STUDY OF TERAZOSIN IN THE TREATMENT OF FEMALE LOWER URINARY TRACT SYMPTOMS

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UNIVERSITI SAINS MALAYSIA

2007

STUDY OF TERAZOSIN IN THE TREATMENT OF FEMALE LOWER URINARY TRACT SYMPTOMS

by

LOW BEE YEAN

Thesis submitted in fulfilment of the

requirements for the degree

of Doctor of Philosophy

December 2007

To my parents, Low Eng Kok and Ng Sook Ying,

brothers, Ee Chai and Ee Leng,

and sister, Mei Fong

ACKNOWLEDGEMENTS

My immense gratitude and appreciation go to my supervisors, Professor Dr Yuen Kah Hay and Dr Nurzalina Abdul Karim Khan as well as my field supervisor Dr Liong Men Long for giving me an opportunity to go through postgraduate experience. Their passion for research, guidance and support has been my inspiration. The clinical part of the study would not have been possible if not for the enthusiasm and commitment of my field supervisor Dr Liong Men Long in helping to recruit subjects and drive the study.

I would like to take this opportunity to thank Abbott Laboratories Malaysia for providing financial support for this study. I would also like to thank urologists from other participating hospitals namely, Dr Christopher Chee, Dr Leong Wing Seng, Dr Chong Wooi Loong, Dr Murali Mohan, Dr Teh Chu Leong, Dr Yap Hin Wai, Dr Loh Chit Sin and Dr Timothy Khor for their valuable comments for the study.

I would also like to thank School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), Institute of Postgraduate Studies (IPS), USM as well as Department of Urology of the participating hospitals for providing me an excellent environment and their generous support for the study.

My sincere thanks go to Dr Cheah Phaik Yeong for her advice and guidance. Also, I am very grateful to all my wonderful labmates and friends for providing an enjoyable working environment and help out in one way or another. Last but not least, I am immensely indebted to my parents, brothers and sister for their understanding and constant encouragement throughout my academic years.

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LIST OF SYMBOLS, ABBREVIATIONS OR NOMENCLATURE

Abbreviation	Full Description
24-H FVC	24-hours frequency volume chart
a_1-AR	alpha$_1$-adrenergic receptor
a_1-ARs	alpha$_1$-adrenergic receptors
a-AR	alpha-adrenergic receptor
Ach	Acetylcholine
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUASI	American Urological Association Symptoms Index
BFLUTS	Bristol Female Lower Urinary Tract Symptoms
BMI	Body mass index
BOO	Bladder outlet obstruction
BPH	Benign prostatic hyperplasia
BPO	Benign prostatic obstruction
CCC	Concordance correlation coefficient
ClCr	Creatinine clearance
C_{max}	Peak concentration
CONSORT	Consolidated Standards of Reporting Trials
CPG	Casual plasma glucose
CRS	Civil Registration System
EMG	Electromyography
FLUTS	Female lower urinary tract symptoms
FLUTS-CS	Patients with FLUTS from clinical setting
FLUTS-GP	Patients with FLUTS from general population

FPG	Fasting plasma glucose
GCP	Good clinical practice
HRQOL	Health related quality of life
IBW	Ideal body weight
IC	Interstitial cystitis
ICC	Intraclass correlation coefficient
ICS	International Continence Society
ICS-BPH	International Continence Society-Benign Prostatic Hyperplasia
IPSS	International Prostate Symptom Score
ISD	Intrinsic sphincter deficiency
IUD	Intrauterine device
KHQ	King’s Health Questionnaire
KO	Knock out
LUT	Lower urinary tract
LUTS	Lower urinary tract symptoms
MRI	Magnetic resonance imaging
NLUTS	Neurogenic lower urinary tract symptoms
NO	Nitric oxide
NPC	National Productivity Centre
OAB	Overactive bladder
OR	Odds ratio
POP	Pelvic organ prolapse
PVR	Post void residual
Qmax	Maximum flow rate
QOL	Quality of life
RCTs	Randomised controlled trials
ROC	Receiver operating characteristic

SD	Standard deviation
SEM	Standard error of mean
SPSS	Statistical Package for Social Sciences
SrCr	Serum creatinine
SUI	Stress urinary incontinence
t_{max}	The time at which the blood sample corresponding the the peak concentration was taken
UH	Urethral hypermobility
UPT	Urine pregnancy test
USM	Universiti Sains Malaysia
UTI	Urinary tract infections
VUR	Vesicoureteral reflux

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KAJIAN TERAZOSIN UNTUK RAWATAN SIMPTOM-SIMPTOM SALUR KENCING BAWAH WANITA

ABSTRAK

Simptom salur kencing bawah wanita adalah satu keadaan biasa yang mempengaruhi wanita dalam semua lingkungan umur dan ia memberi kesan yang buruk terhadap kualiti kehidupan. Walau bagaimanapun, tiada definisi piawai ataupun panduan untuk diagnosis dan rawatan masalah ini. Keputusan rawatan masih tidak memuaskan. Oleh itu, kajian ini dijalankan untuk menentukan keberkesanan klinikal dan keselamatan terazosin dalam rawatan pesakit simptom salur kencing bawah wanita.

Bahagian pertama kajian ini adalah untuk mengesahkan kegunaan Skor Simptom Prostat Antarabangsa dan Soal Selidik Kesihatan King's dalam kalangan pesakit simptom salur kencing bawah wanita. Adalah didapati bahawa kedua-dua Skor Simptom Prostat Antarabangsa dan Soal Selidik Kesihatan King's adalah sah, dapat dipercayai dan bergerak balas terhadap perubahan dalam kalangan pesakit simptom salur kencing bawah wanita dan dengan itu ia sesuai digunakan sebagai ukuran dalam kajian rawatan terazosin.

Daripada kajian prevalens yang dijalankan, kadar prevalens ialah 19% daripada 2732 wanita berumur >19 tahun yang disoal selidik di dua buah negeri di kawasan utara Semenanjung Malaysia (Penang dan Kedah) dari bulan Januari hingga Ogos, 2004. Lebih daripada 50% pesakit simptom salur kencing bawah wanita berasa tidak gembira dengan pembuangan air kecil mereka. Analisis terhadap tingkah laku mencari rawatan bagi pesakit simptom salur kencing bawah wanita mendedahkan bahawa sebab utama pesakit simptom salur kencing bawah wanita menangguh mencari rawatan disebabkan

mereka kekurangan pengetahuan mengenai perkembangan penyakit dan pilihan rawatan yang sedia ada.

Analisis faktor risiko pesakit simptom salur kencing bawah wanita menunjukkan bahawa wanita yang mempunyai risiko yang lebih tinggi untuk mendapat simptom salur kencing bawah wanita (didefinisikan sebagai nisbah ganjil ≥2) termasuk mereka yang berumur ≥50, pariti ≥4, buta huruf, selepas menopos dan mempunyai ≥1 penyakit kronik. Oleh itu, pihak pemberi perkhidmatan kesihatan umum patut melaksanakan strategi yang mensasar kepada golongan ini untuk mewujudkan kesedaran di kalangan mereka.

Seterusnya, adalah didapati bahawa tingkah laku mencari rawatan untuk pesakit simptom salur kencing bawah wanita dari kedua-dua populasi umum dan persekitaran klinikal adalah dikaitkan dengan kesan terhadap kualiti kehidupan dan tidak berkaitan dengan keterukan simptom yang dikategorikan dengan jumlah Skor Simptom Prostat Antarabangsa.

Dalam bahagian terakhir kajian ini, seratus pesakit simptom salur kencing bawah wanita telah diberi terazosin atau placebo secara rawak selama 14 minggu dalam kajian prospektif ini. Terazosin didapati berjaya mengurangkan secara signifikan jumlah Skor Simptom Prostat Antarabangsa dan Indeks Kualiti Kehidupan Skor Simptom Prostat Antarabangsa, semua domain kualiti kehidupan Soal Selidik Kesihatan King's (kecuali domain Ukuran Keterukan) jika dibandingkan dengan placebo di kalangan pesakit simptom salur kencing bawah wanita. Tambahan pula, tidak terdapat perbezaan statistik secara signifikan dalam kejadian kesan sampingan di antara kumpulan yang menerima terazosin atau placebo. Oleh itu, terazosin didapati berkesan dan selamat dalam merawat pesakit simptom salur kencing bawah wanita.

STUDY OF TERAZOSIN IN THE TREATMENT OF FEMALE LOWER URINARY TRACT SYMPTOMS

ABSTRACT

Female Lower Urinary Tract Symptoms (FLUTS) is a common condition affecting women of all ages and it adversely affects quality of life (QOL). However, there are neither standard definitions nor guidelines for its diagnosis and treatment. Treatment outcomes have been unsatisfactory. Hence, this study was conducted to determine the clinical efficacy and safety of terazosin in treating patients with FLUTS.

The first part of the study was to validate the International Prostate Symptom Score (IPSS) and King's Health Questionnaire (KHQ) in patients with FLUTS. It was found that both the IPSS and KHQ were valid, reliable and responsive to changes in patients with FLUTS and hence suitable to be used as outcome measures in the terazosin treatment study.

From the prevalence study conducted, there was a prevalence rate of 19% from 2732 females aged >19 years surveyed within two states in Northern Peninsular Malaysia (Penang and Kedah) from Jan-Aug, 2004. More than 50% of patients with FLUTS felt unhappy with their urinary conditions. Analysis of treatment seeking behaviour of patients with FLUTS revealed the major underlying reason for those deferring treatment was that they lack of knowledge of the disease progress and treatment options available.

Analysis of the risk factors for patients with FLUTS showed that females who are at higher risk to have FLUTS (defined as odds ratio (OR) ≥2) included those with age ≥50,

parity ≥4, illiterate, post menopausal and have ≥1 concomitant chronic medical illness. Therefore, public health service providers should implement strategies targeted at these groups to create awareness among them.

Furthermore, it was found that treatment seeking behaviour of patients with FLUTS from both general population and clinical setting was associated with QOL impact of FLUTS and not symptoms severity categorised using total IPSS.

In the final part of the study, 100 patients with FLUTS were randomised to receive either terazosin or placebo for 14 weeks in the prospective, double-blind, placebo-controlled study. Terazosin was found to show a statistically significant reduction in total IPSS and IPSS QOL assessment index, all domains of QOL of the KHQ (except domain of severity measures) as compared to placebo in patients with FLUTS. Moreover, there was no statistically significant difference between treatment groups in the occurrence of adverse events. As such, terazosin was found to be effective and safe in treating patients with FLUTS.

CHAPTER 1

INTRODUCTION TO FEMALE LOWER URINARY TRACT SYMPTOMS (FLUTS)

1.1 INTRODUCTION

Results of population surveys have shown that the prevalence of female lower urinary tract symptoms (FLUTS) was high ranging from 12% to 39% (Pinnock & Marshall, 1997; Yu *et al.*, 1998; Moller *et al.*, 2000a; Boyle *et al.*, 2003a; Low *et al.*, 2006). Prevalence of specific symptoms such as urgency was found to as high as 61% and incomplete emptying was 43% (Swithinbank & Abrams, 2000). Patients with FLUTS were associated with a lower overall health status (Yu *et al.*, 1998; Boyle *et al.*, 2003b), with patients restricting activities, for example only going to places where there are known toilet facilities (so-called 'toilet mapping'), and having to carry extra underwear and pads (Freeman & Adekanmi, 2005). Many patients even limited drinking in an attempt to prevent symptoms (Freeman & Adekanmi, 2005). Patients with FLUTS experienced both financial and intangible loss such as personal and emotional distress (Kelleher, 2002). Most research on lower urinary tract function have focused on the filling phase of the micturation cycle, or the study of urinary incontinence (Groutz *et al.*, 1999), but not FLUTS. The pathophysiological mechanisms of female voiding phase dysfunction are poorly understood, and there are neither standard definitions nor guidelines for its diagnosis and treatment (Groutz & Blaivas, 2002). At present, the management of FLUTS includes excluding pathology and implementing behaviour changes such as caffeine reduction, bladder and pelvic floor training, as well as antimuscarinic drug therapy. The aetiology in most cases is unknown, and treatment outcomes have been unsatisfactory (Freeman & Adekanmi, 2005).

1.2 DEFINITION

Symptoms are the subjective indicators of a disease. Symptoms or change in health status as perceived by the patient, care provider or partner may lead him/her to seek help from health care professionals. Descriptions of symptoms are either volunteered by, or elicited from the individual or even the individual's caregiver. Such descriptions are usually qualitative in nature (Abrams *et al.*, 2002).

Lower urinary tract symptoms (LUTS) is a term that describes symptoms related to both the storage and emptying phases of the micturation cycle (Chaikin & Blaivas, 2001). The Standardisation Sub-committee of the International Continence Society (ICS) on the Standardisation of Terminology of Lower Urinary Tract Function has divided LUTS into three groups, namely, storage, voiding and post micturation symptoms. LUTS are defined from the individual's perspective. In general, LUTS cannot be used to make a definitive diagnosis. LUTS can also indicate pathologies other than lower urinary tract dysfunction, such as urinary tract infections (UTI) (Abrams *et al.*, 2002).

1.2.1 STORAGE SYMPTOMS

The Standardisation Sub-committee of the ICS on the Standardisation of Terminology of Lower Urinary Tract Function defines storage symptoms as symptoms experienced during the storage phase of the bladder. They include the following (Abrams *et al.*, 2002):

a) Increased daytime frequency

Increased daytime frequency is the complaint by the patient who considers that he/she voids too often by day.

b) Nocturia

Nocturia is defined as waking up at night one or more times to void.

c) Urgency

Urgency is a sudden compelling desire to pass urine, which is difficult to defer.

d) Urinary incontinence

Urinary incontinence is the complaint of any involuntary leakage of urine. In each specific circumstance, urinary incontinence should be further described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life (QOL), the measures used to contain the leakage, and whether or not the individual seeks or desires help because of urinary incontinence.

e) Stress urinary incontinence (SUI)

SUI is involuntary leakage on effort or exertion, or on sneezing or coughing.

f) Urge urinary incontinence

Urge urinary incontinence is involuntary leakage accompanied by or immediately preceded by urgency.

g) Mixed urinary incontinence

Mixed urinary incontinence is involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.

h) Enuresis

Enuresis means any involuntary loss of urine.

i) Nocturnal enuresis

Nocturnal enuresis is loss of urine occurring during sleep.

j) Continuous urinary incontinence

Continuous urinary incontinence is continuous urinary leakage.

k) Other types of urinary incontinence

Other types of urinary incontinence may be situational, for example leakage during sexual intercourse, or giggle incontinence.

l) Bladder sensation

There are five types of bladder sensation, namely:

- Normal: the individual is aware of bladder filling and increasing sensation up to a strong desire to void.
- Increased: the individual feels an early and persistent desire to void.
- Reduced: the individual is aware of bladder filling but does not feel a definite desire to void.
- Absent: the individual reports no sensation of bladder filling or desire to void.
- Non-specific: the individual reports no specific bladder sensation, but may perceive bladder filling as abdominal fullness, vegetative symptom, or spasticity.

1.2.2 VOIDING SYMPTOMS

The Standardisation Sub-committee of the ICS on the Standardisation of Terminology of Lower Urinary Tract Function defines voiding symptoms as symptoms experienced during the voiding phase and include the following (Abrams *et al.*, 2002):

a) Slow stream

Slow stream is reduced urine flow rate and is usually compared with previous performance or with others.

b) Splitting or spraying

Splitting or spraying of the urine stream during voiding.

c) Intermittent stream (Intermittency)

Intermittent stream (Intermittency) is a term used when describing the urine flow, which stops and starts, on one or more occasions.

d) Hesitancy

Hesitancy is a term used when describing difficulty in initiating micturation resulting in a delay in the onset of voiding after the individual is ready to pass urine.

e) Straining

Straining to void occurs when there is muscular effort used to initiate, maintain or improve the urinary stream.

f) Terminal dribbling

Terminal dribbling is when a prolonged final part of micturation, when the flow has slowed to a trickle/dribble.

1.2.3 POST MICTURATION SYMPTOMS

According to the report by the Standardisation Sub-committee of the ICS on the Standardisation of Terminology of Lower Urinary Tract Function, post micturation symptoms are symptoms experienced immediately after micturation. They include the following (Abrams *et al.*, 2002):

a) Feeling of incomplete emptying

Feeling of incomplete emptying is a feeling that the bladder is still full even after passing urine.

b) Post micturation dribble

Post micturation dribble is a term used when an individual describes the involuntary loss of urine immediately after he or she has finished passing urine, usually after leaving the toilet in men, or after rising from the toilet in women.

1.3 EPIDEMIOLOGY

Voiding disorders in men have been extensively studied, but there is a paucity of studies assessing the voiding patterns and prevalence of urinary disorders, other than urinary incontinence in women (Yu *et al.*, 1998; Swithinbank & Abrams, 2000; Takeda *et al.*, 2003). Until recently, data on prevalence of FLUTS are scarce and limited by the non-standardisation of the definitions used. The reported prevalence of FLUTS varied from 12%-39% (Pinnock & Marshall, 1997; Yu *et al.*, 1998; Moller *et al.*, 2000a; Boyle *et al.*, 2003a; Low *et al.*, 2006). Prevalence of specific symptom prevalence was also reported to be high e.g., 61% for urgency, 43% for incomplete emptying (Swithinbank & Abrams, 2000). The wide variation in the prevalence rates can be explained by differences in definitions, target populations and study designs used (Groutz & Blaivas, 2002; Moller *et al.*, 2000a). Having a standardised and accepted international consensus definition on FLUTS will make future research and publication comparable (Low *et al.*, 2006).

As mentioned earlier, FLUTS is a very common condition and it adversely affects QOL. In an interview-based prevalence study conducted on 1686 women aged more than 18 years old in September 1995 in Australia using validated International Prostate Symptom Score (IPSS), the prevalence of one or more troublesome LUTS was 39% for

women of all ages and 16% of the women were substantially dissatisfied with their urinary conditions (Pinnock & Marshall, 1997). The prevalence of LUTS occurring more than weekly was 27.8% for 2860 women aged 40 to 60 years using a self-administered, validated and modified Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire in one rural (Storstrøms) and one urban county (Copenhagen) in Denmark in June 1996 (Moller *et al.*, 2000a). Specific symptom prevalence ranged from 6% to 61% from a postal-based prevalence survey in a group of 2075 women aged over 18 years registered with one general practice in Pill, a small village on the outskirts of Bristol (Swithinbank & Blaivas, 2000). These studies were conducted in western countries and epidemiologic data are not directly transferable from country to country because studies have shown that many factors, such as social status, cultural background, or accessibility of health care resources, contribute to LUTS-related health care-seeking behaviour (Takeda *et al.*, 2003). The prevalence of FLUTS using IPSS >7 in the self-administered prevalence study conducted in Taiwan and an interview-based prevalence study conducted in Korea were 21% and 19.9% respectively (Yu *et al.*, 1998; Boyle *et al.*, 2003a). However, all these studies may not be directly comparable, because different methods were used to evaluate LUTS in women. In addition, of the five published studies, none had considered the treatment seeking behaviour and risk factors of patients with FLUTS. This is particularly important for health care policy providers in designing strategies and targeting it to the correct patient population (Low *et al.*, 2006).

1.4 ETIOLOGIES AND PATHOGENESIS

LUTS occur when the lower urinary tract (LUT) fails to maintain its functions, namely, the storage and timely expulsion of urine (Groutz & Blaivas, 2002; Nordling, 2002). The etiology of LUTS is multi factorial and not fully understood (Moller *et al.*, 2000b; Chaikin & Blaivas, 2001). Symptoms are poor indicators and present only a murky view of the underlying pathophysiology (Chaikin & Blaivas, 2001). Symptoms may be caused by a

finite number of underlying conditions that fall into two main categories: bladder abnormalities and urethral or sphincter abnormalities (Blaivas, 2000).

1.4.1 BLADDER CONDITIONS CAUSING STORAGE SYMPTOMS

1.4.1(a) DETRUSOR OVERACTIVITY

Detrusor overactivity or involuntary detrusor contraction may be further subdivided into detrusor hyper-reflexia (involuntary detrusor contraction caused by neurological conditions) and detrusor instability (from non-neurological conditions) (Robinson, 1998; Blaivas, 2000; Nordling, 2002). Common causes of detrusor hyper-reflexia include stroke, multiple sclerosis, Parkinson's disease, spinal cord injury, transverse myelitis and spinal bifida (Blaivas, 2000). Artibani (1997) suggested classifying the non-neurogenic causes of detrusor instability into obstructive, congenital, behavioural-psychosomatic, age-related, due to pelvic floor/urethral disorder, myogenic, hypersensitivity and mixed causes. Detrusor instability may have similar appearance and is associated with a variety of conditions that are assumed to be causative, e.g. urethral obstruction, infection, pelvic organ prolapse (POP), urethral diverticula and bladder cancer, but in most cases are idiopathic (Blaivas, 2000).

1.4.1(b) SENSORY URGENCY

Sensory urgency refers to an uncomfortable need to void which is not accompanied by (diagnosable) detrusor instability. It is most often idiopathic, but commonly seen in association with infections, bladder stones and cancer. When no cause is discerned, it is called painful bladder syndrome or interstitial cystitis (IC) (Blaivas, 2000).

1.4.1(c) LOW BLADDER COMPLIANCE

Low bladder compliance refers to an abnormal 'stiffness' of the bladder wall that is defined as the relationship between changes in the bladder volume and detrusor

pressure. Low bladder compliance may be functional (from increased detrusor tone), or anatomical (decreased viscoelasticity of the bladder wall). Common causes of low bladder compliance include neurogenic bladder, radiation, interstitial and tuberculous cystitis, and the long-term use of indwelling bladder catheters (Blaivas, 2000).

1.4.2 SPHINCTER CONDITIONS CAUSING STORAGE SYMPTOMS

Sphincter conditions causing storage symptoms are of two generic kinds, i.e. intrinsic sphincter deficiency (ISD) and urethral hypermobility (UH) (Blaivas, 2000).

1.4.2(a) INTRINSIC SPHINCTER DEFICIENCY (ISD)

ISD implies a weakness of the sphincter mechanism itself (Blaivas, 2000). Many factors are associated with the development of ISD. Age greater than 50 years (Horbach & Ostergard, 1994), prolonged menopausal status, sphincteric dysfunction resulting from the simple hysterectomy (Morgan *et al.*, 2000), previous incontinence or prolapse surgery (Veronikis *et al.*, 1997; Takahashi *et al.*, 2000) were found to be associated with the development of ISD. Other causes include either congenital or acquired myelopathy (meningomyelocele or sacral cord lesion/injury), diabetic neuropathy, myeldysplasia, or Shy-Drager syndrome, which is a progressive neuronal degeneration within the brain and spinal cord (Betson *et al.*, 2003)

1.4.2(b) URETHRAL HYPERMOBILITY (UH)

UH refers to abnormal movement of the urethra during increases in intra-abdominal pressure (Blaivas, 2000).

1.4.3 BLADDER CONDITIONS CAUSING EMPTYING SYMPTOMS

Bladder conditions causing emptying symptoms include impaired or absent detrusor contractility and bladder outlet obstruction (BOO) (Blaivas, 2000).

1.4.3(a) IMPAIRED DETRUSOR CONTRACTILITY

Impaired detrusor contractility may be caused by neurogenic disorders or detrusor decompensation. It may also be a learned voiding dysfunction or idiopathic. Neurogenic causes include spinal cord injury, spinal bifida, multiple sclerosis, diabetes mellitus and surgical insult such as radical hysterectomy and abdominoperineal resection of the rectum. Detrusor decompensation may occur after long-standing BOO (Blaivas, 2000).

1.4.3(b) BLADDER OUTLET OBSTRUCTION (BOO)

BOO may be anatomical or functional. Causes of the obstruction in the former include urethral stricture/fibrosis (usually after pelvic surgery or trauma), POP, urethral diverticula and tumour. Functional obstructions on the other hand are caused by detrusor sphincter dyssynergia, primary bladder neck obstruction and learned voiding dysfunction (dysfunctional voiding) (Blaivas, 2000).

1.4.4 MYOGENIC BASIS CAUSING LUTS

Myogenic is a hypothesised cause of detrusor instability, regardless of the etiology of the disease (Brading, 1997). Elbadawi and his colleagues (1993a, 1993b, 1993c, 1993d) have proposed and established that the elderly have an abnormal number of intercellular connections used for communication between smooth muscle cells and could facilitate the generation of unplanned detrusor contractions. This ultrastructural study using electron microscopy was conducted in elderly patients with detrusor overactivity, associated or not associated with outflow obstruction or detrusor hypocontractility (Elbadawi *et al.*, 1993a; Elbadawi *et al.*, 1993b; Elbadawi *et al.*, 1993c; Elbadawi *et al.*, 1993d). Partial denervation of the detrusor may be responsible for altering the properties of the smooth muscle, leading to increased excitability and

increased ability of activity to spread between cells, resulting in coordinated myogenic contractions of the whole detrusor (Brading, 1997).

1.5 NEUROLOGIC CONTROL OF LOWER URINARY TRACT (LUT)

The LUT provides two functional modes of operation, the storage of urine over several hours and periodical micturation without residual urine (De Groat, 1997; Evans & Castleden, 1998; Andersson, 2002; Reitz *et al.*, 2004; De Groat, 2006). The storage and periodic expulsion of urine is regulated by a neural control system in the brain and spinal cord. The neural control system coordinates the reciprocal activity of two functional units in the LUT: (a) a reservoir (the urinary bladder) and (b) an outlet (bladder neck, urethra and striated muscles of the urethral sphincter) (Benson, 1989; De Groat, 1997; Evans & Castleden, 1998; Andersson, 2002; Morrison *et al.*, 2002; Reitz *et al.*, 2004; De Groat, 2006). Control of the bladder and urethral outlet is dependent on three sets of peripheral nerves: sacral parasympathetic (pelvic nerves), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain), and sacral somatic nerves (pudendal nerves). These nerves contain afferent as well as efferent pathways (De Groat, 1997; Evans & Castleden, 1998; Andersson, 2002; Morrison *et al.*, 2002; Reitz *et al.*, 2004; De Groat, 2006). The neural pathways controlling LUT function are organised as simple on-off switching circuits that maintain a reciprocal relationship between the urinary bladder and urethral outlet. The principal reflex components of these switching circuits are listed in Table 1.1 (De Groat, 1997; Morrison *et al.*, 2002; De Groat, 2006) and illustrated in Figure 1.1 (Morrison *et al.*, 2002; De Groat, 2006). Normal storage of urine is dependent on 1) spinal reflex mechanisms that activate sympathetic and somatic pathways to the urethral outlet and 2) tonic inhibitory systems in the brain that suppress the parasympathetic excitatory outflow to the urinary bladder. In contrast, voiding is mediated by inhibition of sympathetic-somatic pathways and activation of a spinobulbospinal parasympathetic reflex pathway passing through a coordination centre (the pontine micturation centre)

located in the brainstem (De Groat, 1997; Evans & Castleden, 1998; Morrison *et al.*, 2002; De Groat, 2006). Many neurotransmitters including acetylcholine (Ach), norepinephrine, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate (ATP), nitric oxide (NO) and neuropeptides are involved in the neural control of the LUT (De Groat, 2006). Please refer to Table 1.2 for the receptors for putative transmitters in the LUT (De Groat, 2006).

Table 1.1 Reflexes to the LUT (De Groat, 1997; Morrison *et al.*, 2002; De Groat, 2006)

Afferent Pathway	Efferent Pathway	Central Pathway
Urine storage	1. External sphincter contraction (somatic nerves)	Spinal reflexes
Low-level vesical	2. Internal sphincter contraction (sympathetic nerves)	
activity (pelvic nerve)	3. Detrusor inhibition (sympathetic nerves)	
	4. Ganglionic inhibition (sympathetic nerves)	
	5. Sacral parasympathetic outflow inactive	
Micturition	1. Inhibition of external sphincter activity	Spinobulbospinal reflexes
High-level afferent	2. Inhibition of sympathetic outflow	
activity (pelvic nerve)	3. Activation of parasympathetic outflow	
	4. Activation of parasympathetic outflow to the urethra	Spinal reflex

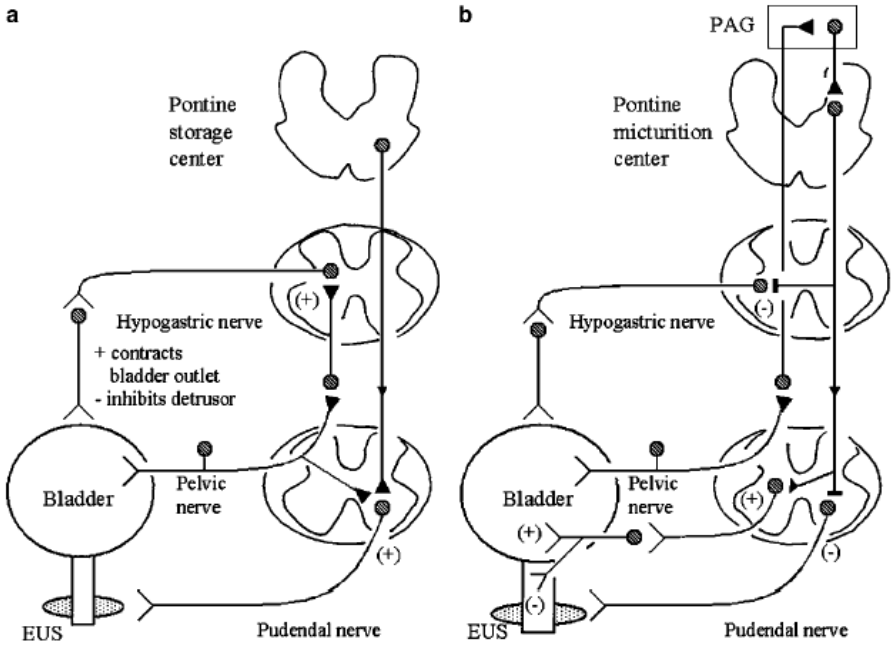

Figure 3 Diagram showing neural circuits controlling continence and micturition. (a) Urine storage reflexes. During the storage of urine, distention of the bladder produces low-level vesical afferent firing, which in turn stimulates (1) the sympathetic outflow to the bladder outlet (base and urethra) and (2) pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits detrusor muscle and modulates transmission in bladder ganglia. A region in the rostral pons (the pontine storage centre) increases external urethral sphincter activity. (b) Voiding reflexes. During elimination of urine, intense bladder afferent firing activates spinobulbospinal reflex pathways passing through the pontine micturition center (PMC), which stimulate the parasympathetic outflow to the bladder and urethral smooth muscle and inhibit the sympathetic and pudendal outflow to the urethral outlet. Ascending afferent input from the spinal cord may pass through relay neurones in the periaqueductal grey (PAG) before reaching the PMG.

Figure 1.1 Diagram showing neural circuits controlling continence and micturation (Morrison *et al.*, 2002; De Groat, 2006)

Table 1.2 Receptors for putative transmitters in the LUT (De Groat, 2006)

Tissue	*Cholinergic*	*Adrenergic*	*Other*
Bladder body	+ (M_2) + (M_3)	−(β_2) −(β_3)	+ Purinergic ($P2X_1$) −VIP + Substance P (NK_2)
Bladder base	+ (M_2) + (M_3)	+ (α_1)	−VIP + Substance P (NK_2) + Purinergic (P2X)
Urothelium	+ (M_2) + (M_3)	α β	+ TRPV1 + TRPM8 + P2X + P2Y + Substance P + Bradykinin (B2)
Urethra	+ (M)	+ (α_1) + (α_2) −(β)	+ Purinergic (P2X) −VIP −Nitric oxide
Sphincter striated muscle	+ (N)		
Adrenergic nerve terminals	−(M_2) + (M_1)	−(α_2)	−NPY
Cholinergic nerve terminals	−(M_2) + (M_1)	+ (α_1)	−NPY
Afferent nerve terminals			+ Purinergic ($P2X_{2/3}$) + TRPV1
Ganglia	+ (N) + (M_1)	+ (α_1) −(α_2) + (β)	−Enkephalinergic (δ) −Purinergic (P_1) + Substance P

VIP, vasoactive intestinal polypeptide; NPY, neuropeptide Y; TRP, transient receptor potential. Letters in parentheses indicate receptor type, for example, M (muscarinic) and N (nicotinic). Plus and minus signs indicate excitatory and inhibitory effects.

1.5.1 CHOLINERGIC CONTROL OF LUT

The sacral parasympathetic outflow provides the major excitatory input to the urinary bladder (De Groat, 2006). Parasympathetic nerve stimulation causes the release of Ach at postsynaptic parasympathetic receptor sites. Ach release produces muscarinic and nicotinic effects. However, the bladder has only muscarinic receptor sites. Thus, parasympathetic nerve stimulation causes contraction of the detrusor muscle and relaxation of the trigone via the muscarinic effect (Beck, 1989; Hoffman & Taylor, 2001). The action of Ach is terminated by its breakdown by acetylcholinesterase (Beck, 1989). Ach release may be inhibited by alpha$_2$ receptor stimulation in the adrenergic control of the LUT (Hoffman & Taylor, 2001). Parasympathetic effect on LUT is modulated not only by adrenergic control but also by the effect of anticholinesterases, prostaglandins, histamine, calcium and potassium channel changes, purinergic nerves, and estrogen (Beck, 1989). The block of Ach effect on the detrusor muscle by atropine (a classical antimuscarinic drug) is less complete than the blockage of Ach by atropine elsewhere in the body (Brown & Taylor, 2001).

1.5.2 ADRENERGIC CONTROL OF LUT

The urethra and bladder have alpha- and beta-adrenergic receptor sites. Alpha-receptor sites predominate in the urethra as compared to the detrusor muscle, and beta-receptor sites predominate in the detrusor as compared in the urethra. Beta$_1$-receptors occur mainly in cardiac muscle, and the LUT has only beta$_2$-receptor. Beta-receptor site stimulation produces relaxation of detrusor muscle. The alpha$_1$- and alpha$_2$- receptors are found in the LUT. Alpha$_1$-receptors predominate at the postsynaptic receptor sites in the smooth muscle and stimulation causes smooth muscle contraction. Alpha$_2$-receptor sites seem to modulate alpha$_1$-stimulatory effect by inhibiting the release of transmitter substance (norepinephrine) and may also inhibit Ach release. The adrenergic transmitter substances are epinephrine and

norepinephrine. Epinephrine acts at beta-receptor sites and alpha$_1$-receptor sites. Norepinephrine acts at alpha$_1$- and beta$_1$-receptor sites and has very little effect on beta$_2$-receptor sites. Norepinephrine is less potent than epinephrine on alpha$_1$-receptor sites and is as potent as epinephrine on beta$_1$-receptor sites (in cardiac muscle) (Beck, 1989). Epinephrine relaxes the detrusor muscle as a result of stimulation of beta-receptor sites and causes contraction of the trigone and urethra as a result of alpha-agonistic action (Hoffman & Taylor, 2001). Norepinephrine has little effect on the detrusor muscle (slight relaxant effect through weak beta$_2$-stimulation), but it does not cause contraction of the urethra smooth muscles through alpha-stimulation (Beck, 1989).

1.5.3 PURINERGIC NERVE CONTROL OF LUT

As mentioned earlier, parasympathetic nerve stimulation is not blocked by atropine and norepinephrine. This is because of the noncholinergic, nonadrenergic innervation of the bladder by purinergic nerves (Beck, 1989) which its excitatory transmission is mediated by ATP, acting on P2X purinergic receptors (Hoffman & Taylor, 2001). Andersson & Hedlund (2002) believed if activation via purinergic receptors is responsible not only for part of the bladder contractions, but also for the LUTS, it should be considered an important target for therapeutic interventions.

1.6 RISK FACTORS

Although studies have shown that FLUTS is highly prevalent in population survey and not only causes considerable loss financially but significantly reduces patients' QOL, there have been a disproportionately low percentage of patients with FLUTS actively seeking treatment. It has been found that the major underlying reasons for those deferring treatment are lack of understanding of the disease progress and treatment options available. Thus, specifically quantified risk factors will be of particularly

importance for health care providers in providing treatment resources to the correct patient population. A properly structured dissemination of public education about FLUTS to the correct population may increase awareness among them and thus help in the early detection of patients with FLUTS as well as its prevention.

Women with LUTS or urinary incontinence were found to be associated with many factors, such as age, childbirth, faecal difficulties, obstetric complications, obesity, pelvic surgery, medications, functional impairment, chronic diseases, menstrual cycle, race, family history, childhood enuresis and POP (Moller *et al.*, 2000b; Minassian *et al.*, 2003; Holroyd & Straus, 2004; Jiang *et al.*, 2004; Zhang *et al.*, 2005). However, most of these studies were conducted in western women. Data of risk factors for women with LUTS or urinary incontinence in Asian women are lacking because of the scarcity of epidemiologic studies (Zhang *et al.*, 2005). Besides, studies so far only included women of certain age groups such as menopausal women (Brown *et al.*, 1999; Moller *et al.*, 2000b; Muscatello *et al.*, 2001; Parazzini *et al.*, 2003; Dallosso *et al.*, 2003; Manonai *et al.*, 2004) and those middle-aged (Kuh *et al.*, 1999; Teleman *et al.*, 2004; Fitzgerald *et al.*, 2006; Danforth *et al.*, 2006), or special cohorts such as nuns (Buchsbaum *et al.*, 2002). Moreover, when women of all ages were studied, the primary focus of research on women with LUTS was on overactive bladder (OAB) (Lapitan *et al.*, 2001; Milleman *et al.*, 2004) or urinary incontinence (Hagglund *et al.*, 1999; Peyrat *et al.*, 2002; Grodstein *et al.*, 2003; Kocak *et al.*, 2005; Song *et al.*, 2005; Song *et al.*, 2006).

1.7 DIAGNOSIS

Ongoing controversy exists as to the extent of the necessary evaluation of women presenting with LUTS, but it is important to exclude pathology such as urinary tract infections in these women. Most would agree that a detailed history, a physical examination and a urine analysis are essential components of the initial evaluation of

patients with FLUTS (Abrams *et al.*, 1988; Dorflinger & Monga, 2001; Rovner & Wein, 2003). Beyond these assessments, however, there is no universally accepted guideline on the diagnosis. In certain patients, a urodynamic, endoscopic and/or radiographic evaluation may be indicated (Rovner & Wein, 2003).

1.7.1 HISTORY

Patient's history begins with a detailed account of the precise nature of the patient's reported LUTS (Blaivas, 2000; Gordon & Groutz, 2001), which should be characterised and quantified as accurately as possible. When one or more LUTS is present, the patient's assessment of the relative severity of each symptom should be noted. Patient's reported LUTS alone is not an accurate tool in the diagnosis and should not be used as the sole determinant of diagnosis or treatment (Bowen, 1989; Gordon & Groutz, 2001).

The patient's medical history should include questions relevant to neurological and congenital abnormalities as well as information on previous urinary tract infections and relevant surgery. The patient's medical history should also include assessment of menstrual, sexual and bowel function, and obstetric history. Information must be obtained on medications with known or possible effects on the LUT (Abrams *et al.*, 1988; Bowen, 1989). Medications that are known to affect bladder and urethral function include anticholinergics, (e.g. probanthine, oxybutynin and tolterodine), tricyclic antidepressants (e.g. imipramine), narcotic analgesics, diuretics, alcohol, psychotropic medications, alpha agonists or antagonists, beta mimetics, calcium channel blockers and over-the-counter 'cold-cure' medicines that contain sympatomimetics (Bowen, 1989; Robinson, 1998; Blaivas, 2000). Also, conditions which can produce symptoms mimicking LUTS should be ruled out. Diabetes, hypercalcemia, edema, congestive heart failure, excessive fluid intake, and volume overload may result in increased renal clearance with resultant symptoms of frequency, urgency, and even urge incontinence

(Robinson, 1998). Diabetes mellitus and hypothyroidism are endocrine abnormalities that may adversely affect bladder emptying. Viral infections such as herpes simplex or herpes zoster involving the sacral dermatomes produce a type of pelvic neuritis resulting in urinary retention. Other infections resulting in spinal cord myelitis such as postinfectious polyneuritis (Guillain-Barre syndrome) or transverse myellitis should be considered (Bowen, 1989).

1.7.2 PHYSICAL EXAMINATION

Physical examination should focus on detecting anatomic and neurologic abnormalities that contribute to the LUT dysfunction (Blaivas, 2000; Gordon & Groutz, 2001). A vaginal examination should be performed with the bladder both empty (to check the pelvic organs) and full (to check for incontinence and prolapse). Uterovaginal descent or prolapse with associated cystocele or a large cystocele alone may result in mechanical obstruction of the urethra and inefficient voiding. Cervical or uterine fibroids, large ovarian cysts or other masses, hypoestrogenism in menopausal women should be ruled out (Bowen, 1989). Assessment of perineal sensation, the perineal reflexes supplied by the sacral segments S2-S4, and anal sphincter tone and control can help to exclude neuropathy (Abrams *et al.*, 1988; Bowen, 1989).

1.7.3 URINE ANALYSIS

Urinalysis and midstream specimen of urine should be undertaken to identify microscopic haematuria and infection. Gross and/or microscopic haematuria require separate evaluation to exclude tumours and stones. If urine analysis shows pyuria, the women should be treated empirically with antibiotics pending the results of culture and antibiotic sensitivities (Blaivas, 2000). Urinary infections can simulate any LUT pathologic condition, including detrusor instability or SUI. More than 60% of women with urodynamically proven stable bladders have temporary detrusor instability when

tested at the time of acute cystitis. Besides, more than 30% of women with a urodynamic diagnosis of stress incontinence made at a time of unsuspected cystitis were found to be continent when testing was repeated after infection was cleared. This is because *Escherichia coli* endotoxin has alpha-adrenergic blocking properties, decreasing urethral pressures (Bergman, 1989).

1.7.4 MICTURATION DIARY

A micturation diary is an important adjunct to the medical history that provides semi-objective data about the patient's micturation habits (Abrams *et al.*, 1988; Blaivas, 2000). The diary gives objective information on the number of voidings, the distribution of voidings between daytime and night-time and each voided volume (Abrams *et al.*, 1988).

1.7.5 PAD TEST

A pad test provides a useful semi-objective measurement of urine loss over a given period (Blaivas, 2000; Gordon & Groutz, 2001). In the simplest pad test, the patient changes his or her pads every 6 hour for one representative 24 hour period while he or she is taking pyridium (200 mg three times daily). The amount of staining on the pads is a rough estimate of the severity of the incontinence. Alternatively, the pads are weighed and the total weight (minus the weight of an unused pad) recorded in the patient's record as an estimate of the volume of the urine loss (as 1 g ≈ 1 mL of urine); up to 8 g per day is considered normal (Blaivas, 2000). Oral pyridium is used to colour the urine, increasing the ability to discriminate urine from other body fluids such as sweat or vaginal discharge (Mutone & Valaitis, 2006). During the testing period, provocative maneuvers to elicit incontinence, such as physical activities to increase intra-abdominal pressure or putting the patient's hands into running water may be included. Both short-term office (Peterson *et al.*, 2005) and long-term home testing is

possible (Ryhammer *et al.*, 1999). Pad testing may be valuable in situations where other objective tests are negative or the history is inconclusive. However, the limitation with this method is that a positive pad test does not specifically identify the cause of the incontinence e.g., stress or urge incontinence (Mutone & Valaitis, 2006).

1.7.6 UROFLOWMETRY ('FREE FLOW') AND POST VOID RESIDUAL (PVR) URINE

Uroflowmetry represents a simple initial test to assess the emptying phase of the LUT. Normal female voiding procedure is a bell-shaped curve on uroflowmetry. Voiding dysfunction may give rise to an intermittent or multiple peaked flows (Lose *et al.*, 1998). Urinary flow rate (uroflowmetry) is a composite measure of the interaction between the pressure generated by the detrusor and the resistance offered by the urethra. Thus, a low flow rate may be caused either by BOO or impaired detrusor contractility (Blaivas, 2000; Gordon & Groutz, 2001). Moreover, the flow may be normal in patients with BOO if they generate a high enough detrusor pressure to overcome the increased urethral resistance (Blaivas, 2000). To distinguish between obstruction and impaired detrusor contractility, detrusor pressure and flow must be measured simultaneously (Blaivas, 2000; Gordon & Groutz, 2001).

Post void residual (PVR) urine is defined as the volume of urine left in the bladder at the end of micturation (Abrams *et al.*, 2002). PVR is a useful measure of the emptying function of the bladder (Blaivas, 2000). Most clinicians would consider a PVR of up to 50 mL as normal (Bowen, 1989; Robinson, 1998; Blaivas, 2000), and a residual of over 200 mL as problematic (Robinson, 1998). A large PVR may be caused by either urethral obstruction or impaired detrusor contractility (Bowen, 1989; Blaivas, 2000). The presence of persistently increased PVR urine warrants clinical attention (Robinson, 1998) and further urodynamic investigation is usually necessary (Bowen, 1989).

1.7.7 URODYNAMIC EVALUATION

Urodynamic investigation was developed as an extension of patient history and physical examination in order to reveal the pathophysiology of a patient's complaints (Gordon & Groutz, 2001; Heesakkers & Vriesema, 2005). Urodynamic investigation tries to copy the function of the LUT, storage and expulsion, in a controlled and measurable setting (Heesakkers & Vriesema, 2005). As such, results of the urodynamic studies should clearly reflect the patient's symptoms and signs (Walters, 1989). A complete urodynamic investigation is not necessary in all symptomatic patients (Walters, 1989; Bergman, 1989). According to ICS (Abrams *et al.*, 2002), there are two principal methods of urodynamic investigation, namely, conventional urodynamic studies and ambulatory urodynamic studies. Conventional urodynamic studies normally take place in the urodynamic laboratory and usually involve artificial bladder filing. Artificial bladder filling is defined as filling the bladder, via a catheter, with a specified liquid at a specified rate. Ambulatory urodynamic studies are defined as a functional test of the LUT, utilising natural filling, and reproducing the subject's every day activities. Natural filling means that the bladder is filled by the production of urine rather than by an artificial medium. A urodynamic investigation consists of cystometry and pressure flow study.

1.7.7(a) CYSTOMETRY

Cystometry is the method by which the pressure/volume relationship of the bladder is measured during bladder filling. The filling phase starts when filling commences and ends when the patient and urodynamicist decide that 'permission to void' has been given (Abrams *et al.*, 2002). Cystometry is used to assess bladder sensation (Table 1.3), activity (Table 1.4), capacity (Table 1.5) and compliance (Table 1.6) during storage phase (Walters, 1989; Blaivas, 2000; Abrams *et al.*, 2002). Also, cystometry is

used to describe urethral function during storage phase (Table 1.7) as competent or incompetent (Abrams *et al.*, 2002).