EFFECT OF CALCIUM CHANNEL BLOCKER WITH OTHER ANTIHYPERTENSIVE AGENTS ON LOWER URINARY TRACT SYMPTOMS AND ITS IMPACT ON PATIENTS' QUALITY OF LIFE

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DEDICATION

It is with my profound gratitude and warmest affection that I dedicate this thesis to my parents (Prof. Dr. Khalid Hussain and Fahmida Kausar) and siblings (Dr. Naureen Shehzadi and M. Ehsan Khalid) for being a constant source of knowledge and inspiration

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LIST OF ABBREVIATIONS

AGFI	Average goodness of fit index
AHK	Amer Hayat Khan
AHT	Antihypertensive
ATC	Anatomical Therapeutic Chemical
AUA-SI	American Urological Association-Symptom Index
BPH	Benign prostatic hyperplasia
CABS	Coronary arteries bypass surgery
CCB	Calcium channel blockers
CESD	Center for Epidemiologic Studies Depression Scale
CFA	Confirmatory factor analysis
CI	Confidence interval
CVD	Cardiovascular disease
DHP	Dihydropyridines
EFA	Exploratory factor analysis
EQ-5D-3L	European Quality of Life-5 Dimension-3 Likert Scale
GFI	Goodness of fit index
HR	Hazards ratio
IBM	International Business Machine Cooperation
ICC	Intra-class correlation
ICS	International Continence Society
IIEF	International Index of Erectile function
IPSS	International Prostate Symptom Score
IPSS-Urdu	International Prostate Symptom Score-Urdu

JSEQ	Jenkins Sleep Evaluation Questionnaire
KH	Khalid Hussain
KMO	Keyser-Meyer-Olkin
LUTS	Lower urinary tract symptoms
NDHP	Non-dihydropyridines
NFI	Normed fit index
NOS	Newcastle-Ottawa-Scale
NR	Not reported
NS	Naureen Shehzadi
NY	New York
OAB-V8	8-item Overactive Bladder Questionnaire
OR	Odds ratio
PPBC	Patient perception of bladder condition
PRISMA	Providing Innovative Service and Assessment
QOL	Quality of life
RAAS	Renin-angiotensin-aldosterone-system
SciELO	Scientific Electronic Library Online
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TURP	Transurethral resection of prostate
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

KESAN PENGHALANG SALURAN KALSIUM DAN AGEN ANTIHIPERTENSI LAIN TERHADAP SIMPTOM TREK URINARI BAWAH SERTA IMPAKNYA TERHADAP KUALITI HIDUP PESAKIT

ABSTRAK

Simptom trek urinari bahagian bawah (LUTS) merangkumi semua gejala urologi yang berkaitan dengan pembuangan air kecil, penyimpanan dan post-mikturasi, yang dikaitkan dengan gangguan emosi yang hebat kepada pesakit dan beban ekonomi yang tinggi kepada masyarakat. Penghasilan LUTS adalah berkaitan dengan ubat-ubatan dan penyakit tertentu. Penghalang saluran kalsium (CCB) dipercayai terlibat dalam penghasilan atau keterukkan LUTS, namun maklumat mengenai korelasi itu jarang ditemui. Oleh itu, kajian ini direka untuk meneliti kesan CCBs pada LUTS dan kesannya terhadap corak tidur, kemurungan dan kualiti hidup pesakit (QOL). Kajian ini dijalankan dalam 2 fasa; Fasa-I termasuk kajian pengesahan psikometrik di mana Skor dalam bahasa Urdu tentang simptom prostate di peringkat antarabangsa (IPSS-Urdu) dibangun dan divalidasikan manakala Fasa-II adalah kajian rentas keratan untuk menilai kesan CCB mono- dan terapi gabungan pada LUTS. IPSS-Urdu dibangunkan melalui terjemahan dua langkah ke depan dan belakang, dan dinilai untuk sifat psikometriknya dalam kajian prospektif yang melibatkan pesakit (n = 267) yang menderita LUTS, yang dijalankan di Jabatan Urologi Pesakit Luar, Hospital Mayo, Lahore, Pakistan. Kebolehpercayaan keseluruhan IPSS-Urdu adalah memuaskan [Cronbach's alpha = 0.72, Koefisien Korelasi Intra Kelas (ICC) of simptom-soalan = 0.92 dan ICC QOL-indeks = 0.75]. Analisis faktor eksplorasi menunjukkan bahawa dua faktor adalah konsisten, yang bersama-sama menjelaskan 59.8% varians. Analisis faktor konfirmator seterusnya menunjukkan model dua faktor, dengan pola pemasangan yang boleh diterima. Hasil-hasil yang disebutkan di

atas menunjukkan kebolehpercayaan, konvergen, dan kebolehulangan yang baik dan keberhasilan IPSS-Urdu. Fasa-II, kajian rentas keratan, dijalankan di 2 farmasi masyarakat dan satu hospital (Institut Kardiologi Punjab) di Lahore, Pakistan. Versi Bahasa Urdu IPSS, Jenkins Sleep Evaluation Questionnaire, Pusat Pengajian Epidemiologi Kajian Skala Kemurungan Pendek dan EQ-5D-3L digunakan untuk menilai LUTS, gangguan tidur, kemurungan dan QOL. Kelaziman keseluruhan LUTS adalah 74.9% (ringan 25.1%, sederhana 49% dan LUTS teruk 25.9%). Tidak terdapat perbezaan yang signifikan dalam skor IPSS antara dihydropyridine dan pengguna bukan-dihydropyridine (54.50 vs 48.88, $p = 0.402$). Skor IPSS adalah jauh lebih rendah dalam kalangan pengguna monoterapi CCB daripada pesakit yang mengambil CCB dengan penghalang beta (79.81 vs 106.54, $p = 0.001$), serta CCB dengan penghalang beta dan diuretik (62.25 vs 94.12, $p < 0.001$). Sekitar 33% pesakit dilaporkan mengalami masalah tidur yang kerap. Selepas penyesuaian pelbagai, polifarmasi, skor CESD dan LUTS didapati mempunyai perkaitan kemungkinan gangguan tidur yang lebih tinggi. Kelaziman kemurungan dalam kalangan peserta kajian adalah 67.6% dan LUTS, gangguan tidur dan penyakit kardiovaskular adalah peramal positif yang signifikan. Selain itu, pesakit dengan LUTS penting secara klinikal melaporkan kualiti hidup yang jauh lebih teruk dalam semua dimensi EQ-5D-3L jika dibandingtan dengan mereka yang mengalami LUTS yang ringan. Sebagai kesimpulan, penemuan kajian semasa memperkukuhkan hubungkait CCB dan agen antihipertensi lain dengan gejala kencing dan kesannya mampu menyebabkan impak yang teruk pada corak tidur pesakit dan QOL.

EFFECT OF CALCIUM CHANNEL BLOCKER WITH OTHER ANTIHYPERTENSIVE AGENTS ON LOWER URINARY TRACT SYMPTOMS AND ITS IMPACT ON PATIENT'S QUALITY OF LIFE

ABSTRACT

Lower urinary tract symptoms (LUTS) include all urological symptoms related to voiding, storage and post-micturition, which are associated with great emotional distress to sufferers and high economic burden to the society. The development of LUTS is deemed to be associated with certain medications and diseases. Among the former, calcium channel blockers (CCBs) are believed to be involved in development or worsening of LUTS, however, information concerning such correlation is sparse. Therefore, the present study was designed to investigate the effects of CCBs on LUTS and its impact on patients' sleep pattern, depression and quality of life (QOL). This study was carried out in 2 phases; Phase-I included a psychometric validation study wherein the International Prostate Symptom Score-Urdu (IPSS-Urdu) was developed and validated, whereas Phase-II was a cross-sectional study to evaluate the effect of CCB mono- and combined-therapy on LUTS. IPSS-Urdu was developed by a two-step forward and back translation, and evaluated for its psychometric properties in a prospective study involving patients (n = 267) suffering from LUTS, conducted at the Outpatient Urology Department, Mayo Hospital, Lahore, Pakistan. Overall reliability of IPSS-Urdu was satisfactory [Cronbach's alpha = 0.72, Intra-Class Correlation Coefficient (ICC) of symptom-questions = 0.92 and ICC of QOL index = 0.75]. Exploratory factor analysis revealed that two factors were consistent, which together explained 59.8% of the variance. Confirmatory factor analysis further showed two-factor model, with acceptable fitting patterns. The aforementioned results indicated good discriminant, convergent, and

constructive validity and reproducibility of the IPSS-Urdu. Phase-II, a cross-sectional study, was conducted at 2 community pharmacies and one hospital (Punjab Institute of Cardiology) at Lahore, Pakistan. Urdu versions of IPSS, Jenkins Sleep Evaluation Questionnaire, Center for Epidemiologic Studies Short Depression Scale and EQ-5D-3L were used to assess LUTS, sleep disturbances, depression and QOL, respectively. Overall prevalence of LUTS was 74.9% (mild 25.1%, moderate 49.0% and severe LUTS 25.9%). There was no significant difference in IPSS score between dihydropyridine and non-dihydropyridine-users ($p = 0.402$) IPSS score was significantly lower among CCB monotherapy users than patients on CCB plus beta-blockers (79.81 vs 106.54, $p = 0.001$) and CCB plus beta-blockers and diuretics (62.25 vs 94.12, $p < 0.001$). Around 33% patients reported having frequent sleep problems. After multivariable adjustment, polypharmacy, CESD score ≥ 10 and LUTS were found to be associated with higher odds of sleeping disturbances. The prevalence of depression among study participants was 67.6% and LUTS, sleep disturbances and cardiovascular disease were its significant positive predictors. Moreover, patients with clinically significant LUTS reported significantly worse quality of life in all dimensions of EQ-5D-3L as compared to those with mild LUTS. In conclusion, findings of the current study further strengthen the association of CCB and other antihypertensive agents with urinary symptoms and its deleterious impact on patients sleep and QOL.

CHAPTER 1

INTRODUCTION

1.1 Urinary tract

Urinary tract is comprised of two components, upper and lower urinary tract, that are mutually dependent. Upper urinary tract includes kidneys and ureter while bladder and urethra are parts of lower urinary tract. This provides an intricate system of conduits that converts perpetual involuntary urine production by the kidneys into the voluntarily controlled elimination of urine under the right circumstances [1].

1.2 Lower urinary tract

1.2.1 Bladder

It is a hollow muscle-organ that plays key role in collection and storage of urine, and voiding at a right time and in a right place [1, 2]. It is tetrahedral when unfilled and oval-shaped after filling. The bladder apex is attached to the abdominal wall by urachus [3]. It consists of two main parts; the bladder body, situated above the two ureteric orifices, and the base, consisting bladder wall, trigone, deep detrusor and urethrovesicular junction [2]. Histologically, the bladder is formed of three layers; an adventitia (connective tissue layer), a middle smooth muscle layer known as detrusor urinae muscle, and urothelium (innermost layer) that provides an elastic barrier impervious to urine [1]. Detrusor urinae muscle is under the control of autonomic nervous system. Detrusor muscle is abundantly innervated with the following nerves [1]:

- Predominant population consisting cholinergic nerves (parasympathetic) that provide motor control of detrusor urinae muscle by releasing acetylcholine

- Sympathetic innervation which is present in high concentration towards the base and are very important in controlling the vasculature
- Third population is non-adrenergic-non-cholinergic sensorimotor nerves and their role in controlling urinary bladder is unclear

1.2.2 Urethra

It is a fibromuscular tube that spans from bladder to the urinary meatus. It is 13-20 cm long in males and is divided into three parts [3]:

- Prostatic urethra
- Membranous urethra
- Spongy or penile urethra

In females, it is 3.8-5.1 cm long and is extended from the bladder neck to the external urethral orifice [3].

1.2.3 Urination process

The urination cycle involves two different phases: storage phase and voiding phase [4]. During storage phase, the distensible properties of the urinary bladder let it increase its volume with slight alteration in intravesical pressures. Moreover, there is an inhibition of bladder contractions and increased resistance of bladder outlet due to the activation of smooth muscles by spinal sympathetic reflexes [5]. Resistance of bladder neck also increases due to an increased activity of external urethral-sphincter through a guarding reflex [6].

When the bladder is filled with urine, afferent signals from increased volume, tension, and nociceptive receptors are sent via pudendal and pelvic nerves to the sacral spinal cord [5]. From the spinal cord, these signals travel to the pontine micturition center. After processing these signals, voiding reflex is initiated from the brain. The efferent activity that follows produce craniosacral outflow and inhibit both sympathetic and somatic pathways. Consequently, the external urethral-sphincter relaxes and a synchronized bladder contraction causes disposal of urine [5, 7].

1.3 Lower urinary tract symptoms (LUTS)

1.3.1 LUTS terminology

Historically, a number of pseudo-diagnostic terms were used to describe urinary symptoms in men namely ―prostatism", ―symptoms of benign prostatic hyperplasia", and ―clinical benign prostatic hyperplasia". In early nineties, Paul Abrams coined the term ―lower urinary tract symptoms" (LUTS) to label patient complaints without implying their cause [8].

1.3.2 Classification of LUTS

As per the International continence Society guidelines shown in Table 1.1, LUTS are divided into three categories of symptoms: voiding, storage and post-micturition symptoms [9]. Firstly, voiding symptoms are experienced during voiding phase of bladder and include weak stream, splitting or spraying, intermittent stream, hesitancy, straining and terminal dribble. Secondly, storage symptoms are experienced during filling phase and include increased daytime frequency, nocturia, urinary urgency and urinary incontinence. Lastly, post-voiding symptoms are experienced right after

micturition and include post-voiding dribble and sensation of incomplete bladder emptying. This corroborates well with an earlier classification suggested by Wein [4, 10] who suggested that urinary disorders would be more elegantly characterized as ―failure to store" or ―failure to empty." These urinary symptoms are progressive, age-related, non-gender-specific and non-organ-specific [11].

Table 1.1: Classification of lower urinary tract symptoms as recommended by the International Continence Society

Classification	Individual symptoms	Description
Storage symptoms	**Increased daytime frequency**	It is the complaint by the patient who considers that he/she voids too often by day
	Urgency	It is the complaint of a sudden strong desire to pass urine which is difficult to defer
	Nocturia	It is the complaint that the individual has to wake at night one or more times to void
	Urinary incontinence	It is the complaint of any involuntary leakage of urine
	Stress urinary incontinence	It is the complaint of involuntary urination on effort or exertion, or on sneezing or coughing
	Urge urinary incontinence	It is the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency. It can present in various symptomatic forms; such as frequent small losses between micturitions or as a terrible leak with complete bladder emptying
	Mixed urinary incontinence	It is the complaint of involuntary loss of urine associated with urgency and also with exertion, effort, sneezing or coughing
	Enuresis	Any involuntary loss/leakage of urine. However, if patient complains loss of urine occurring during sleep then it should be labeled as nocturnal enuresis
	Continuous urinary incontinence	It is the complaint of continuous leakage of urine
	Other types of urinary incontinence	Urinary incontinence that may be situational e.g. incontinence during sexual intercourse or giggle incontinence
	Bladder sensation	It is defined by five categories; ***Normal:*** individual is fully aware of bladder filling and increasing sensation up to a strong desire to void ***Increased:*** individual feels an early and persistent need to void ***Decreased:*** individual is aware of bladder filling but does not feel the need to void ***Absent:*** individual reports no feeling of bladder filling or desire to void ***Non-specific:*** individual reports no specific bladder sensation but may recognize bladder filling as abdominal fullness, vegetative symptoms, or spasticity.

Table 1.1: Continued...

Classification	Individual symptoms	Description
Voiding symptoms	**Weak stream**	It is described by the individual as his/her perception of decreased urine flow, generally compared to previous performance or in contrast to other individuals.
	Splitting or spraying	It is described by the individual as urine splitting into two or more streams or spraying of urinary stream
	Intermittency	It is described by the individual as urine flow which stops and starts, on one or more occasions, during urination
	Hesitancy	It is described by the individual as difficulty starting micturition resulting in a delay in the onset of voiding after the individual is ready to urinate
	Straining	It is described by the individual as muscular effort exerted to start, maintain or improve the urinary stream.
	Terminal dribbling	It is described by the individual as prolonged last part of urination, when the flow has slowed to a trickle/dribble
Post micturition symptoms	**Sensation of incomplete emptying**	It is a self-explanatory term for a sensation experienced by the individual after passing urine
	Post micturition dribbling	It is described by the individual as an involuntary loss of urine immediately after he/she has finished passing urine, commonly after leaving the toilet in males, or after rising from the toilet in females

Adapted from Abrams et al. [9]

1.4 Epidemiology of LUTS

The prevalence rates of LUTS in different regions of the world are presented in Table 1.2. Majority of the studies were conducted among men aged 40 years or older and either used the International Prostate Symptom Score (IPSS) or American Urological Association-Symptom Index (AUA-SI) to estimate the prevalence of LUTS. The overall prevalence of LUTS ranges from 19.4 to 30% in North and South America [12-16]. Guess et al. compared the prevalence of LUTS between Minnesota and Scottish men and found out that Minnesota men had higher symptom frequency and symptom bother scores [14]. Moreover, individuals at both study locations reported dribbling as the most common and bothersome symptom followed by the urgency to urinate.

Estimated overall prevalence of LUTS in European nations ranges between 14-30% [17-24] whereas it has been reported to be 25-30% in Turkey [25-27]. In Asian countries, the lowest (6.3%) prevalence was reported in Malaysians [28]. Chapple et al. reported that 61% of their study participants fulfilled the criteria for LUTS in their study (South Korea: 68.2, China: 59.0 and Taiwan: 58.5%) [29]. Multi-national study of Boyle et al. revealed that 16.2 and 19.9% of Korean men and women had LUTS [17]. Moreover, they also showed that the prevalence of LUTS did not differ much in European and Asian individuals. Data from the New Zealand and Australia also showed that approximately 23-26% of men and 39% of women had LUTS [31, 32].

Table 1.2: Epidemiology of lower urinary tract symptoms around the globe

Author (s) [Ref.]	Country	Study design	Study population	Research instrument (s)	Prevalence of LUTS
Meigs et al. [12]	USA	Population-based Cohort study	N = 1019 men, age 40-70 years	Self-designed questions to assess clinical BPH	Prevalence of clinical BPH was 19.4%.
Joseph et al. [13]	USA	Population-based study	N = 708 African-American men, age 40-79 years	AUA-SI	Overall = 29.7% (moderate: 25.9% and severe: 3.8%)
Guess et al. [14]	USA (Olmsted County, Minnesota) and Scotland	Community-based survey	N = 2119 Minnesota men and 1385 Scottish men, age 40-79 years	Self-designed questionnaire identical to AUA-SI	Overall = NR, Men at both study sites reported dribbling as the most common and bother symptoms followed by urgency
Norman et al. [15]	Canada	NR	N = 508 men, age ≥ 50 years	Telephonic interview having questions similar to AUA-SI	Overall = 23%
Moreira Jr et al. [16]	Brazil	Cross-sectional, population-based survey	N = 3000 (M: 1500, F: 1500), age ≥ 30 years	Self-designed questionnaire including items from IPSS, OAB-V8, PPBC	Overall = NR, Prevalence of any LUTS was 81.5 and 84.1 % in male and females, respectively

AUA-SI = American Urological Association Symptom Index; BPH = Benign prostatic hyperplasia; IPSS = International prostate symptom score; LUTS = Lower urinary tract symptoms; NR = Not reported; OAB-V8 = 8-item overactive bladder questionnaire; PPBC = Patient perception of bladder condition; USA = United States of America

Table 1.2: Continued...

Author (s) [Ref.]	Country	Study design	Study population	Research instrument (s)	Prevalence of LUTS
Boyle et al. [17]	The Netherlands, France, UK, Republic of Korea	Population-based, cross-sectional survey	N = 8769 (M:4979, F:3790), age 40-79 years	IPSS	Overall LUTS in males and females, respectively Netherlands = 20.7 and 18% France = 19.2 and 12.6% UK = 25.1 and 23.7% Republic of Korea = 16.2 and 19.9%
Bosch et al. [18]	The Netherlands	Community-based, randomized pilot study	N = 502 men, age 55-74 years	IPSS	Overall = 30% (moderate: 24% and severe 6%)
Andersson et al. [19]	Sweden	Population-based prospective cohort study	N = 40,000 men, age 40-79 years	IPSS	Overall = 23%
Seim et al. [20]	Norway	Population-based study	N = 21964 men, age ≥ 20 years	IPSS	Overall = 15.8% (moderate: 13.2% and severe: 2.6%)
Haidinger et al. [21]	Austria	Population-based cross-sectional study	N = 2400 men, age 15-89 years	IPSS	Overall = 16.9%
Norby et al. [22]	Denmark	Population-based study	N = 5379 (M:4952 and F:427)	IPSS	Overall = 28% for males and 20% for females
Rohrman et al. [23]	Switzerland	Cohort study	N = 8627 men, age 35-75 years	IPSS	Overall = 24.7% (moderate: 22% and severe: 2.7%)

IPSS = International prostate symptom score; LUTS = Lower urinary tract symptoms; UK = United Kingdom

Table 1.2: Continued...

Author (s) [Ref.]	Country	Study design	Study population	Research instrument (s)	Prevalence of LUTS
Sagnier et al. [24]	France	Community-based nationwide study	N = 2011 men, age 50-80 years	AUA-SI	Overall = 14.2% (moderate: 13% and severe: 1.2%)
Zumrutbas et al. [25]	Turkey	Cross-sectional population-based survey	N = 1555 (M:636 and F:919), age ≥ 18 years	Self-designed questionnaire using ICS definition to assess LUTS	Overall =NR, Prevalence of voiding, storage and post-viding symptoms were 39.3, 56.1 and 30.7%, respectively.
Aki et al. [26]	Turkey	Cross-sectional study	N = 266 men, age ≥ 40 years	IPSS	Overall = 24.9% (moderate: 21.4% and severe: 3.5%)
Ulock et al. [27]	Turkey	Population-based cross-sectional study	N = 754 men, age ≥ 40 years	IPSS	Overall = 30% (moderate: 24% and severe: 10%)
Mariappan et al. [28]	Malaysia	Cross-sectional population-based survey	N = 353 men, age ≥ 40 years	AUA-SI and IIEF	Overall = 6.3% (moderate: 6.0% and severe: 0.3%)
Chapple et al. [29]	China, Taiwan and South Korea	Cross-sectional population-based study	N = 8284 (M: F:), age ≥ 40 years	IPSS and other ICS symptom questions	Overall = 61% (South Korea: 68.2, China: 59.0 and Taiwan: 58.5%)

AUA-SI = American Urological Association Symptom Index; ICS = International continence Society; IIEF = International index of erectile function; IPSS = International prostate symptom score; LUTS = Lower urinary tract symptoms; NR = Not reported

Table 1.2: Continued...

Author (s) [Ref.]	Country	Study design	Study population	Research instrument (s)	Prevalence of LUTS
Tsukamoto et al. [30]	Japan	NR	N = 289 men, age 40-79 years	Questionnaire worded similarly to IPSS	Overall = NR, the frequency of individuals in IPSS categories (mild, moderate and severe) increased significantly with age.
Pinnock et al. [31]	Australia	Interview-based prevalence survey	N = 2890 (M: 1204 and F: 1686), age ≥ 18 years	IPSS	Overall =NR, Prevalence of ≥ 1 troublesome LUTS was 26% for men and 39% for women.
Nacey et al. [32]	New Zealand	NR	N = 495 men, age ≥ 40 years	IPSS	Overall = 23% (mild: 381, moderate: 89 and severe 25 men)

IPSS = International prostate symptom score; LUTS = Lower urinary tract symptoms; NR = Not reported

1.5 Factors associated with LUTS

Published data advocate that increasing age [12-32], geographical differences [33], level of education [33-37], working status [35], smoking [13, 33, 37-41], alcohol consumption [13, 21] diet [33, 40, 41] and obesity [32] are contributory factors of LUTS. High total energy and sodium intake increases the likelihood of LUTS. Total fat (saturated or monounsaturated) or carbohydrate intake do not impact LUTS. However, increased protein intake decrease the likelihood of LUTS [40]. Maserejian et al. reported that greater consumption of dietary lycopene, β-carotene, total carotenoid, or vitamin A decreased likelihood of LUTS whereas vitamin C had positive association with LUTS [41].

Apart from afore-mentioned factors, medical diseases and conditions such as autoimmune diseases, diabetes, hypertension, renal impairment, persistent cough, constipation, chronic obstructive pulmonary disease, chronic heart failure, sleep apnea, spinal injuries, spondylitis, and neurological and psychiatric diseases cause lower urinary tract dysfunction [42, 43]. In addition, men may suffer LUTS due to prostatitis, benign prostatic hyperplasia or prostate cancer whereas females due to childbirth or as a consequence of post-menopausal urogenital changes [44]. Moreover, surgeries or operations such as simple hysterectomy, radical hysterectomy, ovarian and prolapse surgeries can precipitate or exacerbate LUTS [45].

Several medications can also precipitate or worsen LUTS through effects on bladder detrusor muscles and urinary sphincter function [46, 47]. The use of antihypertensive medications (diuretics, calcium channel blocker, angiotensin converting enzyme inhibitors, and alpha-blockers), antidepressants, anti-psychotics, sedative/hypnotics,

anti-Parkinson drugs, anti-dementia drugs, decongestants and antiallergics, antihistamines, non-steroidal anti-inflammatory drugs, bronchodilators, sympathomimetic, anticholinergics, drugs for acid-related disorders, antiarrhythmics (class 1 and 3), cardiac stimulants (excluding cardiac glycosides) and opioids have all been implicated to some extent in the onset or aggravation of LUTS [44, 48-66]. Effects of several medications that can contribute to urinary symptoms, particularly urinary incontinence, are shown in Table 1.3.

Table 1.3: Effect of several medications on the lower urinary tract of frail elderly persons

Medications	Effects
Alpha agonists	Increase smooth muscle tone in urethra and prostatic capsule and may precipitate obstruction, urinary retention, and related Symptoms
Alpha blockers	Decrease smooth muscle tone in the urethra and may precipitate stress urinary incontinence
Angiotensin converting enzyme inhibitors	Cause cough that can exacerbate urinary incontinence
Anticholinergics	May cause impaired emptying, urinary retention, and constipation that can contribute to UI. It may also cause cognitive impairment and reduce effective toileting ability
Calcium antagonists	May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May also cause dependent edema which can contribute to nocturnal polyuria
Cholinesterase inhibitors	Increase bladder contractility and may precipitate urgency urinary incontinence
Diuretics	Cause diuresis and precipitate urinary incontinence
Lithium	Polyuria due to diabetes insipidus
Opioids	May cause urinary retention, constipation, confusion, and immobility, all of which can contribute to urinary incontinence
Psychotropic drugs	
Sedatives Hypnotics Antipsychotics	May cause confusion and impaired mobility and precipitate urinary incontinence Anticholinergic effects
Histamine 1 receptor antagonists	Confusion
Selective serotonin reuptake inhibitors	Increase cholinergic transmission and may lead to urinary incontinence
Miscellaneous	
Gabapentin Glitazones Nonsteroidal anti-inflammatory drugs	Can cause edema, which can lead to nocturnal polyuria and cause nocturia and nocturnal incontinence

Adapted from Dubeau et al. [43]

1.6 Impact of LUTS on patients and society

LUTS are known to be associated with great emotional burden to people [67] as well as high economic burden to the society [68-70].

1.6.1 Impact on patients' quality of life

Published literature shows that LUTS cause significant reduction in quality of life (physical health, psychological health, vitality and social relationships). A cross-sectional survey of Turkish men aged ≥ 50 (N = 450) reported significantly less mean scores in all dimensions (physical functions, physical role, bodily pain, general health perceptions, vitality, emotional role, mental health and social functions) of Short-Form 36 health-related QOL scale among individuals suffering from moderate or severe LUTS than those with none-mild urinary symptoms [37]. Similarly, Welch et al. [71] reported that increased LUTS severity from the none-mild through to the severe LUTS displayed a strong dose-related influence of LUTS severity on all eight dimensions of Short-Form 36 health-related QOL scale. Pintarelli et al. [72] used World Health Organization-QOL (WHOQOL) scale to assess the QOL among individuals (aged ≥ 65) with moderate-severe and none-mild LUTS. They reported that individuals having moderate or severe LUTS had significantly worse mean scores in all domains of WHOQOL-Bref scale (physical health, psychological health, social relationships and environment) than those with no or mild LUTS. Using International Prostate Symptom Score-QOL index, Foucade et al. [73] revealed a significant impact of LUTS on individuals' QOL. Only 10% of their study participants claimed they would be satisfied if they had to spent rest of their lives with their present urinary state.

1.6.2 Economical burden

A study conducted in 6 European nations (Germany, France, Italy, Poland, Spain and the UK) to evaluate the medical consumption associated with LUTS suggestive of BPH and its treatment expenditures reported that the mean annual treatment costs per patient were €858 [69]. Pharmacotherapy was the most significant cost driver, accounting for approximately three quarters of total treatment expenditure. Surgery/operation and diagnostic testing accounted for 15 and 8% of total costs, respectively. Moreover, annual treatment costs for patients with mild, moderate and severe obstructive symptoms were €673, €906 and €960, respectively ($p < 0.001$). For patients with mild, moderate and severe irritative symptoms, mean annual treatment costs were €623, €865 and €1,043, respectively ($p < .001$) Another pharmacoeconomic study conducted in Spain reported that mean annual cost of diagnostic testing and clinical visits of mild, moderate and severe BPH-related LUTS were €124, €207, and €286 per patient, respectively [70]. These findings demonstrate the enormous economic burden of LUTS not only on patients and their families but also on healthcare system.

1.7 Problem statement

Around 40% of adults aged 25 years and above suffer from hypertension across the globe [74]. Calcium channel blockers (CCBs) are among the most commonly used agents for the treatment of hypertension, arrhythmias and angina pectoris [75]. The Eighth Joint National Committee (JNC-8) recommended the use of either thiazide-type diuretics or CCBs or angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers as the preferred first line therapy for the treatment of hypertension [76].

CCBs can precipitate or exacerbate voiding, storage and post-voiding urinary symptoms due to their natriuretic and diuretic properties [77-84], anticholinergic activity (Nifedipine) [85, 86], and inhibition of bladder contraction by blocking L-type voltage-dependent calcium channels in the detrusor muscles [87-90]. Urinary symptoms can lead to decreased quality and quantity of sleep [91], depression [92], and a significant reduction in patient‘s QOL [37, 69-71].

Despite CCB‘s widespread use to treat various cardiovascular diseases worldwide, there is limited data concerning the association of these agents with urinary symptoms (Table 2.3 in chapter 2). Additionally, due to the advancement in medical research, many new medications containing CCBs combinations with other antihypertensive agents and lipid lowering agents are available in the drug market. This justified further investigation to explore the effect of CCB mono- and combined therapy with other antihypertensive agents on LUTS.

1.8 Research objectives

The objectives of the current study were as follows;

1. To translate and validate the international prostate symptom score into Urdu language.
2. To evaluate LUTS among CCB mono- and combined therapy users and determine the factors associated with moderate-severe and severe LUTS.
3. To assess the association of LUTS with sleep disturbances and depression among CCB-users.
4. To assess the impact of urinary symptoms on patients‘ health-related quality of life.

1.9 Significance of the study

This study will provide much needed insight on the association of CCB with LUTS and reveal the burden of urinary symptoms among CCB-users. In addition, a validated Urdu instrument/questionnaire to measure urinary symptoms will be developed in this study. It will be a part of scientific literature and therefore assist the future investigators regarding the involvement of CCB therapy in the development or worsening of LUTS and its impact on patients‘ sleep, depression and health-related QOL.

1.10 Conceptual frame work

Conceptual frame work of Phase-I (psychometric validation study) and Phase-II (cross-sectional study) are illustrated in Figure 1.1 and 1.2, respectively. A valid and reliable instrument (International prostate symptom score-Urdu) to assess the frequency and severity of urinary symptoms among Urdu-speaking population was developed in the Phase-I. This validated instrument was used to evaluate the effect of CCB mono- and combined therapy with other antihypertensive agents on urinary symptoms in Phase-II.

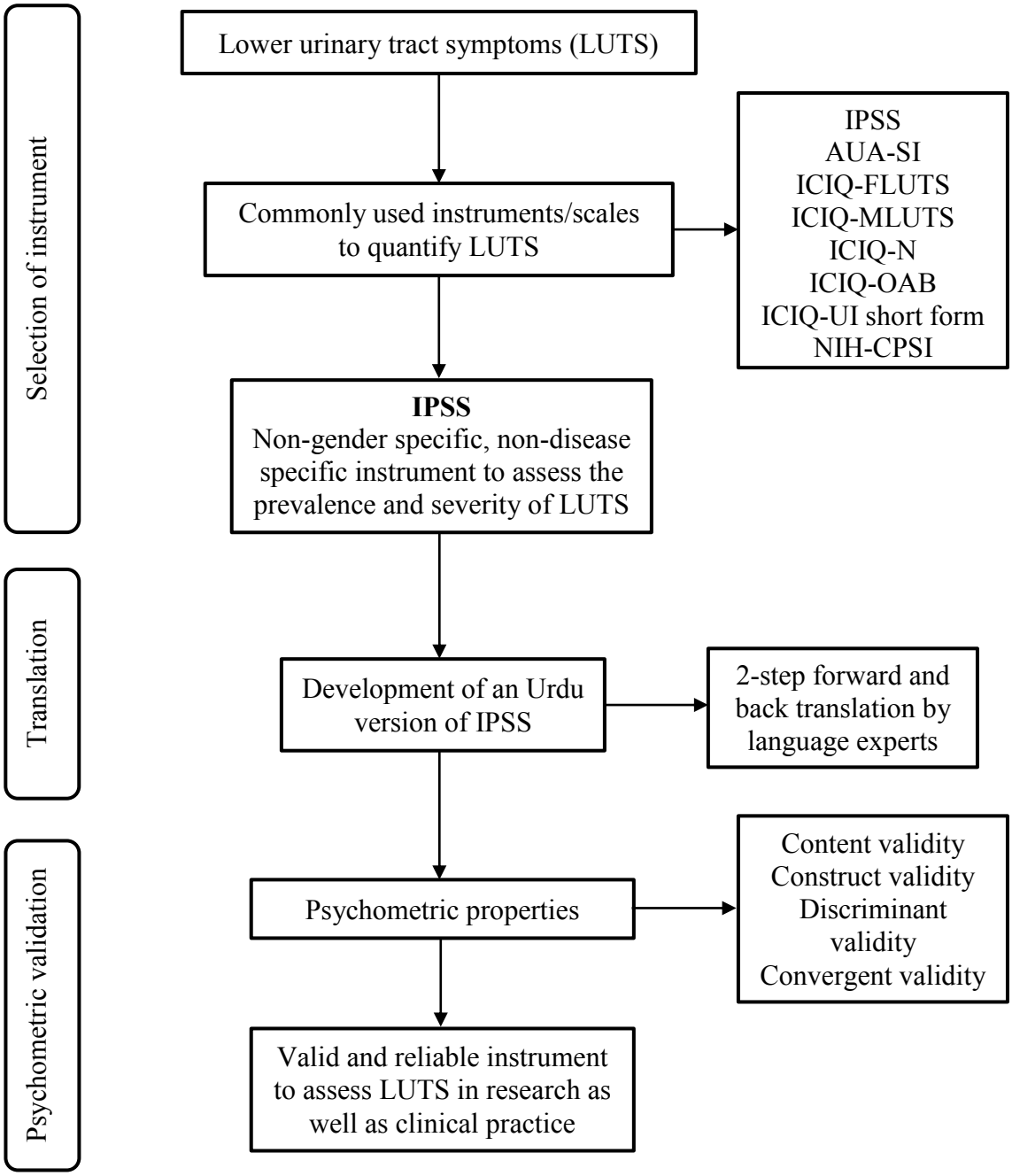

Figure 1.1: Conceptual framework of psychometric validation study (Phase-I)

Abbreviations: AUA-SI = American Urological Association Symptom Index; NIH-CPSI = National Institute of Health Chronic Prostatitis Symptom Index; ICIQ-MLUTS = International Consultation on Incontinence Modulation Questionnaire-Male Lower Urinary Tract Symptoms; ICIQ-FLUTS = International Consultation on Incontinence Modulation Questionnaire-Female Lower Urinary Tract Symptoms; ICIQ-N = International Consultation on Incontinence Modulation Questionnaire-Nocturia; ICIQ-OAB = International Consultation on Incontinence Modulation Questionnaire-Overactive bladder; IPSS-International Prostate Symptom score

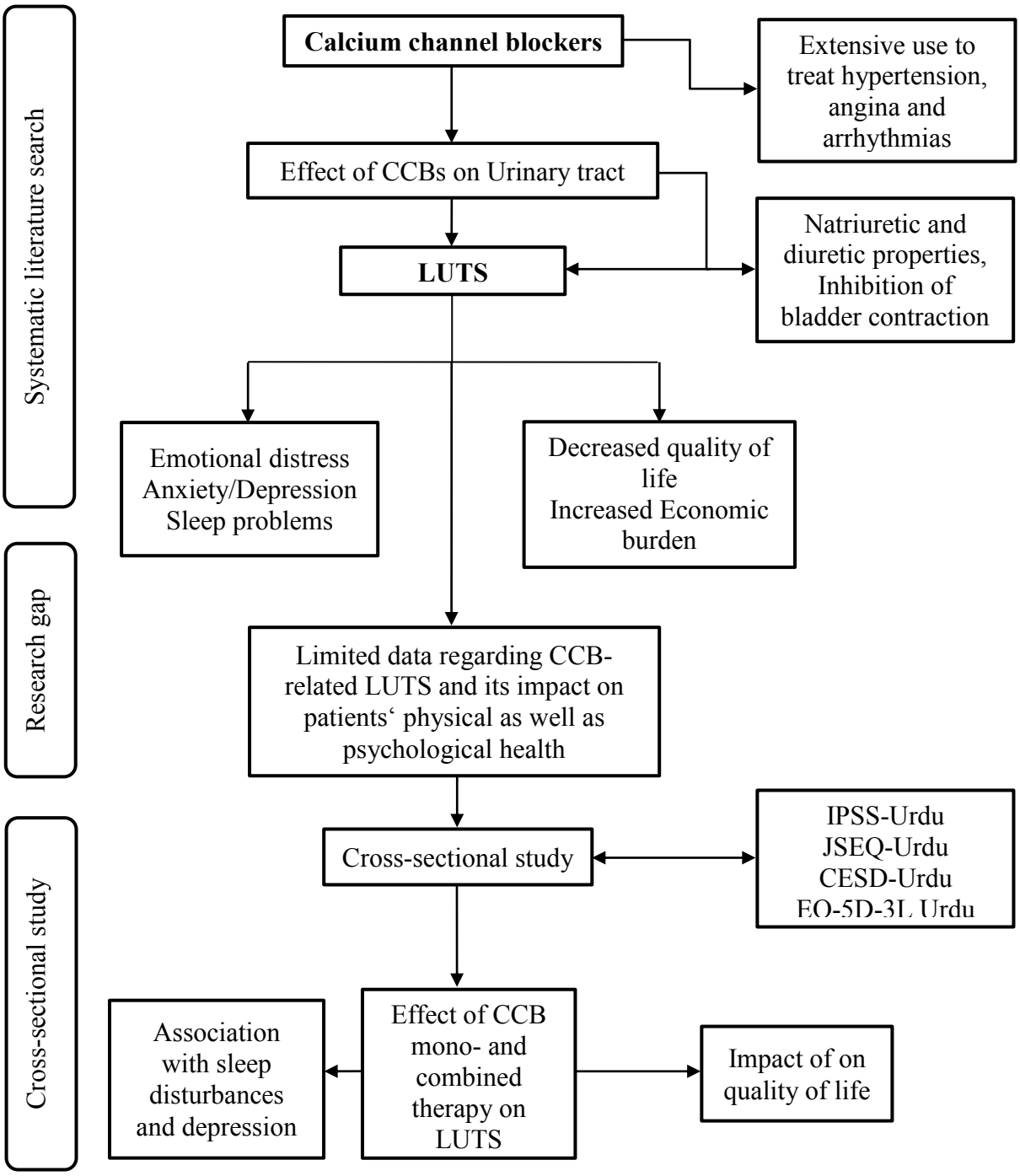

Figure 1.2: Conceptual framework of cross-sectional study (Phase-II)

Abbreviations: CCB = calcium channel blockers; CCB = calcium channel blockers; CESD = Center for Epidemiologic Studies Short Depression Scale LUTS = lower urinary tract symptoms; IPSS-International Prostate Symptom score; JSEQ = Jenkins Sleep Evaluation Questionnaire

CHAPTER 2

SYSTEMATIC LITERATURE REVIEW

2.1 Background

2.1.1 Calcium channel blockers (CCBs)

Discovered by Albrecht Fleckenstein in 1960s [93], calcium channel blockers (CCBs) were introduced for the first time in medical practice in 1980s. These are commonly used agents for the treatment of hypertension, angina pectoris, and supraventricular arrhythmias. CCBs are a group of heterogeneous agents having distinct chemical structure and pharmacological action [75].

2.1.2 Clinical Pharmacology of CCBs

Several classifications of CCBs have been suggested since their introduction into the market. The oldest and most acknowledged classification is based upon their chemical structures. According to which CCBs are classified into three subclasses namely, benzothiazepine derivatives (e.g. diltiazem), phenylalkylamine derivatives (e.g. verapamil), and dihydropyridine deriatives (e.g. amlodipine, felodipine, nifedipine, nicardipine, lercanididpine, nimodipine, isradipine, nisoldipine etc.) [94].

Another classification system classified CCBs into three categories namely, A, B and C. Of these, class A and B block calcium-dependent excitation-contraction coupling whereas class C possess less specific, less effective on excitation-contraction coupling [95, 96]. After the identification of numerous types and sub-types of calcium channels (Table 2.1), CCBs were categorized into ―selective" or ―non-selective". Selective

CCBs act on voltage-gated L-type slow Ca2+ channels whereas nonselective on voltage-gated L-type, N-type, and P-type Ca2+ channels [97]. Toyo-Oka and Nayler proposed that CCBs be categorized into three main groups namely, 1st, 2nd and 3rd generation agents [98, 99]. This classification was based on the clinical effects of CCBs on receptor binding properties, tissue selectivity, and pharmacokinetics. Nifedipine, verapamil and diltiazem were included in the first generation CCBs. Second generation CCBs had two subclasses (class IIa and IIb). Class IIa included slow/extended release nifedipine, nicardipine, felodine, diltiazem and verapamil whereas class IIb included agents with high vascular selectivity (e.g. felodipine, israpidine, nicardipine, nimodipine etc.). Third generation class included amlodipine.

Table 2.1: Classification of voltage-gated calcium channels

Type	Voltage	Localization	Major functions	Inhibited by
L (long-lasting)	High	Mostly myocardium and smooth muscles	Muscular contractions	Verapamil, diltiazem and dihydropyridine calcium channel blockers
N (neuronal)	High	Presynaptic nerve terminals	Catecholamine release	Omega-Conotoxin GVIA
P (Purkinje)	High	Presynaptic nerve terminals, mainly in cerebellar Purkinje neurons	Neurotransmitter release	Agatoxin FTX
Q	High	Presynaptic nerve terminals	Neurotransmitter release	Agatoxin FTX
R (residual)	High	Nural tissue	Neurotransmitter release	Cadmium
T (transient)	Low	Postsynaptic nerve terminals and nodal tissue (sinoatrial, atrioventricular)	Pacemaker activity	Mifebradil

Adapted from Flynn and Pasko [97]

All afore-mentioned agents are vasodilators and their vasodilator potency differs according to subclasses, with dihydropyridine derivatives being more potent than the benzothiazepine and phenylalkylamine derivatives [94]. Dihydropyridine derivatives variably affect heart rate. Acutely, these agents tend to cause reflex tachycardia, however long-term investigations reveal similar heart rates prior and during dihydropyridine CCBs therapy. Moreover, dihydropyridine derivatives are less likely to decrease cardiac output than non-dihydropyridine CCBs. Non-dihydropyridines (verapamil and diltiazem) can reduce pulse rate by 10% and increase negative inotropic effect [94].

2.1.3 Prevalence of CCBs use

An evidenced-based guideline of JNC-8 for the treatment of high blood pressure (BP) recommends the selection among four antihypertensive medication classes (CCBs, ACEIs, ARBs and thiazide-type diuretics) as preferred Initial pharmacological therapy to treat hypertension [76]. Around 30-50% of patients are prescribed CCBs for the treatment of hypertension [100-104]. CCBs are the most commonly prescribed antihypertensive agents followed by beta-antagonists and ACEIs in Indo-Asian nations [100-102]. In Pakistan, CCBs are the most frequently used antihypertensive monotherapy (34%) whereas beta-antagonists as most frequently used combination therapy [100].

2.1.4 Side effects profile of CCBs

Side effects of CCBs depend upon the individual CCB within the subclasses, but can include nausea, headache, dizziness or light-headedness, constipation, peripheral edema, flushing, transient hypotension, bradycardia or heart block, and rash [105-107]. CCBs are also reported to be associated gastroesophageal reflux disease symptoms (e.g. heart burns, indigestion, acid reflux, chest pain, bloating, burning throat and bitter taste) by interfering with lower esophageal sphincter [108] and polyuria due to natriuresis [77].

2.1.5 CCBs and bladder function

Several mechanisms have been suggested to explain CCBs involvement in the development of urinary symptoms: (1) natriuresis and diuresis, (2) anticholinergic activity, and (3) detrusor muscle relaxation.

2.1.5(a) Natriuretic and diuretic effects

CCBs have been found to possess natriuretic and diuretic properties in acute studies conducted in both experimental animals and humans [77-84]. Zanchetti and Leonati suggested that natriuresis and diuresis associated with CCBs might be attributable to one or more of the following mechanisms: (1) an alteration in glomerular filtration rate and/or renal blood flow, (2) interference with renin secretion, (3) interference in aldosterone secretion and/or its action on distal convoluted tubules, (4) interference with adrenergic sodium handling and (5) a direct tubular action [82]. However, the most likely mechanism is diminished tubular sodium reabsorption [83]. This provides reasonable explanation of CCBs-induced storage symptoms. However, it does not provide any justification related to CCBs-related voiding symptoms.