OAB. Guidelines for treatment propose a pathway from conservative treatment, then drugs, then minimally invasive surgery and last invasive surgery. For a start, conservative treatment can be initiated, consisting of lifestyle advice, and/or pelvic muscle floor therapy. Second, there a several forms of neuromodulation therapies, like percutaneous tibial nerve stimulation, transcutaneous electrical nerve stimulation, transvaginal electrical stimulation or sacral neuromodulation. The advantage of neuromodulation treatment are very low rates of adverse events. The disadvantage of neuromodulation treatment modalities, except the sacral form, is that the effect diminishes over time when treatment is not applied anymore. Third there is the possibility of pharmacotherapeutic treatment. The predominant treatment option consists of oral antimuscarinics. Treatment with antimuscarinics result in reduction in voiding frequency, urgency episodes and or urgency urinary incontinence[9, 10]. However, treatment persistence is low, with around 30% of patients continuing therapy after one year[11, 12]. Adverse events, the most bothersome associated with

antimuscarinic drugs being a dry mouth, are often a reason for treatment discontinuation[13]. Since 2014 a beta 3 adrenoceptor (ADRB3) agonist is available in pharmacological treatment of OAB. It has been proven clinically and urodynamically effective in the treatment for OAB and is well tolerated[14]. In a recent retrospective observational study, the persistence and adherence of mirabegron versus antimuscarinic agents was compared[15]. Although persistence of mirabegron was better than the persistence of antimuscarinic agents, persistency rates after one year were 38% for mirabegron and 20% for antimuscarinic drugs. The combination of mirabegron and the antimuscarinic agent solifenacin in treatment for OAB was reported in the BESIDE-study[16]. Combined treatment resulted in better outcome than single agent treatment and was well tolerated in older patients as well[17]. In conclusion, pharmacotherapeutic treatment in its current form needs improvement.

Fourth, OAB can be treated with botulinum A toxin (Bont-A) injections. Bont-A is the most potent neurotoxic poison known. The first administration in the bladder in treatment for lower urinary tract dysfunction was reported in 2006[18]. Bont-A blocks acetylcholine release in the presynaptic membranes, resulting in paralysis at the injected location. In 2011, the FDA approved this treatment for neurogenic bladder dysfunction, later it was also approved for treatment of idiopathic OAB, when pharmacological treatment has failed. Common adverse events in the treatment with BontA-injections are the need for clean intermittent self-catheterization and urinary tract infections. The advantage of this treatment is the local application, systemic side effect as in pharmacological treatment do not occur.

From the abovementioned data can be concluded that unfortunately no therapy is beneficial and applicable for all OAB patients. This is due to the fact that patients with OAB represent a very heterogeneous group of patients, with the same social invalidating symptom complex in common. Until recently, research on OAB has mainly focused on detrusor overactivity (DO) as a cause for the symptoms. However, DO is present in only 50% of female OAB patients and can also be present in asymptomatic patients. In the past decade, further research has been performed to the existence of alternative underlying mechanisms leading to OAB. There is growing evidence that increased activity of bladder afferent signaling, originating from the urothelium or suburothelium and influenced by the urinary microbiome, contributes to OAB symptom complex[19]. Research to the role of the urethra within micturition reflex was initiated in the early 20$^{th}$

century by Barrington in an animal model. He described seven reflexes involved in bladder storage and micturition in cat, of which four had their afferent origin in the urethra[20, 21]. Later, Jung et al hypothesized that leakage of urine into the urethra can stimulate urethral afferents, causing stress induced urgency with or without urinary incontinence[22]. In patients surgically treated for stress urinary incontinence (SUI), storage function improves in some patients with mixed urinary incontinence. Unfortunately, de novo urgency and or increased urgency is also reported after surgery for SUI. In the last 20 years of the 20$^{th}$ century, various studies were performed to further elucidate the role of urethral function in lower urinary tract dysfunction on the basis of urethral pressure variations during filling cystometry of urodynamic studies[23-25].

Urodynamic studies are part of the work-up of patients with OAB syndrome. Detrusor overactivity (DO) is defined as detrusor contractions of any extent during filling phase of urodynamic investigation. However, this phenomenon can also be observed in symptomatic patients. In association and apart from detrusor overactivity, urethral pressure variations (UPV) can been observed during urodynamic investigation. The clinical relevance of UPV, although associated with urinary urgency, in the pathophysiology of OAB syndrome is not yet precisely established. In 1980, the ICS defined urethral instability (URI) as a condition in which there is involuntary fall in urethral pressure during filling, resulting in urinary leakage in the absence of detrusor activity. URI was abandoned within terminology shortly after because of the rarity of this condition. Opponents consider urethral pressure variations as an artefact during filling cystometry and for a long time, research on OAB has focused on detrusor function as a cause. Maintaining urinary continence however requires a coordinated function between the bladder as storage room for urine and the urethra as gatekeeper. Recently, a think tank session of the ICI-RS was dedicated to urethral pressure variations urethral instability[26] . This session was followed by a summarizing report based on literature review and discussions during this ICI-RS meeting[27]. This report also concluded that UPV certainly is associated with LUTS and thus, future research on this topic is relevant.

## ANATOMY

With an average length of 3-4cm, the female urethra is shorter than the male urethra with an average length of 17cm. In both sexes, is a distensible, partly muscular tube. Differences in length, pelvic floor anatomy and the absence of the prostate result in a different functionality. The urethra is composed of striated and smooth muscles. The smooth muscles bundles within the urethral wall have a relatively thick inner layer, arranged predominantly longitudinal. Outside this is layer, there is a thinner circular muscle layer. The urethral smooth muscle layer extends to the bladder neck, where they merge in detrusor smooth muscle bundles. Contrary to the male anatomy, a well-defined circular smooth muscle component comparable with the preprostatic sphincter is absent in the female bladder neck. As a consequence, active smooth muscle contraction in the female bladder neck region will not have a major contributing role in maintaining urinary continence. In male, the striated muscle layer extends from the bladder base and the anterior urethra tot the full length of the membranous urethra. In females, the striated muscle layer extends from the proximal urethra and is horseshoe shaped. The muscle arrangement forming the distal sphincter has an additional muscle structure termed the compressor urethrae. When there is adequate support from the pelvic floor, the posterior wall remains rigid. In males there is no striated component posteriorly. Despite the limited length of the female urethra, anatomical and functional differences exist. The proximal urethra, above the urogenital diaphragm is subject to abdominal pressure while the distal parts are not. From proximal to distal, the transitional epithelium changes into a non-keratinizing stratified squamous epithelium. At the external meatus, this epithelium is keratinized and becomes continuous with the skin of the vestibule.

## INNERVATION

Both the autonomic and somatic nervous system are involved in the innervation of the bladder and urethra[28]. The autonomic nervous system is under unconscious control and typically acts on smooth muscles. The somatic nervous system is under conscious control and typically acts on striated muscles. The autonomic nervous system consists of sympathetic adrenergic nerves and parasympathetic cholinergic nerves.

Branches of the nervous system here are referred to by the names of the chemical transmitters responsible for transmitting signals from the nerves. The chemical transmitter of the sympathetic system is noradrenaline or a similar substance. The nerve branches of the sympathetic system are divided in alfa adrenergic and beta adrenergic subtypes. For the parasympathetic system the chemical transmitter is acetylcholine or a similar substance. For the lower urinary tract, sympathetic innervation is through the hypogastric nerve bundles, initiating from spinal cord segments thoracic 12 to lumbar 2. The parasympathetic innervation is through pelvic nerve bundles, originating in second to fourth sacral spinal cord segments. The somatic innervation through the pudendal nerve, also originates from this part of the spinal cord. All abovementioned nerve bundles contain afferent or sensory axons, transmitting information from the lower urinary tract back to the lumbosacral spinal cord up to higher central brain centers. From the central nervous system, motor or efferent impulses are transmitted back to the lower urinary tract. Afferent and efferent impulses are transmitted by different bundles of the same nerve. For micturition, the most important afferent bundles are the myelinated Ad-fibers and the unmyelinated C-fibers. Pelvic nerve afferents monitor the volume of the bladder and mediate the sensation associated with normal bladder filling and pain[29]. In storage phase, the pelvic nerve has a low level of vesical afferent activity and the hypogastric nerve afferent activity is high. This results in a stimulated sympathetic outflow to the bladder base outlet and pudendal flow to the external urethral sphincter by spinal reflex pathways (guarding reflex). Detrusor muscle contraction and transmission in bladder ganglia are also inhibited. When voiding phase is initiated, the level of afferent activity of abovementioned nerves are switched. This results in inhibition of the spinal guarding reflex and stimulation of parasympathetic outflow to the lower urinary tract, resulting in detrusor contraction. The urethral smooth muscle tonus and intra-urethral pressure is predominantly regulated by adrenergic sympathetic nerves. In their review on neural control of the lower urinary tract, Birder and Andersson[29, 30] concluded that the urothelium itself also contributes in afferent signaling. As a response to sensory or mechanical stimuli, the neurotransmitters nitric oxide (NO), adenosine triphosphate (ATP) and acetylcholine can be released by the urothelium, resulting in afferent activity allowing the micturition reflex to be initiated.

## URETHRAL PRESSURE

The urethral closure pressure is defined as the difference between the urethral pressure and the intravesical pressure. The urethral pressure varies along the length of the urethra and can be measured continuously or as a plot of pressure against distance. The latter is defined as the urethral closure pressure profile. The functional urethral length is length of the urethra where urethral pressure is higher than intravesical pressure. Since the urethra is not a closed reservoir like the bladder and since it's not filled with liquid at rest, it is difficult to understand what is measured. Besides, the urethra has a different shape of cross-section from point to point. What we do know is that as long as the urethral pressure is higher than intravesical pressure, leakage of urine should be resisted. In the literature, two controversies exist about the urethral pressure profile. First about the role of urethral pressure within lower urinary tract symptoms and second about the contributing role of the urethral smooth, striated circular muscles and the lamina propria to urethral pressure profile. In addition there is also controversy about the role of urodynamic investigation, since so far it has not been so successful in suggesting treatments for OAB or predicting postoperative results in surgery for urinary incontinence or for urogenital prolapse [31]. However, these studies mainly focused on bladder-function related outcomes, and far less on urethral function. Especially urethral pressure variations as measured in urodynamics correlated to clinical symptoms has not so extensively been investigated and as aforementioned, may be of clinical importance. In 2007, Groenendijk concluded that URI appeared to be a valuable urodynamic parameter for predicting the outcome of SNS[32].

## URETHRAL INSTABILITY

When continuous urethral pressure is measured during filling cystometry of urodynamic investigation, sudden pressure variations can be observed. Different patterns[33] and definitions have been described in the past. The lower the cut-off value used, the higher the mentioned prevalence, with variations in prevalence reported from 2 to 95% [32, 34]. The chance to demonstrate UPV will be higher when multiple urethral sensors are used and possibly also dependent on which type of urodynamic catheter is used. Measurements with dual air-balloon sensor, with one

sensor in the urethra- is the most reported technique, but measurements with up to 5 urethral sensors have been reported[35]. For this study, two different types of catheters have been used. In the centers in The Hague, continuous urethral measurements have been performed with a dual air-balloon catheter, with the urethral sensor catheter positioned at the point of maximal pressure. In the LUMC, measurements have been performed with a multi urethral sensor catheter, with three urethral sensors and one bladder sensor. The mid-urethral pressure sensor is positioned at the maximal pressure point. Urethral and detrusor pressure are continuously measured during storage and during voiding phase. The use of three urethral sensors reduces the chance of measurement artifacts due to movement of the catheter. Past research proposed that for the definition of URI, pressure variations of at least 15cm H2O should be present in all urethral sensors. The question is whether a fixed cut-off value is relevant in all measurement points and whether it is not more important that the pattern of pressure variations is registered in all measurement points, regardless of the absolute value. For this study, we have defined URI as follows. In the measurements performed with the dual air-balloon sensor catheter we have used a cut-off value of an urethral pressure drop of 30cm H2O or more. For measurements performed with the three urethral sensor catheter, urethral pressure drops exceeding 30cm H2O must be demonstrated in at least one sensor and the pattern of the urethral pressure drops should be demonstrated in at least two out of three measurement point, because in some cases it was not possible to obtain registration in measurement points due to the anatomy of the urethra. In addition, the urethral pressure drop should be independent of detrusor contraction. In other words, when DO occurred, the preceding drop in urethral pressure was considered physiological. EMG recordings were performed in all measurements but were not considered of any importance in the definition of URI. Examples of urodynamic investigations with URI, with and without accompanying DO are shown in figures 1.1 and 1.2.

In figures 1.3 and 1.4, examples of urodynamic investigation with three urethral sensors are demonstrated. Figure 1.3 shows a normal urodynamic investigation, figure 1.4 shows an urodynamic investigation with URI.

If further research can confirm that URI is good predictor for successful clinical outcome of certain treatments in a subgroup of patients with OAB, or that patients with URI should be considered as a different group of patients within OAB, we can make an important contribution to tailored-treatment of patients with OAB.

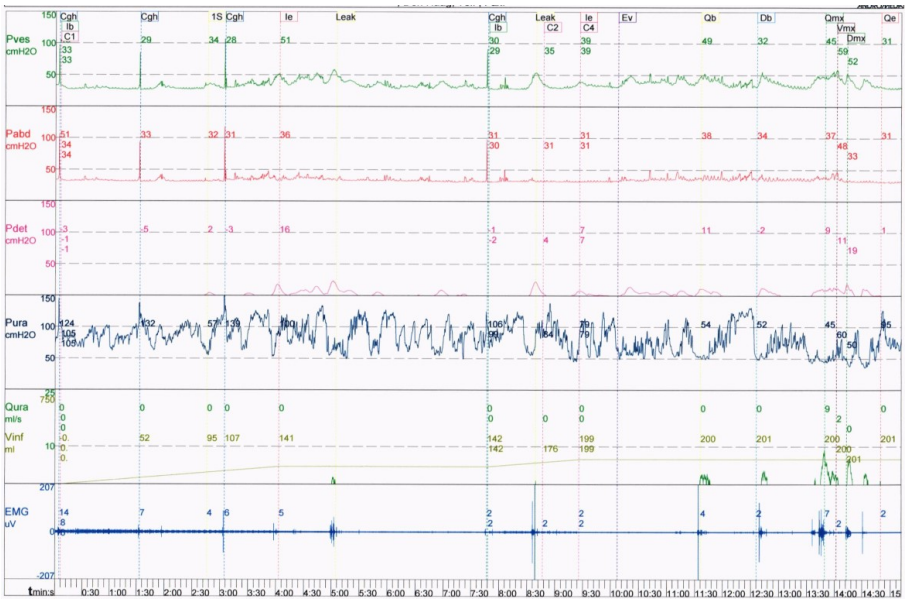


**Figure 1.1** Example of filling cystometry with dual microtip catheter, demonstrating URI and DO

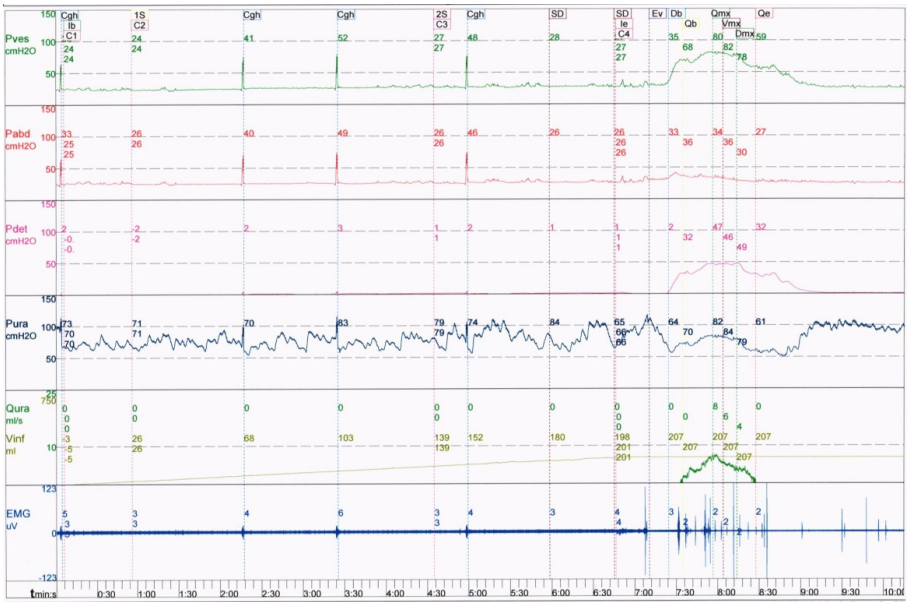


**Figure 1.2** Example of filling cystometry with dual microtip catheter, demonstrating URI

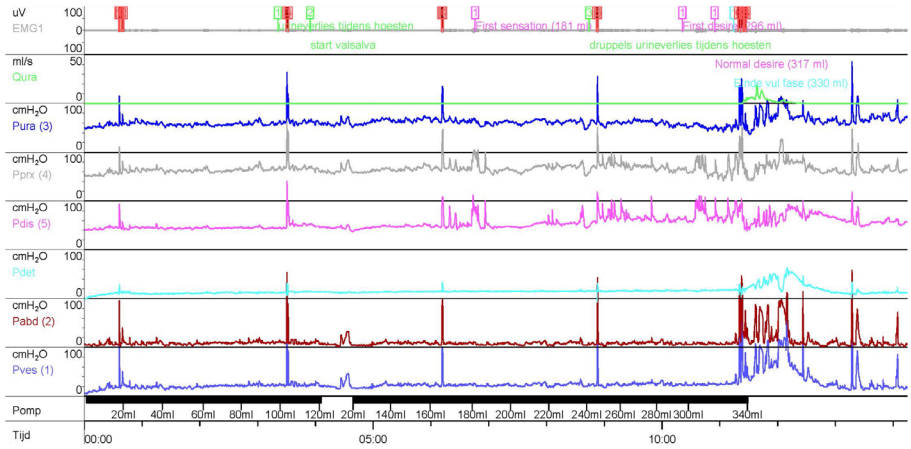


**Figure 1.3** Example of a normal filling phase of urodynamic investigation with three urethral sensors

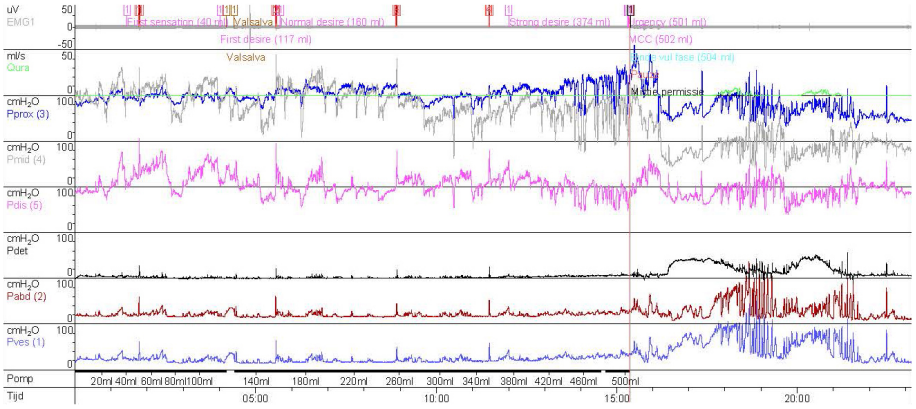


**Figure 1.4** Urethral pressure variations exceeding 30 cm H2O are present in two out of three urethral pressure sensors.

## OUTLINE OF THE THESIS

The aim of this is to further elucidate the role of urethral function within OAB to contribute to better targeted therapy in patients with OAB. This thesis consists of seven chapters and contains the results of an anatomical study, a review of the literature on this subject, a functional urodynamic study and a combined clinical and urodynamic study to the effect of pharmacotherapy in patients with urethral pressure variations and a pilot study to the efficacy of a localized treatment for patients with urethral pressure variations (UPV). The question is whether urethral pressure variations should be seen as an own entity within OAB with possibilities of tailored therapy, or whether it is a prognostic factor which can be used for prediction of success for certain treatment modalities, or whether it should be considered as a rare phenomenon of which it is difficult to establish clinical significance.

In Chapter 2 the results of the anatomical study to the presence and distribution of beta 3 adrenoceptor (ADRB3) in the female human urethra are described. The maintaining of urethral tonus is considered to be mainly under sympathetic control. Since five years, a beta 3 adrenoceptor (ADRB3) agonist is available for treatment of OAB. If ADRB3 is present in the urethra, an ADRB3 agonist will have a local influence which possibly is of importance in patients with urethral pressure variations.

Chapter 3 describes a systematic review of the literature on urethral instability. We have assessed the various measurement methods, materials used, definitions and the methodological quality of reported studies in current literature. This background information is essential to put UPV in perspective of OAB and to define a working definition for this thesis.

Chapter 4 describes a prospective study to determine the additional value of triple-sensor urethral catheter in demonstrating urethral pressure variations during filling cystometry. For further research and definition of UPV, it is important to determine how this condition can best be demonstrated and if the use of a single urethral sensor catheter is as representative as the use of triple urethral sensor catheters in the demonstration of UPV.

In Chapter 5, we present the results of a prospective study to the effect of the beta 3 adrenoreceptor agonist (Mirabegron) on urodynamic sensation parameters and urethral pressure variations during filling cystometry. Previous studies have demonstrated no effect of antimuscarinic agents on urethral function [36]. The aim of this study was to assess the influence

of mirabegron on urethral pressure variations during urodynamic investigation and the association of symptoms and voiding diary data before and on treatment.

In the five years since ADRB3 agonist has been available, no studies have been performed to effect of ADRB3 agonist on urethral function.

In an attempt to develop localized treatment for patients with UPV, we performed a pilot study to the effectiveness of subtrigonal Botulinum A toxin injections in the treatment of patients with high urethral pressure and/or urethral pressure variations. These results are described in Chapter 6.

Chapter 7 summarizes the results of abovementioned chapters by their abstracts in English.

In Chapter 8 the main findings and recommendations for future research are discussed

In Chapter 9 the Dutch summary of this thesis is provided.

# REFERENCES


1. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I: National community prevalence of overactive bladder in the United States stratified by sex and age. *Urology* 2011, 77(5):1081-1087.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003, 61(1):37-49.
3. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU international* 2001, 87(9):760-766.
4. Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I: Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. *BJU international* 2009, 104(7):954-959.
5. Lagro-Janssen T, Smits A, Van Weel C: Urinary incontinence in women and the effects on their lives. *Scandinavian journal of primary health care* 1992, 10(3):211-216.
6. Dmochowski RR, Newman DK: Impact of overactive bladder on women in the United States: results of a national survey. *Current medical research and opinion* 2007, 23(1):65-76.
7. Vaughan CP, Johnson TM, 2nd, Ala-Lipasti MA, Cartwright R, Tammela TL, Taari K, Auvinen A, Tikkinen KA: The prevalence of clinically meaningful overactive bladder: bother and quality of life results from the population-based FINNO study. *European urology* 2011, 59(4):629-636.
8. Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I: Economic burden of urgency urinary incontinence in the United States: a systematic review. *Journal of managed care pharmacy : JMCP* 2014, 20(2):130-140.
9. Chapple C, Cruz F: Open to debate. The Motion: antimuscarinics are the mainstay of therapy for overactive bladder. *European urology* 2008, 54(1):226-230.
10. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ: Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev* 2012, 1:CD005429.
11. Wagg A, Compion G, Fahey A, Siddiqui E: Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU international* 2012, 110(11):1767-1774.
12. Sicras-Mainar A, Rejas J, Navarro-Artieda R, Aguado-Jodar A, Ruiz-Torrejon A, Ibanez-Nolla J, Kvasz M: Antimuscarinic persistence patterns in newly treated patients with overactive bladder: a retrospective comparative analysis. *Int Urogynecol J* 2014, 25(4):485-492.
13. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D: The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *European urology* 2008, 54(3):543-562.
14. Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC: Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodyn* 2014, 33(1):17-30.
15. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F, Khemiri A, Siddiqui E, Wagg A: Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. *European urology* 2017, 72(3):389-399.

16. Drake MJ, Chapple C, Esen AA, Athanasiou S, Cambronero J, Mitcheson D, Herschorn S, Saleem T, Huang M, Siddiqui E *et al*: Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). *European urology* 2016, 70(1):136-145.
17. MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, Saleem T, Huang M, Siddiqui E, Stolzel M *et al*: Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy: Responder Analyses and Patient-Reported Outcomes from the BESIDE Study [corrected]. *J Urol* 2016, 196(3):809-818.
18. Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006, 49(4):644-650.
19. Merrill L, Gonzalez EJ, Girard BM, Vizzard MA: Receptors, channels, and signalling in the urothelial sensory system in the bladder. *Nat Rev Urol* 2016, 13(4):193-204.
20. Barrington F: The components reflexes of micturition in the cat, Parts I and II. *Brain* 1931, 54:177-188.
21. Barrington F: The component reflexes of micturition in the cat: Part III. *Brain* 1941, 64:239-243.
22. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, Chancellor MB: Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol* 1999, 162(1):204-212.
23. Vereecken RL: Physiological and pathological urethral pressure variations. *UrolInt* 1996, 57(3):145-150.
24. McLennan MT, Melick C, Bent AE: Urethral instability: clinical and urodynamic characteristics. *Neurourol Urodyn* 2001, 20(6):653-660.
25. Groenendijk PM, Heesakkers JP, Ouwerkerk TJ, Lycklama ANAA: Urethral instability: current pathophysiological concept. *Urol Int* 2009, 83(2):125-133.
26. Gammie A, Bosch R, Djurhuus JC, Goping I, Kirschner-Hermanns R: Do we need better methods of assessing urethral function: ICI-RS 2013? *Neurourol Urodyn* 2014, 33(5):587-590.
27. Kirschner-Hermanns R, Anding R, Rosier P, Birder L, Andersson KE, Djurhuus JC: Fundamentals and clinical perspective of urethral sphincter instability as a contributing factor in patients with lower urinary tract dysfunction--ICI-RS 2014. *Neurourol Urodyn* 2016, 35(2):318-323.
28. de Groat WC, Griffiths D, Yoshimura N: Neural control of the lower urinary tract. *Compr Physiol* 2015, 5(1):327-396.
29. Birder LA, Andersson KE, Kanai AJ, Hanna-Mitchell AT, Fry CH: Urothelial mucosal signaling and the overactive bladder-ICI-RS 2013. *Neurourol Urodyn* 2014, 33(5):597-601.
30. Birder L, Andersson KE: Urothelial signaling. *Physiol Rev* 2013, 93(2):653-680.
31. Kummeling MT, Rietbergen JB, Withagen MI, Mannaerts GH, van der Weiden RM: Sequential urodynamic assessment before and after laparoscopic sacrocolpopexy. *Acta Obstet Gynecol Scand* 2013, 92(2):172-177.
32. Groenendijk PM, Heesakkers JP, Lycklama ANAA: Urethral instability and sacral nerve stimulation-a better parameter to predict efficacy? *J Urol* 2007, 178(2):568-572.

33. Farrell SA, Tynski G: The effect of urethral pressure variation on detrusor activity in women. *Int Urogynecol J Pelvic Floor Dysfunct* 1996, 7(2):87-93.
34. Sand PK, Bowen LW, Ostergard DR: Uninhibited urethral relaxation: an unusual cause of incontinence. *ObstetGynecol* 1986, 68(5):645-648.
35. Kummeling MT, Rosier PF, Elzevier HW, Groenendijk PM: Continuous urethral pressure measurements; measurement techniques; pressure variations; clinical interpretations; and clinical relevance. A Systematic Literature Analysis. *Neurourol Urodyn* 2017, 36(1):51-56.
36. Thind P, Lose G, Colstrup H, Andersson KE: The influence of beta-adrenoceptor and muscarinic receptor agonists and antagonists on the static urethral closure function in healthy females. *Scand J Urol Nephrol* 1993, 27(1):31-38.