School of Pharmacy

Calcium Antagonists-Induced Lower Urinary Tract Symptoms

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

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Abstract

Lower urinary tract symptoms (LUTS) are a group of obstructive and irritative urinary symptoms. These include storage, voiding, and post-micturition symptoms. LUTS are prevalent and bothersome in the rapidly growing ageing Australian population and they are associated with a significant deterioration in patients' quality of life (QoL). There are a number of risk factors for LUTS. These include medical conditions such as diabetes, stroke, Parkinson's disease along with some surgical procedures involving the pelvis or spinal cord. Ageing is also associated with structural and physiologic changes of the lower urinary tract which may contribute to LUTS. LUTS are often inappropriately thought of as a male only problem because of the high prevalence of benign prostatic hypertrophy (BPH) in older men; however, the development of LUTS is not gender specific and women may develop LUTS following menopause or post-hysterectomy.

A number of drugs have been found to affect the bladder and the micturition process including the commonly prescribed calcium antagonists (CAs). CAs were the ninth most frequently prescribed group of drugs in Australia in the year 2008, with more than seven million prescriptions dispensed during that year. Apart for their effects relaxing the detrusor smooth muscle hence impairing micturition, CAs can also increase the production of urine through their natriuretic effect and cause constipation through their muscle relaxation and anti-cholinergic activity, which can further exacerbate LUTS. The association between CA use and LUTS is not well investigated. The aim of this research was to investigate the association between CA use and LUTS in males and females. Further to assess the consequences of CA-associated LUTS on users' QoL and receipt of treatment for LUTS.

During the Phase 1 of this research, a review was conducted for all reports submitted to the Adverse Drug Reaction Advisory Committee (ADRAC) of Australia up until January 2009. The review revealed 80 reported cases (females 45 [56.2%], males 34

[42.5%]). The mean age of the patients was 63.4±14.1 years (range 36-99 years). Amlodipine was the most frequently reported drug and lercanidipine was the least reported. Pollakiuria and other obstructive urinary symptoms were the most commonly reported symptoms. More than half of the patients (46; 57.5%) had complete resolution of their LUTS after medication discontinuation while 10 (12.5%) patients did not recover; an outcome was not reported for the remaining 24 (30%) patients. The review highlighted the importance of including females and younger patients in future studies. Further, it also suggested that LUTS associated with CA use is reversible in the majority of cases following medication discontinuation.

A study was conducted, in Phase 2 of this research, to investigate the relationship between CA-use and LUTS amongst hospitalised medical patients at Royal Perth Hospital. The study also looked at the impact of CA-associated LUTS on patients' urological QoL. A demographic questionnaire was used along with the validated International Prostate Symptoms Score (IPSS) -for measuring LUTS- and BPH Impact Index (BII) -for measuring urinary related QoL-. A total of 278 patients (151 males, 127 females, mean age 72.1±13.7 years) were recruited into the study. About one third of the patients were using CAs. The males mean IPSS of 12.2 ± 8.19 was higher compared to that of the females (9.74 ± 6.59, $p = 0.007$), indicating significantly worse LUTS. CA-users were found to have a statistically significantly higher mean IPSS (15.22 ± 8.1) compared to non-CA-users (9.25 ± 6.6, $p < 0.0001$). CA-users were found to be more likely to suffer from severe and moderate-to-severe LUTS ($p < 0.0001$ for both).

The association between CA use and LUTS was not a class effect. A strong association emerged between amlodipine/nifedipine and diltiazem/verapamil use and severe LUTS, adjusted odds ratios (AOR) of 9.8 (95% CI, 3.98-24.34) and 8.2 (95% CI, 1.93-34.92), respectively. However, none of the patients receiving felodipine/lercanidipine suffered from severe LUTS. A similar association was also observed with moderate-to-severe LUTS.

This increased risk of suffering from moderate and/or severe LUTS was matched by a similar deterioration of QoL measured by patients' level of dissatisfaction (AOR

amlodipine/nifedipine 2.80 [95% CI, 1.68-4.68] and diltiazem/verapamil 3.65 [95% CI, 1.02-13.01]). The AOR was not statistically significant for felodipine/lercanidipine, 1.12 (95% CI, 0.47-2.67). Further, an estimated 22.4% of the CA-users group were taking medications to treat LUTS compared to 9.3% in the non-CA-users group, p = 0.003. Both male and female CA-users were three times more likely to be on an alpha-blocker than non-CA-users (p=0.0001). Male CA-users were two times more likely to have undergone urological surgeries (Fisher exact test, p=0.07) whilst female CA-users were nine times more likely (Fisher exact test, p=0.029).

In Phase 3 of the research, a prescription sequence symmetry analysis was conducted in collaboration with the Department of Veteran affairs (DVA), Australia. This method was developed to create signals of a potential adverse event of drugs. The DVA prescription database for a 5-year period (2004-2008) was used to estimate the sequence ratio and the adjusted sequence ratio (ASR). The data revealed that there was about two-fold-increase in prazosin use after the first CA commencement, ASR 1.91 (95% CI 1.69-2.17). The use of urinary antispasmodics was also higher after CA use, ASR of 1.31 (95% CI 1.15-1.49). These results present a strong signal of an association between CA use and prazosin and urinary antispasmodic use (markers for LUTS).

The final phase of the research involved an audit of dispensing records of 1,548 patients from a number of Australian residential aged care facilities (RACFs). In this study, CAs users were more likely to be on alpha blockers (as a group of drugs), AOR 2.11 (95% CI 1.05-4.26); and on prazosin, AOR 4.22 (95% CI 1.76-10.12). CA-users were also found to be more likely to be on urinary antispasmodics, AOR 2.18 (95% CI 1.32-3.61).

The research had demonstrated a strong association between CA use and LUTS. This association could lead to a significant deterioration in QoL and it does not appear to be a class effect. CA-users are more likely to have more severe LUTS and to be on a treatment for LUTS or to have undergone urological interventions.

Based on these findings it is recommended that CA-users should be monitored for the development or the deterioration of LUTS. Moreover, CAs should always be considered as a possible cause for LUTS and consideration to be given to ceasing or switching CAs.

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Communications Related to the Thesis

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   Abstract: Conference Proceedings, USANZ Annual Scientific Meeting, October 2010
3. Elhebir E, Hughes J, Hilmi S. Calcium Antagonists-Induced Lower Urinary Tract Symptoms in Medical Patients. Conference Proceedings, Federation International Pharmaceutical (FIP) 16th International Social Pharmacy Workshop, August 2010, Lisbon Portugal

   Abstract: Conference Proceedings, Pharmacy Practice Journal Vol 8, Suppl 1, August 2010:52
4. Elhebir E, Hughes J, Hilmi S. The Impact of Calcium Antagonists-Induced Lower Urinary Tract Symptoms on Quality of Life. Symposium Proceedings, Australian Society of Medical Research (ASMR) Annual Scientific Meeting, June 2010, Perth, Australia

   Abstract: Symposium Proceedings, ASMR Annual Symposium, June 2010:30
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   Abstract: Conference Proceedings, APSA Annual Scientific Meeting, December 2009
6. Elhebir E, Hughes J, Hilmi S. Calcium Antagonists-Induced Lower Urinary Tract Symptoms in Medical Patients. Conference Proceedings, Society of Hospital

Pharmacists Australia (SHPA) Annual National Scientific Conference, November 2009, Perth, Australia

Abstract: Conference Proceedings, SHPA Annual Conference, November 2009:110

7. Elhebir E, Hughes J, Hilmi S. Calcium Antagonists-Induced Lower Urinary Tract Symptoms. Symposium Proceedings, Western Australian Medication Safety Group (WAMSG) Annual Scientific Meeting, July 2009, Perth, Australia

   Abstract: Symposium Proceedings, WAMSG Annual Symposium, July 2009:10
8. Elhebir E, Hughes J, Hilmi S. Calcium Antagonists-Induced Lower Urinary Tract Symptoms. Symposium Proceedings, Australian Society of Medical Research (ASMR) Annual Scientific Meeting, June 2009, Perth, Australia

   Abstract: Symposium Proceedings, ASMR Annual Symposium, June 2009:49
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Chapter 1

1 Introduction and Objectives

1.1 Introduction

The term, lower urinary tract symptoms (LUTS), was developed to describe a group of obstructive and irritative voiding symptoms. It covers storage, voiding, and post-micturition symptoms. The LUTS term was first introduced in 1994 to distinguish urinary symptoms in males from prostatism. Now it is used broadly to describe all male/female urinary symptoms.(1) LUTS include, but are not limited to, urinary hesitancy, poor "stream", straining, frequency, incomplete bladder emptying, urgency, terminal urinary dribbling, and nocturia.

Both men and women experience different types of LUTS in a similar way as they become older. A review by Chapple et al (1) found that LUTS are very common and have the same prevalence in both men and women. However, there is a variation between males and females for individual symptoms existence. The review also revealed that LUTS include a ‘progressive, age-related, non-sex-specific, non-organ-specific group of symptoms.

Apart from their natural progression with age, LUTS can also be caused by a number other factors. Spinal injuries, spinal spondylitis, stroke, Parkinson’s disease, pelvic surgery, and diabetes are some of the factors that are known to cause LUTS in both men and women. In addition, males may develop LUTS as a result of benign prostatic hypertrophy (BPH), prostate cancer, and after trans-urethral resection of the prostate (TURP); while females may develop LUTS as a result of post-menopausal urogenital changes, after child birth, or after hysterectomy.(2) Some drugs are known to cause LUTS by affecting the bladder contraction and micturition processes. One such group of drug is the calcium antagonists (CAs) for which LUTS have been reported amongst their side effects.(3)

To our knowledge, no study has been conducted to evaluate the association between CA use and LUTS, and the impact of CA associated LUTS on the quality of life of both males and females.

1.2 Objectives and Significance

1.2.1 Objectives

The aim of this study was to determine the relationship between CA use and LUTS in Australian males and females. The secondary objective was to determine their urological consequences and their impact on QoL.

1.2.2 Significance

CAs are a class of cardiovascular medications that are used to treat hypertension and ischemic heart disease. They are commonly prescribed group of drugs in Australia and around the world. The recognition of these agents' potential role in LUTS, in both males and females, may contribute to a significant reduction in unnecessary investigations, medication use, and interventions. The findings may potentially benefit patients who are using CAs as a result of improvement of their urinary related QOL. As a result, they may result in a significant reduction in healthcare costs.

Chapter 2

2 Literature Review

2.1 Urinary Bladder's Anatomy

The urinary bladder plays an important role in storage and emptying of urine. It is a hollow, muscular organ which is covered with a peritoneal layer on the superior surface to assist in stabilising its position.(4) The urinary bladder consists of the following parts: bladder wall, trigone, detrusor muscle, internal sphincter, and external sphincter. The urinary bladder wall consists of a lining of mucosa, which forms rugae that disappears as bladder fills. The trigone is a triangular area bounded by the urethral openings and urethra entrance. The bladder lining is formed of mucosa to prevent urine absorption. The detrusor muscle is a fibre that forms the underlying muscle, runs in two different interlacing directions.(5) The smooth muscles of the bladder are involuntary, single-unit smooth muscles, which are arranged as diamond-shaped lattice.(6) Urinary bladder wall detrusor contains mucosa, sub-mucosa and muscularis layers.(4) The excretion of urine into the urethra occurs as a result of detrusor muscle contraction. The entrance of the urethra is surrounded by a group of smooth muscles, which provide involuntary control of urine, known as the internal sphincter.(4) Another group of muscles, which voluntarily control the excretion urine, exist at the urogenital diaphragm known as the external sphincter. In males the urethra passes through the prostate gland.(4)

2.1.1 Micturition Process

Urinary bladder's contraction and relaxation involve a coordinated interaction between nervous control system and structural/anatomical parts of the urinary tract.

During filling (relaxation) phase, the detrusor elongate and rearrange over a large length interval in the wall to produce the relaxation of the bladder. During micturition, a relatively fast, synchronised force generation and shortening is initiated. Specific receptors for the transmitters and modulators exist in each part of the urinary tract to ensure the adequate response to the nervous and hormonal control systems.(7)

2.2 Factors Involved in Micturition

Autonomic and somatic nerve inputs play an important role in controlling the bladder function. The autonomic input involves adrenergic (sympathetic), cholinergic (parasympathetic), and non-adrenergic-non-cholinergic (NANC) nervous control. NANC is also known as purinergic system. Although the NANC is possibly only important in disease state, animal studies have demonstrated that both cholinergic and NANC mechanisms control the bladder contraction.(8, 9) Nevertheless, the adrenergic input into the bladder contraction appears to be relatively small via alpha-adrenoceptor. Noradrenaline has a predominant effect in facilitating the relaxation of the detrusor muscle via beta-adrenoceptors. The activation of the parasympathetic input (detrusor contraction) and the inhibition of sympathetic input (detrusor relaxation) are necessary for the micturition process to occur.(7) Figure 2-1 shows the different factors involved in the micturition process.

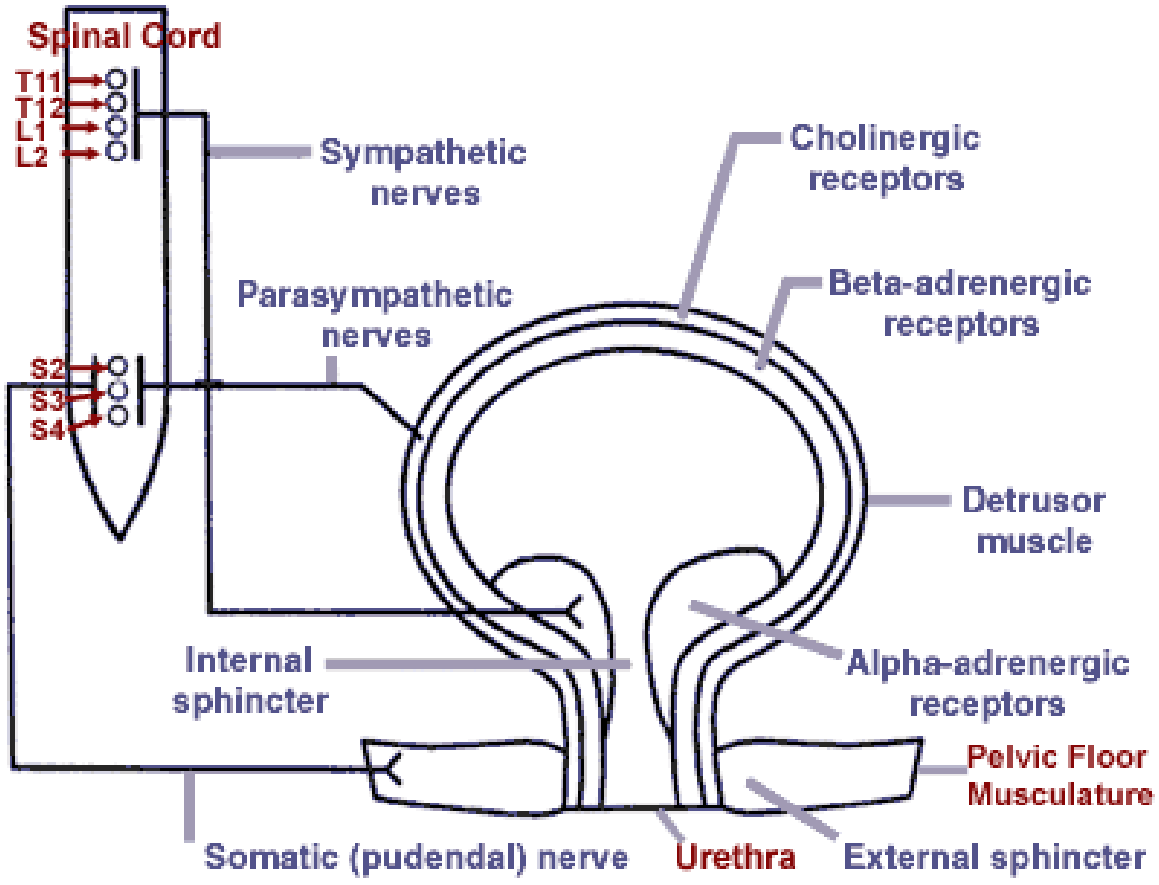

Figure 2-1 **Nervous Control of the Bladder**

Figure shows the different nervous control for the bladder and urethra. It also shows the different receptors on the bladder and the detrusor. Adapted by permission from Kansas University Landon Center on Aging (Wiggins SA et al. Urinary Incontinence. Kansas University Landon Center on Aging, Kansas: 2009 (http://www2.kumc.edu/coa/Education/AMED900/UrinaryIncon.htm). (10)

2.2.1 Cholinergic Mechanisms

Activation of parasympathetic system is the major pathway by which bladder contraction, and hence voiding, occurs. The parasympathetic drive is normally suppressed during the filling phase to assist in the relaxation of the bladder wall, and to facilitate low pressure urine storage. Acetylcholine stimulates the contractile muscarinic receptors on the bladder detrusor smooth muscles. For this reason, normal physiological voiding and generation of abnormal bladder contractions in diseased states are critically dependent on this acetylcholine-induced stimulation.(11)

Muscarinic receptors of the M_2 and M_3 subtypes exist on the detrusor smooth muscles. Both M_2 and M_3 are found to have a significant contribution to the micturition process. However, the exact functional role of M_2 receptors and their signalling mechanisms are less clear compared to M_3 receptors. It has been suggested that M_2 receptors may oppose the sympathetically mediated smooth muscle relaxation, exert a modulatory effect on relaxation, and enhance M_3 stimulated contraction.(7)

M_3 muscarinic receptors are generally responsible for the micturition contraction, mediated direct contraction of the detrusor muscle. M_3 stimulation has been shown to stimulate phosphoinositide hydrolysis, therefore, stimulate calcium release in the detrusor muscle. Calcium stimulation is the signalling mechanism responsible for the direct contractile responses to muscarinic agonists.(7) L-type calcium channels play a major role in muscarinic receptor facilitation of acetylcholine and noradrenaline release. An illustration of M_3 muscarinic receptor activation of the detrusor muscle is shown in Figure 2-2.

Acetylcholine is the predominant neurotransmitter in the normal human bladder. The generation inositol triphosphate happens when acetylcholine interacts with M_3 muscarinic receptors and activates phospholipase C through coupling with G proteins. Inositol triphosphate facilitates the release from the sarcoplasmic reticulum and hence the contractions of bladder smooth muscle. M_2 receptors are believed to possibly regulate bladder contraction by inhibiting adenylate cyclase activity and decreasing intracellular cyclic adenosine monophosphate (AMP) levels, which mediate bladder relaxation. The presence of a small amount of atropine resistant muscle contractions is minimal in normal human bladder. The interaction of adenosine triphosphate (ATP) with purinergic receptors, including P2X1 receptors is the possible cause of this atropine resistance. ATP and other non-cholinergically mediated processes may have a more important role in disorders that cause overactive bladder. On the other hand, relaxation of bladder smooth muscles may occur because of beta3-adrenergic receptors stimulation.(12) (Figure 2-2)

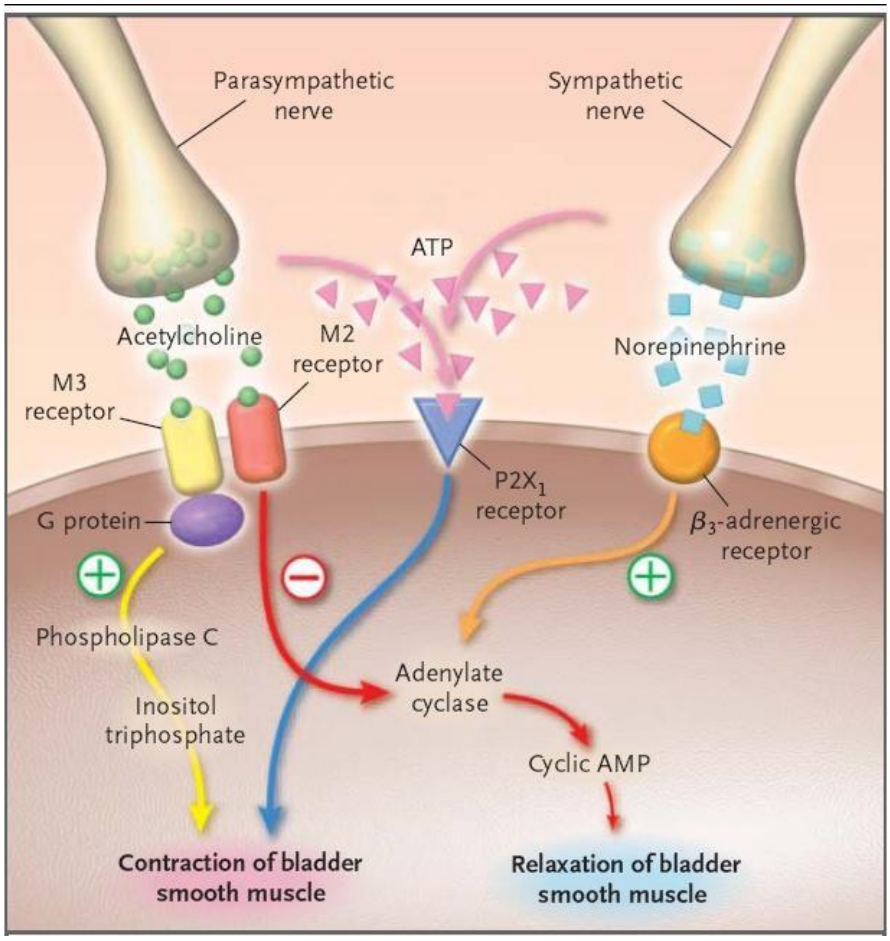

Figure 2-2 Current Concepts of Autonomic Efferent Innervations Contributing to Bladder Contraction and Urine Storage.

Adapted by permission from The New England Journal of Medicine (Ouslander JG. Management of overactive bladder. N Engl J Med. 2004 Feb 19;350(8):786-99), copyright (2004)(12)

Cholinergic activation of the urethral sphincter and urethra promote urethral relaxation and funnelling during micturition. Muscarinic receptors in the urethra play an important role in mediating the contraction and facilitating the micturition by inhibiting noradrenaline release. The contraction involves a reduction of the urethral length and an increase in the urethral diameter.(13)

2.2.2 Adrenergic Mechanisms

2.2.2.1 Alpha Adrenoceptors

Alpha adrenoceptor agonists, in high concentrations, can stimulate small and variable bladder contractions.(7, 14) However, further studies have failed to detect the presence of alpha$_1$ adrenoceptors in human detrusor muscles while confirming their existence in the trigone and bladder dome.(15) In patients with BPH, treatment with alpha adrenoceptor antagonists leads to disappearance of detrusor overactivity which suggests the presence of alpha adrenoceptors in the detrusor.(16)

Adrenergic activity on the urethral sphincter and the urethra facilitate urethra closure and facilitates the storage of urine. During storage the adrenergic receptors facilitates the urethral smooth muscle tone, and thus facilitates the urethral closure. The closure is promoted by the neurotransmitter noradrenaline and its action on alpha$_1$ adrenoceptor.(13)

2.2.2.2 Beta Adrenoceptors

The sympathetic nervous system inhibits the reflex activation of the detrusor muscle during filling; thereby, it contributes to the urine storage function. The exact role of beta adrenoceptor activity has been questioned and its importance remains unclear, however. The presence of beta$_1$, beta$_2$, and beta$_3$ receptors has been demonstrated on human detrusor muscles. Only selective beta$_3$ agonists have been shown an effective relaxation of the human detrusor muscles unlike selective beta$_1$ and beta$_2$.(7)

2.2.3 Non-Adrenergic-Non-Cholinergic (NANC) Transmission

There is a disputation about the role of the NANC (Purinergic) mechanism in the contractile activation of the bladder. NANC neurotransmission has a small contribution to the ‘functionally-well’ human bladder.(7) The NANC mechanism appears to be more predominant in overactive bladder and other diseased states where NANC mechanism is responsible for up to 50% of human detrusor’s nerve induced contraction.(17) ATP is most likely the transmitter responsible for NANC component of the contraction.

Additional animal evidence suggests that the NANC component of the contraction involves calcium influx via the L-type calcium channels, with smaller evidence that N-type, Q-type, and T-type calcium channels may play a minor role.(7)

2.2.4 Calcium Role in Contraction Mechanism

The regulation of smooth muscles tone depends on the amount of intracellular free calcium. Human and animal studies have demonstrated the significant role of calcium movement, through calcium channels, in the relaxation, filling, and contraction of the bladder.(7, 18)

The contraction process of the smooth muscles is facilitated by intracellular calcium ions. After calcium ions entry into the cell, they bind with calmodulin (intracellular protein similar to troponin) to form calcium - calmodulin complex. The resulting complex then binds and activates myosin light-chain kinase, which phosphorylates myosin. A cross-bridge cycling in smooth muscle contraction may occur only after phosphorylation of myosin.(19) During relaxation, calcium ions are pumped back, by active transport, into the extracellular fluid as well as the sarcoplasmic reticulum by calcium ATPase. After the decrease of the intracellular calcium will be released from the calmodulin and thus deactivate myosin light-chain kinase and reversal of the cross-bridge cycling.(19)

Entry of extracellular calcium is driven in the cell by a large electrochemical gradient, present across the plasma membrane, through activation of various entry channels. Voltage-gated calcium channels are one of the different calcium channels. They are the best understood plasma membrane calcium channels, which are found in excitable cells and create a rapid calcium reflex that manages cell contraction and other rapid cell processes. Another important source of intracellular calcium is in the endoplasmic/sarcoplasmic reticulum, in which calcium release is regulated by inositol-1,4,5-triphosphate (IP_3) or ryanodine receptors (RYR).(20)

Bladder contraction involves calcium influx via the L-type calcium channels, with smaller evidence that N-type, Q-type, and T-type calcium channels may play a minor role.(7) The L-type Calcium channel is further classified into four subgroups $Ca_V1.1$, $Ca_V1.2$, $Ca_V1.3$, and $Ca_V1.4$.(21) The Ca_V1 subgroup conducts L-type calcium currents that initiate muscle contraction, endocrine secretion, and gene transcription. They are regulated by a second messenger-activated protein phosphorylation pathway.(21)

Figure 2-3 explains the role of calcium in the bladder contraction process. During the 'on' reactions, stimuli induce both the entry of external calcium and the formation of second messengers that release internal calcium that is stored within the endoplasmic/sarcoplasmic reticulum (ER/SR). The ER is an extensive system of membrane-enclosed cavities inside the cytoplasm of the cell, while the SR is the smooth agranular ER of striated muscle cells that surround each myofibril and serves to store calcium during muscle rest.(4-6) Most calcium (shown as red circles) is bound to buffers, whereas a small proportion binds to the effectors that activate various cellular processes that operate over a wide temporal spectrum. During the 'off' reactions, calcium leaves the effectors and buffers and it is removed from the cell by various exchangers and pumps. The Na^+/Ca^{+2} exchanger (NCX) and the plasma-membrane calcium-ATPase (PMCA) extrude calcium to the outside, whereas the sarco(endo)plasmic reticulum calcium-ATPase (SERCA) pumps calcium back into the ER. Mitochondria also have an active function during the recovery process in that they sequester calcium rapidly through a uni-porter, and this is then released more slowly back into the cytosol to be dealt with by the SERCA and the PMCA. Cell survival is dependent on calcium homeostasis, whereby the calcium fluxes during the off reactions exactly match those during the on reactions (Figure 2-3).(20)

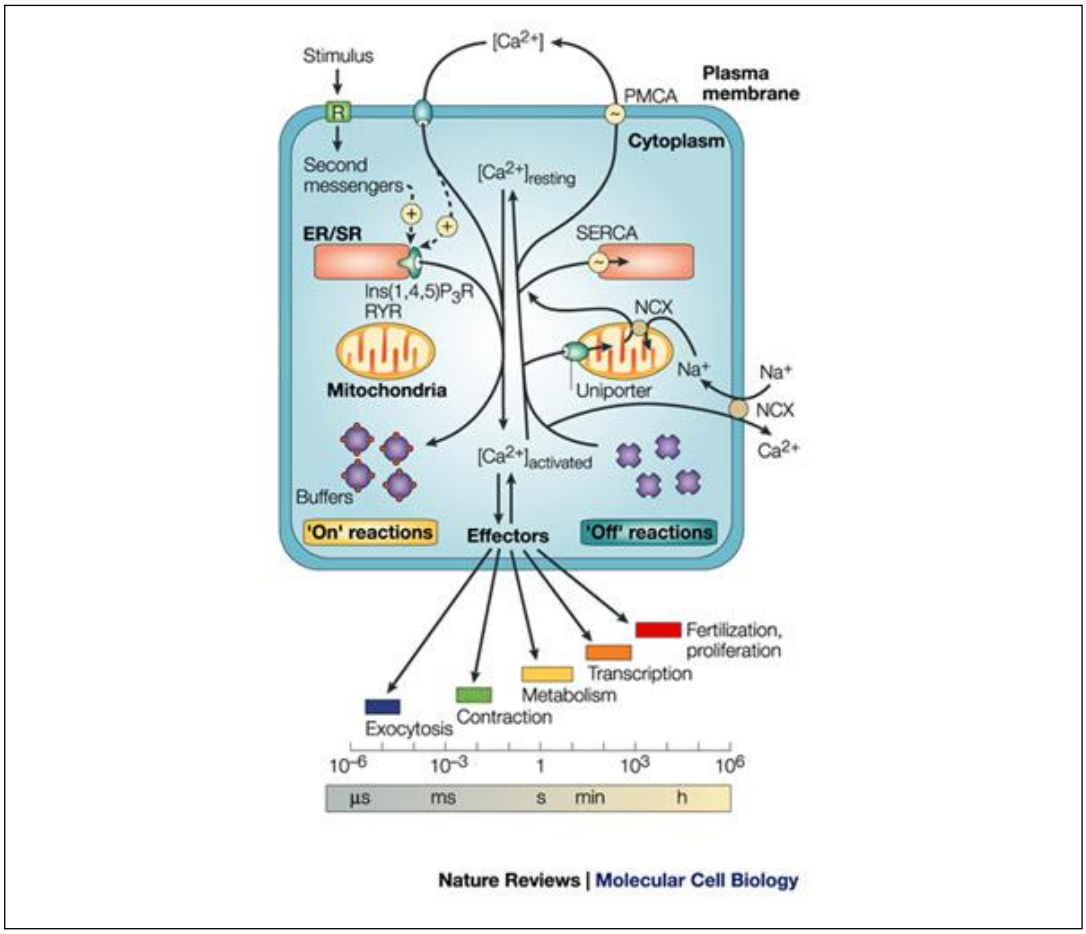

Figure 2-3 Calcium-signalling dynamics and homeostasis
[Ca^{2+}], calcium concentration; Ins(1,4,5)P3R, inositol-1,4,5-trisphosphate receptor; RYR, ryanodine receptor. Adapted by permission from Macmillan Publishers Ltd: [Nature Reviews Molecular Cell Biology] (Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol. 2003;4(7):517-29.(20)), copyright (2003)

Any disturbance to the normal storage and emptying function of the bladder causes lower urinary tract symptoms (LUTS).

2.3 Definition and Prevalence Lower Urinary Tract Symptoms (LUTS)

The term, LUTS, was developed to describe a group of obstructive and irritative voiding symptoms. It covers storage, voiding, and post-micturition symptoms. The LUTS term was first introduced in 1994 to distinguish urinary symptoms in males from prostatism. Now it is used broadly to describe all male/female urinary symptoms.(1) LUTS includes, but is not limited to, the following symptoms:

i. **Storage (filling, irritative) Symptoms**: increased daytime frequency, nocturia, urgency and various types of urinary incontinence

ii. **Voiding (Obstructive) Symptoms**: slow stream, splitting or spraying, intermittent stream of urine, hesitancy (difficulty in starting), straining to initiate, maintain or improve the urine stream

iii. **Postmicturition Symptoms**: feeling of incomplete emptying and terminal dribble, a prolonged final part of micturition

Both men and women experience different types of LUTS in a similar way as they become older. A review by Chapple et al found that LUTS are very common and has the same prevalence in both men and women.(1) However, there is a variation between males and females for individual symptoms existence. This review also revealed that LUTS include a 'progressive, age-related, non-sex-specific, non-organ-specific group of symptoms.(1)

LUTS and other urinary disorders are prevalent and bothersome in the rapidly growing ageing population. A number of studies have been conducted to evaluate the prevalence of LUTS amongst males and females. The proportion of individuals suffering from LUTS varies dramatically between regions and by gender. The prevalence of LUTS could be more than 90% as reported in a study for Canadian males aged 50 years or older (22) while other studies show a prevalence of less than 50%.(23-26)

2.3.1 LUTS Prevalence in Males

An Australasian study, for men over 40 years of age, looking at the prevalence of LUTS to assess the significance of BPH was conducted in Australia and nine other Asian countries.(27) The study revealed that 18% of men aged 40-49 years have been reported to have symptomatic LUTS. This proportion increased with age to 29% for patients in their 50s and 40% for patients in their 60s and 56% for subjects in their 70's.(27)

The EPIC study (25), is a large population-based survey, which was conducted in five European countries. The study investigated the prevalence of overactive bladder, urinary incontinence, and LUTS amongst more than 19,000 males and females aged 18 years or older. The EPIC study revealed that 11.8% of the participants had suffered from overactive bladder; the prevalence of overactive bladder increases with age and there was no difference between the prevalence of overactive bladder in males and females. The EPIC study has also confirmed the high prevalence of LUTS, and that the symptoms are not gender specific. About 50% of males and 60% of females had suffered from storage symptoms, while 25.7% of males and 19.5% of females suffered from voiding symptoms. The study also confirmed that the prostate was often not the only cause of voiding symptoms, because females have similar symptoms prevalence. Despite the common belief, that male LUTS are generally voiding related, the study has revealed that the prevalence of male storage symptoms (51.3%) is higher than voiding symptoms (25.7%). Further analysis of EPIC data was conducted to evaluate the impact of LUTS on QoL.(24) The analysis showed that there is a positive correlation between IPSS (International Prostate Symptoms Score) and BII (BPH Impact Index). Nevertheless, the BII scores were significantly higher for females.

A South Australian study to determine the prevalence of LUTS in the community revealed that 37% of males and 42.2% of females aged 45 years or older suffer from one or more LUTS.(28) These numbers rise to about half for the population (both males and females) aged 65 years or older. Despite the high prevalence of bothersome LUTS amongst males and females only 28% of males and 27% of women had consulted their doctors about the problem.(28)

The percentages of patients suffering from LUTS vary between countries. However, their impact on daily activity and QoL is similar for patients living in different countries.(29) The reported prevalence of LUTS is very high in some studies (e.g. 90% of Canadian men over 50 years suffer from LUTS).(22) A Japanese study looking at the prevalence and severity of LUTS in men and women found that LUTS was age-related and that LUTS were significantly more prevalent among men. The percentage of

patients suffering from moderate to severe symptoms in men and women aged 40 - 50 years was 12% and 8.3% respectively, compared with 48.7% and 31.8% for patients over 70 years.(30)

Apart from their natural progression with age, LUTS can also be caused by a number other factors. Spinal injuries, spinal spondylitis, stroke, Parkinson's disease, pelvic surgery, and diabetes are some of the factors that are known to cause LUTS in both men and women. In addition, males may develop LUTS as a result of prostatism, prostate cancer, and after trans-urethral resection of the prostate (TURP); while females may develop LUTS as a result of post-menopausal urogenital changes, after child birth, or after hysterectomy.(2) Some drugs are known to cause LUTS by affecting the bladder contraction and micturition processes. One such group of drug is the calcium antagonists (CAs) for which LUTS have been reported amongst their side effects.(3)

2.4 Medical/Surgical Conditions and LUTS

A number of diseases and medical conditions have been reported to cause LUTS.

2.4.1 Stroke

Bladder dysfunction is very common among stroke patients. Patients generally present with bladder hyperreflexia, which may be compounded by immobility, urinary tract infections, and prestroke bladder outflow obstruction.(31) LUTS are highly prevalent in stroke patients and have an impact on their QoL. A recent study indicated that about 94% of stroke patients suffer from at least one symptom and that QoL was also was negatively impacted upon.(32)

2.4.2 Benign Prostatic Hyperplasia (BPH)

Before the development of the term LUTS, all males LUTS were believed to be secondary to prostatism.(1) Prostate enlargement causes urinary obstruction and urinary retention. The most common complaints are nocturia and other obstructive symptoms, which lead to a significant deterioration of patients' QoL.(33)

2.4.3 Pelvic Surgeries

2.4.3.1 Transurethral Resection of the Prostate (TURP)

The TURP operation is conducted for the treatment of BPH (prostatism) induced urinary retention and other voiding symptoms. Urinary retention and recurrent urinary tract infections occur as a complication of TURP in about 9% and 8.2% of the patients, respectively.(34) Stress incontinence occurs in up to 87% of the patients following prostatectomy.(35)

2.4.3.2 Hysterectomy and Other Gynaecological Procedures

LUTS are common complications of gynaecological operations. It has been reported that about 17% of females experience LUTS (urinary incontinence and voiding symptoms) following simple hysterectomy operation.(2) This number increases to about 21% in the radical procedures. Nevertheless, there is little evidence for the long term bladder dysfunction after radical hysterectomy (in terms of obstructive symptoms and urinary incontinence).(36) Moreover, women who have caesarean section or normal vaginal delivery have a high risk of developing urinary incontinence.(37)

2.4.3.3 Incisional Hernia Repair

There are a number of case reports linking LUTS complications to hernia repair operation. Urinary retention and urinary incontinence are known complications of incisional hernia repair surgery.(38-40)

2.4.4 Parkinson's Disease

Parkinson's disease often causes voiding dysfunction, and thereby leads to a significant deterioration of patients' QoL. It is reported in some studies that 37 – 70% of patients with Parkinson's disease had visited a urologist because of voiding symptoms, however this number may be an under estimation.(41, 42)

2.4.5 Diabetes

Diabetes and diabetic cystopathy are known causes of LUTS. Diabetes causes overflow, stress, and urge incontinence by decreasing bladder sensation, increasing bladder capacity, and weakening detrusor contractility.(43, 44) In addition, diabetes may also induce voiding dysfunction. When compared to normal women, diabetic women have a statistically significantly higher nocturia scores, weaker urinary streams, less voided volumes, and lower maximal flow rates.(45) It has been reported that there is a two fold increase of the risk of developing LUTS amongst diabetic, male patients.(46) Despite the significant association between diabetes and LUTS, it has been found that intensive glycaemic control does not lead to improvement in LUTS.(47)

2.4.6 Alcoholism

Alcohol consumption has been reported to be associated with higher IPSS and increased urgency and intermittence.(48) Alcohol consumption was reported to increase the risk of developing moderate and severe symptoms in Norwegian men.(49) Fortunately, after withdrawal from alcohol, LUTS generally improve, however they do not resolve completely.(50)

2.4.7 High Body Mass Index (BMI)

Increased BMI is directly associated with the prevalence of moderate and severe LUTS.(49) In addition to that, increased BMI is associated with urinary incontinence in both males and females.(51)

2.4.8 Other Risk Factors

A number of other risk factors have been reported to be associated with development and/ or worsening of LUTS. Some of these factors are listed below:

- Spinal injuries (thoracic and lumbar) and diseases including disc disease
- Age
- Shy-draper syndrome

- Dementia
- Multiple sclerosis
- Congestive cardiac failure
- Recurrent urinary tract infections
- Impaired mobility
- Recurrent cough

2.5 Medications and LUTS

Many drugs are known to cause LUTS and other bladder disorders. The bladder is very susceptible to drug effects as many active drugs and their metabolites are excreted through the urine. Appendix 1 contains a list of the drugs that are known to cause LUTS.(52)

2.5.1 Drug-Induced Urinary Retention

Urinary retention happens when interference to the normal bladder contraction/sphincter relaxation process occurs. Urinary retention may be a result of bladder outflow obstruction, neurogenic bladder dysfunction, urinary tract infection, acute pain, an unfamiliar environment, constipation, and immobility.(53) Some of these factors may be as a result of medication use.

2.5.1.1 Anticholinergic Drugs

Anticholinergic drug use, including inhaled, induces a failure of bladder contraction. Therefore, anticholinergic drugs may cause/exacerbate urinary retention especially in patients with outflow obstruction.(53) Anticholinergic activity is however not limited to the anticholinergic drugs; a number of medications from other classes of drugs have been reported to have anticholinergic side-effects.(54) Nifedipine has been reported to be one of the top five drugs which have high atropine-like effects.(54) Diltiazem has also been shown to have anticholinergic side-effects, despite showing no atropine-like activity.(54) Nifedipine and diltiazem have been shown have a similar activity and ranked among the top 25 drugs, with anticholinergic activity, prescribed for elderly in

the USA.(55) The reported anticholinergic side-effects of these two drugs include increased risk of urinary tract infections, urinary hesitancy, and urinary retention.(54)

2.5.1.2 Anaesthesia and Analgesia

Administration of some medications, in patients with no previous urinary symptoms, during anaesthesia may cause post-operative urinary retention in up to 50% of patients.(56, 57) Administration of atropine, an anticholinergic drug, during anaesthesia increases the risk of developing post-operative urinary retention. Narcotic analgesics induced urinary retention has been reported frequently, but the exact mechanism is unclear. The urinary retention usually resolves sponteneously after discontinuation of the treatment.(53)

2.5.1.3 Other Drugs

Antihistamines, monoamine oxidase inhibitors, skeletal muscle relaxants, antidepressants, antipsychotics, and some herbal medicines have been reported to induce urinary retention by their anticholinergic-like activity.(53, 54) Urinary obstruction/ retention also can be a result of bladder neck contraction following alpha adrenoceptor agonists' administration. Apart from the well known drug classes, a range of other drugs have also been reported to cause urinary retention, such as metoclopramide, hydralazine, and vincristine.(53)

2.5.2 Drug-Induced Urinary Incontinence

Numerous medications have been reported to cause urinary incontinence. However, the level of evidence is weak in many cases and in some cases either theoretical or equivocal.(58) The mechanism by which medications contribute to urinary incontinence varies dramatically between different classes of drugs.

2.5.2.1 Urge incontinence

Urge incontinence can be caused by increased urine production, and this may result from the use of some medications e.g. diuretics, which increase the volume and hence output of urine. A study performed to investigate the relationship between diuretic use and urge

incontinence confirmed an association in females and in males with pre-existing bladder overactivity.(59) drugs, like verapamil and pseudoephedrine, which can cause constipation may subsequently cause urge incontinence.

Another mechanism by which drugs may cause urge incontinence is by inducing or exacerbating detrusor overactivity. A number of drugs have been reported or hypothesised to induce urge incontinence by this mechanism, e.g. antidepressants, hormone replacement therapy, parasympathomimetics, and serotonin receptor antagonists.(58)

2.5.2.2 Overflow Incontinence

Drugs and other risk factors, which are reported to cause urinary retention, can also cause overflow incontinence. This happens as a result of increased intavesical pressure and consequent involuntarily loss of urine.(53) Anticholinergics, antiparkinson's drugs and beta blockers are some examples of drugs that are suspected to cause overflow incontinence as a result of incomplete bladder emptying. The evidence of this association is however theoretical .(58)

2.5.2.3 Stress Incontinence

Stress incontinence is the most commonly occurring form of urinary incontinence; a number of drugs have been reported as possible causes. Alpha adrenoceptor blockers, which are used to treat voiding dysfunction, have been reported to cause stress incontinence.(58) The association between alpha blockers use and urinary incontinence was investigated in a study of hospitalised women. About 41% of the alpha blocker users were found to be suffering from some form of urinary incontinence compared to only nine percent of the non-users. The proportion decreased dramatically to 14% after medication discontinuation.(60)

Antipsychotic medications have often been reported as a potential cause of stress incontinence. The mechanism by which antipsychotics may cause incontinence remains unclear with most theories centred on central dopamine blockade and peripheral alpha

blockade.(61, 62) It is difficult to establish a direct causality for these medications, despite the reversibility of the incontinence after medication discontinuation, because psychosis is considered one of the risk factors for stress incontinence. The stress incontinence has been reported with all classes of antipsychotic medications.(53, 58)

By causing striated muscles relaxation, induced by their GABA receptors effects, benzodiazepines may induce urinary incontinence. This effect was confirmed in a study conducted amongst aged care facilities residents, but the generalisability was questioned for other patient settings.(63)

2.6 Calcium Antagonists (CAs) Background

CAs are a group of heterogeneous compounds which act on the calcium channels and have different mechanism of actions, chemical structures and tissue selectivity. There are three main chemical groups of CAs available in Australia – phenylalkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (nifedipine, amlodipine, felodipine, lercanidipine). CAs are one of the most frequently prescribed groups of drugs in Australia. In the year 2007-2008 there were more than seven million prescriptions for CAs dispensed in Australia of which about two million were for amlodipine.(64) Table 2-1 shows the prescribing trends in 2008 and the cost for CAs in Australia according to Pharmaceutical Benefits Scheme (PBS) data.(64)

Table 2-1 Australian CA Use and Cost According to PBS

CA	Number of Prescriptions	Cost in AU$
Amlodipine	2,951,627	65,568,204
Lercanidipine	1,378,857	45,968,141
Diltiazem	1,390,374	30,669,712
Felodipine	1,378,857	29,477,892
Verapamil	1,143,839	18,992,769
Nifedipine	947,954	20,878,505
Total	**7,049,835**	**211,555,223**

2.6.1 CAs Mode of Action and Receptors

CAs are used in the treatment of a range of cardiovascular disorders including hypertension, atrial arrhythmias, and angina pectoris. Their effects on the cardiovascular system include depression of mechanical contraction of myocardial and smooth muscle, and depression of both impulse formation (automaticity) and conduction velocity.

The different pharmacological profiles for these agents are in part based on their ability to bind to different receptor sites at the calcium channel. Dihydropyridines are strong vasodilators acting via relaxation of vascular smooth muscle cells. They have little direct effect on myocardial contractility or SA/AV nodal conduction. The non-dihydropyridines (diltiazem and verapamil) have an increased effect on AV nodal conduction compared to that of the dihydropyridines and although they also cause vasodilatation via relaxation of vascular smooth muscle, they are less potent vasodilators than the dihydropyridines. There are different calcium channels subtypes, which are distributed in cardiovascular and smooth muscles. Their nomenclature was created based on potassium channel nomenclature. The names start with (Ca) for calcium, followed by

($_v$) for voltage, then a number representing the subfamily. Table 2-2 illustrates the distribution of different calcium channels and the corresponding calcium antagonists.

Table 2-2 Calcium Channel Classification and Distribution

Channel	Current	Localisation	Specific Antagonists	Cellular Functions
$Ca_V1.1$	L	Skeletal muscle; transverse tubules	Dihydropyridines; phenylalkylamines; benzothiazepines	Excitation-contraction coupling
$Ca_V1.2$	L	Cardiac myocytes; smooth muscle myocytes; endocrin, neuronal cell bodies; proximal dendrites	Dihydropyridines; phenylalkylamines; benzothiazepines	Excitation-contraction coupling; hormone release; regulation of transcription; synaptic integration
$Ca_V1.3$	L	Endocrine cells, neuronal cell bodies and dendrites	Dihydropyridines; phenylalkylamines; benzothiazepines	Hormone release; regulation of transcription
$Ca_V1.4$	L	Retina	Not established	Neurotransmitter release from rods of bipolar cells
$Ca_V2.1$	P/Q	Nerve terminals and dendrites	ω-Agatoxin IVA	Neurotransmitter release; dendritic Calcium transients
$Ca_V2.2$	N	Nerve terminals and dendrites	ω-Conotoxin-GVIA	Neurotransmitter release; dendritic Calcium transients
$Ca_V2.3$	R	Neuronal cell bodies and dendrites	SNX-482	Repetitive firing
$Ca_V3.1$	T	Neuronal cell bodies and dendrites	None	Pacemaking; repetitive firing
$Ca_V3.2$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	None	Pacemaking; repetitive firing
Cav3.3	T	Neuronal cell bodies and dendrites	None	Pacemaking; repetitive firing

*This table is adopted from Catterall et al. at Pharmacol Rev. 2003 ;55(4):579-81.(65)

2.7 Non-cardiovascular Effects of CAs

Nifedipine, diltiazem, and verapamil have been associated with impaired intestinal motility and hence constipation.(19, 65) CAs have also been found to be associated with an increased risk of GORD.(66) CAs also act on the respiratory smooth muscle in

asthmatic patients and have been shown to decrease the incidences of asthma attacks.(65)

They also act on the neurotransmitters and synaptic functions of the nervous system. In addition they alter the action of some endocrine and exocrine glands such as the adrenal gland, pituitary gland, pancreas, thyroid gland, parathyroid glands, testis, and ovaries.(65)

CAs are amongst a number of drugs that have been reported to cause LUTS. CA act on the bladder by affecting the ability of the detrusor muscle to create enough contractile force to overcome obstruction to normal voiding. CAs have been also reported to cause constipation (one of the risk factors for LUTS) through their muscle relaxation and anti-cholinergic activity (67) and increase the production of urine (polyuria) by inducing natriuresis.(68-71)

2.8 CAs and and Bladder Function

A number of mechanisms were proposed to explain the mechanism by which CAs induce LUTS: (1) natriuresis, (2) anticholinergic activity, and (3) direct smooth muscle relaxation.

2.8.1 Natriuresis

It has been suggested that CA use leads to increased sodium excretion in the urine by altering the re-absorption of sodium, which may result in increased urine output.(69, 72-75) A similar mechanism was thought to be the plausible explanation for the polyuria caused by felodipine and nicardipine in other studies.(70, 75) Further studies have also confirmed the increased sodium excretion and increased urine output amongst CA users.(68, 69, 74, 76) This mechanism, despite providing a conceivable justification of CA induced polyuria and other storage symptoms, does not provide a rational explanation for the obstructive/voiding symptoms and the post-micturition symptoms reported with CA use.

2.8.2 Anticholinergic Activity

A number of drugs have been reported to have a degree of anticholinergic activity.(54, 55) This activity is divided into two groups according to the similarity of drugs detectable activity to atropine. Nifedipine has been reported to have a detectable atropine-like activity in a review article by Mintzer and Burns, while diltiazem was reported to have no detectable atropine-like activity.(55) The review ranked nifedipine to be the fifth of 25 drugs that had a detectable atropine-like activity and diltiazem was ranked as the eighth under drugs in no atropine-like activity group. (54) This mechanism provides a reasonable explanation for obstructive urinary symptoms associated with CA use. Nonetheless, no data could be located regards the anticholinergic activity of other CAs.

2.8.3 Smooth Muscle Relaxation

CAs have been reported to cause detrusor muscle relaxation and hence reduce the ability of the bladder to produce enough contractile force to overcome obstruction to normal voiding of the sphincter.(77-85) Unlike the previous two methods, this method has been well investigated, both in vitro and in vivo. It provides a reasonable theoretical explanation for the existence of both obstructive and irritative LUTS.

2.9 Bladder and Vascular Tissue Selectivity of CAs

The older CAs like nifedipine, diltiazem and verapamil have lower vascular selectivity, and they have been reported to act on the cardiac tissues.(19, 86) Felodipine was developed to be the first compound with high vascular selectivity that acts on resistant blood vessels.(87) It was tested both in vitro and in vivo, and was found to have up to 100-fold increase in its vascular selectivity.(87, 88) Godfraind et al have ranked CAs according to their tissue selectivity and the ratio of vascular cardiac selectivity.(89) The ratios were about one for diltiazem and verapamil: about 10 for nifedipine and amlodipine: about 100 for felodipine, isradipine, lacidipine. nicardipine, nitrendipine, and about 1000 for nisoldipine.(89) Similar findings were reported by Nordlander et al from in vitro and in vivo studies, where felodipine had higher vascular selectivity than

nifedipine and amlodipine.(90) Another study produced a slightly different results, with amlodipine reported to have a higher vascular/cardiac selectivity ratio compared to felodipine.(91) The same study also listed lercanidipine as the drug with the highest vascular selectivity followed by lacidipine, amlodipine, felodipine, and nitrendipine.(91)

Lercarnidipine's aorta selectivity was investigated against its bladder selectivity and found to be 177 times higher.(92, 93) The potential role of CAs in the treatment of overactive bladder has been identified by manufacturers who have attempted to produce bladder selective CAs.(94) However, an extensive literature search failed to locate any data on the comparative bladder selectivity to vascular selectivity for other CAs.

2.10 Possible Benefits of CAs

The relaxation effect of CAs on the bladder detrusor muscle has seen researchers investigate their potential role in the treatment of overactive bladder.(81, 95, 96) A number of text books and urological guidelines have listed CAs as a potential treatment for overactive bladder.(12, 13, 40, 52, 97-102) Clear guidelines are yet to be established because of the conflicting results obtained from various studies. Diltiazem has been proven to have a significant role in relieving the symptoms of overactive bladder.(81) Whereas the evidence for verapamil is conflicting. In one study verapamil use was reported to lead to increased the bladder capacity and an improvement in the symptoms in patients with detrusor hyperreflexia, but not in patients with detrusor instability.(85) However, another study involving verapamil failed to identify any treatment benefits.(103) A randomised control trial for the use of nimodipine for the treatment of urinary incontinence in men showed no significant difference between the intervention and the control groups.(104) Another study was conducted to investigate the effects of amlodipine, terazosin, or their combination on the urodynamics of male rats with BPH and female rats with detrusor instability.(105) This study has shown that amlodipine use has improved the bladder index, decreased urinary frequency and improved both threshold and micturition pressure. However, the greatest improvement was reported with the combination of amlodipine and and terazosin.(105) A randomised, double-blind, clinical trial was designed to investigate the efficacy and safety of amlodipine

(alone or in combination with terazosin in the treatment of hypertension and LUTS in males.(106) After randomising the patients into three groups (amlodipine 5mg, terazosin 2mg, or both combined), a follow-up was completed after four weeks. In consistency with the latter study (105), the combination of amlodipine and terazosin was again proved to be superior in term of blood pressure reduction and in lowering IPSS.(106)

2.11 Previous Studies for CAs and LUTS

The contribution of CAs to LUTS in male patients aged 45 years and older has been investigated in two previous studies conducted by Baker et al (107) and Coles et al (108) through the School of Pharmacy, Curtin University. However, both studies focused on males and there have been no studies to evaluate the relationship between CA use and LUTS in females.

The first study by Baker et al (107) investigated the relation between CA use and acute urinary retention (AUR) in males aged over 60 years. The use of CAs was found to be associated with a statistically significant increased risk of AUR in patients with bladder disorders (OR=4.38) or Type II Diabetes Mellitus (OR=3.0). CAs were also found to significantly increase the risk of AUR when used in combination with tricyclic antidepressants (OR=6.5). Similar distribution of symptoms was found in the presence and absence of calcium antagonists. Further, it was found that males taking CAs were statistically more likely to be commenced on prazosin or for the dose of this drug to be increased. The study showed that death post-discharge and AUR recurrences were significantly more likely to occur where CAs were used.

The second study by Coles et al (108), involving 40 males aged above 45 years, was undertaken to determine the influence of CA use on LUTS. Despite the small sample size of the study, it demonstrated that the use of CAs was associated with a patient reported significant worsening of LUTS. The mean IPSS increased from 3.13 (95% CI, 2.09-4.17) before commencement of CAs to 9.82 (95% CI, 7.83-11.80) after commencement. This increase remained significant even after adjustment for natural progression of LUTS with time, with the mean increase of IPSS being 5.85 (95% CI,

4.09-7.72; p< 0.001). The mean QoL score changed significantly from 1.42 (95% CI 0.86-1.99) to 3.66 (95% CI 2.49-3.66) after commencement of CAs. This shows a highly significant increase in the mean QoL score after commencement of CAs (2.27; 95% CI 1.40-3.15; p< 0.001) indicating a significant worsening in the patient's QoL. The changes in IPSS and QoL scores showed a significant correlation (Pearson correlation coefficient = 0.595; p< 0.001) indicating the worsening of patients' QoL was closely correlated with their worsening of LUTS after commencement of CAs. Based on their findings, Coles et al (108) recommended a LUTS monitoring program should be introduced for male patients above 45 years of age receiving CAs.

Chapter 3

3 ADRAC Reports on CA Use and LUTS

3.1 Introduction

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) was formed in 1970. As a subcommittee of the Australian Drug Evaluation Committee (ADEC), ADRAC's mission was to advise Therapeutic Goods Administration (TGA) on medication safety. Independent medical experts on areas of importance to medication safety forms ADRAC's membership. In 2010 the ADRAC was replaced by the Advisory Committee on the Safety of Medicines (ACSOM). The ADRAC receives voluntarily reported adverse drug reactions forwarded by medical professionals.

The aim was to look at all LUTS reports where CAs were reported as a potential cause.

3.2 Methodology

The Primary Investigator contacted the ADRAC requesting all reported cases urological side effect associated with CA use. The ADRAC had conducted a database search (from 1972) for all generic and trade names for CAs against the terms dysuria, micturition disorder, pollakiuria, urethral disorder, urinary incontinence, and urinary retention. The data was then forwarded to the investigator and subsequently entered and analysed using SPSS v.15.0. The data provided includes: case number, date of the report, patient age, hospitalisation, adverse event outcome, causality, adverse drug reaction details, medicines details, and laboratory test data in some cases.

3.3 Results

ADRAC forwarded a total of 80 cases (78 cases were received in January 2008 and 2 cases in January 2009), with some cases were dated as early as 1979. The majority of the reported cases involved females 45 (56.2%), while 34(42.5%) involved males. For the remaining case the gender was not stated. The average age of the patients was 63.4±14.1 (range: 36-99 years) with no significant age different between males and females. Table 3-1 shows the distribution of patients between different age groups. Only four patients were younger than 40 years of age. For patients younger than 50 years of age,

the majority of the reported cases were females (10 cases, with the youngest was 36 years old) compared to males (4 cases, with the youngest being 47 years old).

Table 3-1 Participant Age Distribution

Age group	No of Patients	Percent
Less than 40	4	5.0
41-50	12	15.0
51-60	14	17.5
61-70	23	28.75
71-80	16	20.0
81-90	3	3.75
More than 90	3	3.75
Not given	5	6.25
Total	**80**	**100**

Table 3-2 shows the distribution of different CAs amongst the patients. Amlodipine was the most reported drug amongst the group. Three patients were taking two CAs when the adverse event happened.

Table 3-2 CAs Distribution

CAs used	Frequency	Percent
Amlodipine	29	36.25
Felodipine	17	21. 25
Nifedipine	13	16. 25
Verapamil	9	11. 25
Diltiazem	8	10.0
Amlodipine and verapamil	2	2.5
Nifedipine and verapamil	1	1. 25
Lercanidipine	1	1. 25
Total	**80**	**100**

The causality of CAs induced LUTS was reported as certain in five (6.2%) of the cases, while in 49 (61.2%) it was reported as possible and 26 (32.5%) probable. Rechallenge was done for three patients to establish the certainty and that lead to symptoms relapse. More than half the patients 46 (57.5%) recovered completely after medication discontinuation while 10 (12.5%) did not recover; the outcome was not reported for the reminder of the patients 24 (30%). Table 3-3 shows the outcome of CAs discontinuation for individual drugs.

Table 3-3 Recovery Rates after CA Cessation

	Outcome		
CA	**Not yet recovered**	**Recovered**	**Unknown**
Amlodipine	2 (6.9%)	12 (41.4%)	15 (51.7%)
Amlodipine/verapamil	1 (50%)	1 (50%)	-
Diltiazem	2 (25%)	4 (50%)	2 (25%)
Felodipine	1 (5.9%)	13 (76.5%)	3 (17.6%)
Lercanidipine	-	1 (100%)	-
Nifedipine	1 (7.7%)	10 (76.9%)	2 (15.4%)
Verapamil	3 (33.3%)	4 (44.4%)	2 (22.2%)
Nifedipine/verapamil	-	1 (100%)	-

Obstructive symptoms were the dominant side effects. The most commonly reported adverse effects were pollakiuria (abnormally frequent passage of relatively small quantities or urine), urinary retention, and nocturia, respectively. Amlodipine was the most commonly implicated drug followed by felodipine, nifedipine, and verapamil. Table 3-4 shows the distribution of the side effects per individual drugs. Some reports included more than one LUTS per patient.

Table 3-4 LUTS Distribution by CA-Use

LUTS	Gender	Amlodipine	Felodipine	Nifedipine	Verapamil	Diltiazem	Amlo/Verap	Nife/Verap	Lercanidipine	Total
Pollakiuria	M	9	3	6	1	1	-	-	-	**37***
	F	5	7	-	2	2	-	-	-	
Urinary Retention	M	1	3	-	1	-	-	-	-	**18**
	F	5	-	2	3	1	2	-	-	
Nocturia	M	1	1	2	-	1	-	-	-	**12**
	F	4	1	-	1	1	-	-	-	
Micturition Disorder	M	1	1	2	1	-	-	-	-	**11**
	F	2	2	2	-	-	-	-	-	
Urinary Incontinence	M	-	-	1	-	1	-	-	-	**9**
	F	3	1	-	1	1	-	1	-	
Dysuria	M	-	1	1	-	1	-	-	1	**6**
	F	1	-	1	-	-	-	-	-	
Polyuria	M	1	-	-	-	-	-	-	-	**4**
	F	-	1	-	1	1	-	-	-	
Total		**34***	**21**	**17**	**11**	**10**	2	1	**1**	**97**
Total ADRAC Reports		**2073**	**888**	**1038**	**1071**	**887**			**142**	**6,099**

* The total number is more than the individual male/female summation because there is a report with missing gender.

3.4 Discussion

The review of the ADRAC cases revealed that there was more cases involving females with LUTS than males. This was clear for all individual symptoms except pollakiuria and dysuria. Previous demographic information suggested that more males would suffer from obstructive LUTS. Therefore, it was predicted that there would be more male reported obstructive symptoms which was not the case. The minimum reporting age for females (36years) was much lower than that of males (47 years). This raises the concern that there may be a possible under reporting among men.

The dominance of amlodipine, with involvement in about one third of the total reports, may be correlated with the annual prescribing trends in Australia. This does not appear to be true of lercanidipine which had the lowest number of reports, but its annual prescription rate is higher than diltiazem and verapamil. (Refer Table 2-1 Australian CA Use and Cost According to PBS) Both diltiazem and verapamil have been reported previously to cause constipation, which is one of the known risk factors for LUTS).

The ADRAC data also showed a relatively high recovery from the symptoms after drug cessation. The certainty, however, was asserted when rechallenge confirmed the association and when CAs were the only drugs that patients are taking. The high prevalence of obstructive LUTS could be explained by the relaxation effect of CAs on bladder detrusor muscle, which leads to contractility force reduction and suppression.

The main limitation of this study is the voluntary reporting of adverse events to ADRAC. This means the data may not reflect the true prevalence and thus could not be generalised.

3.5 Conclusions

Results from this study highlighted the fact that there had been a number of reported cases of CA associated LUTS with differing degrees of certainty in regards to the causality. The results also suggested that the symptoms are reversible in many cases after drug discontinuation. Further the study showed that reports involving LUTS and

CAs were more common amongst female. The latter finding demonstrated the importance of including females in any future studies looking the prevalence of LUTS amongst CA-users.

Chapter 4

4 The association between CA use and LUTS in Medical Patients

4.1 Introduction

Previous studies discussed in section 2.11 by Baker et al (107) and Coles et al (108) have provided some evidence of the association between the use of CAs and LUTS amongst males. Coles et al's study provided evidence of an association between LUTS and CA use amongst community dwelling males, both retrospectively and prospectively.(108) Their findings had limitations related to the relatively small sample size and the reliance on the participants' recall of how their LUTS had changed over time. Both studies focussed on males as the initial hypothesis was that males may be more prone to obstructive LUTS because of other risk factors such as the development of prostatic enlargement with ageing and other idiopathic factors. This assumption does not appear to be valid based of a review of ADRAC case reports which showed that the majority of the reported cases involved females. (on CA Use and LUTS, page: 32)

4.1.1 Aim

The aim of this study was to determine the relationship between CA use and LUTS in medical inpatients and to evaluate the impact of CA use on urological QoL.

4.2 Methodology

4.2.1 Study Setting

The recruitment of patients for the study was undertaken in three long stay and one short stay medical wards at Royal Perth Hospital, Perth, Western Australia. The data was collected over a three month period between 1st of August and 31st October, 2008.

4.2.2 Study Design

This study was a retrospective observational study with two groups of patients (CA-users and non-CA-users). The non-CA-users group acted as a control group. The data were collected using structured interviews and by reviewing the participants' medical records.

4.2.3 Procedure

4.2.3.1 Participants

Patients eligible for enrolment into the study were those who were admitted to long stay or short stay medical wards at Royal Perth Hospital. Unlike previous studies by Baker et al (107) and Coles et al (108), this study involved both males and females. Females were included after a review of ADRAC case reports revealed that there were more reports of CA-induced LUTS amongst female than males. The ADRAC reports also suggested that patients report LUTS at a relatively young age 47 years for males and 36 years for females. Therefore, all patients aged 40 years or older were included in the study.

4.2.3.2 Inclusion Criteria

All patients (both males and females) admitted to medical wards and who satisfied the following inclusion criteria were invited to participate:

- Aged 40 years or older
- Able to read and converse in English

4.2.3.3 Exclusion Criteria

Patients were excluded from the study if they:

- Did not give a written informed consent
- Could not read or converse in English
- Were deemed to be unwell by their doctors
- Had cognitive impairment
- Were catheterised

4.2.3.4 Withdrawal from the study

Patients were withdrawn from the study if their consent was withdrawn.

4.2.4 Power and Sample Size Estimation

The power and sample size calculation was based on the previous study by Baker et al (107), which assessed the relationship between CA use and LUTS in males. That study investigated the relationship between CA use and acute urinary retention (AUR) in males aged over 60 years. The use of CA was found to be associated with a statistically significant increased risk of AUR where bladder disorders (OR=4.38) or Type II Diabetes Mellitus (OR=3.0) existed. CAs were also found to significantly increase the risk of AUR when used in combination with tricyclic antidepressants (OR=6.5).

The study also revealed that 18.8% of CA-users experienced LUTS compared to 5.0% of non- users. This study, however, was conducted on male patients above the age of 60 years.

The current study assessed the impact of CA use on both males and females above the age of 40 years. In the absence of previous information regarding the percentage of bladder disorders in the CA and non-CA groups, the results of the previous study were used to calculate the sample size. The admission pattern in the hospital ensured that the sample would include both males and females.

In 2006, there were approximately 750,000 patients on CAs in Australia (based on the number of prescriptions per year divided by 12 months).(64) This number represents 6-10% of the Australians aged 40 years or older. Thus, the number of CA-users and non-CA-users admitted to the medical wards were not expected to be equal (i.e. the number of patients on CAs is less than the number of non-CA-users) with an estimated allocation ratio of 1:10 or higher. However, the allocation ratio could have been smaller because the study involved only hospitalised patients.

Therefore, a smaller allocation ratio of CA-users to non-CA-users could meet power estimation requirement. For this study a sample size of 250 patients (50 CA-users and 200 non-CA-users) was estimated to be able to detect a difference of 13.75% in the LUTS score with a power of 83% power at 95% level of significance.

The sample sizes were calculated using PASS 2008 software (NCSS Statistical & Power Analysis Software, 329 North 1000 East, Kaysville, Utah, 84037, USA).

4.2.4.1 Two Proportions Power Analysis

Null Hypothesis: P1=P2, Alternative Hypothesis: P1<>P2.

Table 4-1 Two Proportion Power Analysis

Power	N1	N2	Allocation Ratio	P1	P2	Odds Ratio	Alpha	Beta
0.82987	50	200	4	0.1875	0.05	0.228	0.05	0.17
0.84838	50	250	5	0.1875	0.05	0.228	0.05	0.15

4.2.4.2 Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

N1 is the size of the sample drawn from the CA-users.

N2 is the size of the sample drawn from the non-CA-users.

Allocation Ratio is N2/N1 so that N2 = N1 x R.

Alpha is the probability of rejecting a true null hypothesis. It should be small.

Beta is the probability of accepting a false null hypothesis. It should be small.

P1 is the proportion for group one.

P2 is the proportion for group two under the alternative hypothesis.

Odds Ratio is [P2/(1-P2)] / [P1/(1-P1)].

4.2.4.3 Summary Statements

Group sample sizes of 50 and 200 achieve 83% power to detect a difference of 0.1375 between the null hypotheses that both group proportions are 0.1875. The alternative hypothesis that the proportion in Group 2 is 0.05 using a two-sided Chi-square test without continuity correction and with a significance level of 0.05.

4.2.4.4 Chart Section

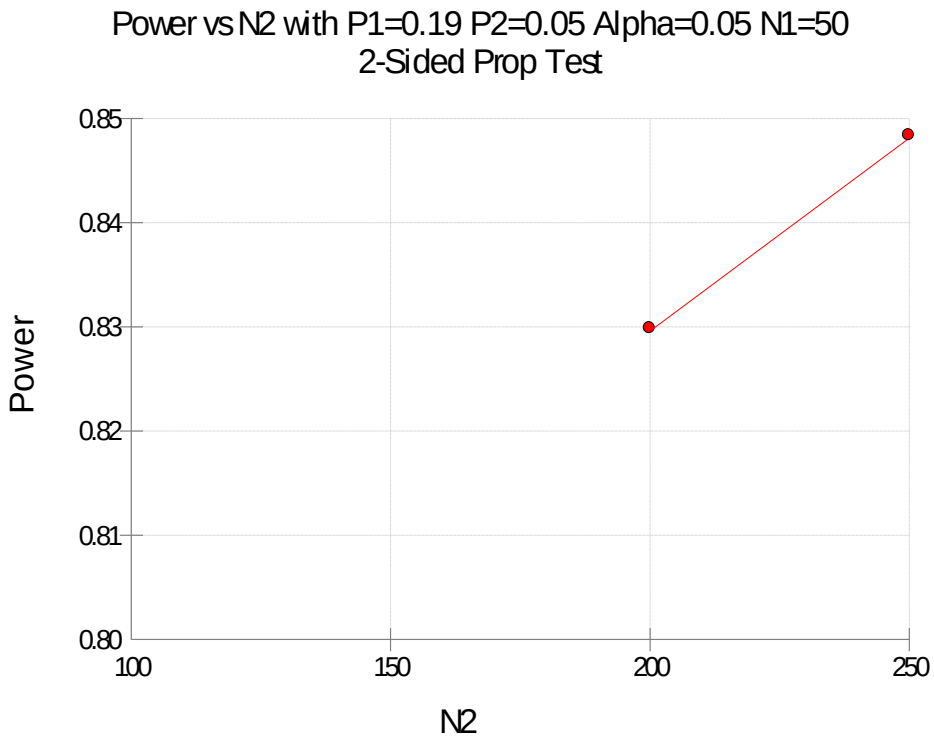

Figure 4-1 Power Estimation

The above Figure 4-1 shows that for a sample of 50 CA-users a power of 83% can be obtained by recruiting 200 non-CA-users. This power can increase to about 85% if the non-CA-users arm increased to 250.

4.2.4.5 Patient identification and recruitment

All patients were recruited from medical wards at Royal Perth Hospital, Perth. Patient identification and recruitment were performed by the Primary Investigator.

4.2.4.6 Department of Internal Medicine Approval

An application was lodged with the Department of Internal Medicine at Royal Perth Hospital in order to obtain approval for the study. Initial approval was given by the Head of Department awaiting the other consultants' approval. A presentation was conducted for all the consultants, registrars, and other doctors in the department during one of their monthly departmental meetings; and the study protocol was distributed to all medical consultants (Appendix 2). A study summary (explaining the background, methodology, and significance of the study) was also provided to the medical staff. (Appendix 3) Subsequently, all the doctors gave their unconditional approval and support for the study.

4.2.4.7 Ethical Approval

Ethical approval for the study was obtained from Curtin University of Technology Ethics Committee (43/2008) and Royal Perth Hospital Ethics Committee (2008/125).

All patients and their corresponding data were assigned an alphanumeric code ensuring the de-identification of study data after completion of data collection. Further, all patient data was grouped for the purpose of analysis to ensure the confidentiality of the participants.

Questionnaires and consent forms are to be archived in a locked cabinet at the School of Pharmacy for 7 years.

4.2.4.8 Patient Identification

Eligible patients were identified by the Primary Investigator by reviewing patient admission lists and medical records. The Primary Investigator reviewed list of medical admissions daily to exclude patients younger than 40 years. A quick review of patient

medical files was conducted to identify patients with cognition impairment. Patients were excluded if either their mini mental score was below 23 or abbreviated mini mental score was below eight.

4.2.4.9 Recruitment

Eligible patients were invited to participate in the study. The purpose of the study, their role, the questionnaire design, and possible benefits from taking part in the study were clearly explained to the patients. They were also given the patient information sheet (Appendix 4), which explained the background behind the study, the purpose of the study, their role in the study, possible risks, confidentiality issues, data handling, and that they could withdraw from the study at any time during the data collection process without affecting their medical care.

4.2.4.10 Patient Consent

Patients who agreed to participate in the study were then asked to sign the consent form. (Appendix 5) The consent form identified that they had understood the patient information sheet and had been provided a copy of it, and that they had the right to withdraw from the study at any time without affecting their medical treatment. The form also explained that the investigators would comply with the usual standards of confidentiality.

For patients with physical impairment who could not provide a hand written consent, a verbal consent in the presence of relatives was accepted.

4.2.5 Questionnaire Design

Three sets of questionnaires were used to obtain patient demographic information, LUTS symptoms, and the effect of LUTS on the patient's Quality of Life (QoL). The questionnaires were: (a) Demographic questionnaire, (b) International Prostate Symptoms Score (IPSS), and (c) BPH Impact Index (BII). All questionnaires were designed to be completed by direct patient interview and from patient medical records.

4.2.5.1 Demographic Questionnaire

The demographic questionnaire used for this study was a modified version of that used by Coles et al.(108) The questionnaire was designed to be completed by direct patient interview. The collected information was then confirmed by checking the patient's medical records. Medical records were also used to complete any missing information, obtain drug history, and/or medical and surgical history.

The demographic questionnaire contained the following items (See Appendix 6):

i. Patient's location, gender, and age.
ii. Reason and date of admission.
iii. Medical and surgical history. This included all known risk factors for LUTS.
iv. CA use, drug, dose, strength, reason for use, and duration of use.
v. Current and past medication history for the past 6 months, excluding non-regular medications.
vi. Any other non-documented medical condition reported by the patients and the patient was not taking treatment for.

For the purpose of the study, patients with minor strokes were not separated from those with major strokes with disabilities because the questionnaire design was not meant to evaluate the severity of the stroke.

Patients with history of alcoholism were considered under alcoholism because the collected data does not include questions about the quantity and duration of alcohol use and/or the withdrawal dates.

Only morbidly obese patients, as classified in doctors' note, were considered as obese. The exact weight and height were not documented by the investigator during patient interviews.

4.2.5.2 International Prostate Symptoms Score (IPSS)

The IPSS is a validated, seven-point questionnaire used to assess LUTS severity and associated QoL. The American Urological Association (AUA) developed the AUA Symptoms Index for evaluating prostate induced LUTS. The questionnaire was later adopted and validated by international consultations on BPH and named the International Prostate Symptoms Score (IPSS).(109) (Appendix 7)

4.2.5.2.1 IPSS Description

The IPSS consists of seven simple self or investigator-administered, questions measuring different LUTS. The questionnaire covers the following symptoms: incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. The questions were designed as a scale ranging from zero to five. For nocturia (the seventh question) each number represents the number of times where the patient has to wake up at night to urinate (0 => zero times; ...; 5 => 5 times or more). For the other six symptoms the numbers represent the frequency of symptoms (0 => Not at all; 1 => Less than one time; 2 => Less than half the time; 3 => About half the time; 4 => More than half the time; 5 => Almost Always). The scores to these questions were summed to obtain a total IPSS ranging from 0 to 35. The AUA has developed a reference range for the scores as shown in Table 4-2.(110)

Table 4-2 AUA Classification for LUTS Severity

Score	Severity of Symptoms
Less than 7	Mild / No symptoms
8- 19	Moderate
20- 35	Severe

For the seventh question (nocturia), where patients were asked to provide the number of times they wake up at night to urinate, some patients provide a range rather than a

definitive number. For such cases, the average score was calculated (e.g. if a patient provided 3-4 times as the answer, a score of 3.5 was used).

For the purpose of the study, symptoms were categorized as mild/ no symptoms (less than 7), moderate (7.5-19), and severe (19.5-35). However, the cut-off point for severity is arbitrary. Two patients may have similar LUTS scores and symptoms (e.g. 19 and 20), yet fall into different severity categories, whilst patients may be in the same severity category, but have vastly different symptoms (e.g. two patients may have moderate LUTS but scores of 8 versus 19).

The IPSS has a QoL question to measure LUTS associated QoL. Clinically, increases in LUTS score are associated with deterioration in QoL. The degree to which patients are bothered about their symptoms predicts the likelihood of seeking medical advice.(110)

The IPSS also has been validated as a non-BPH specific questionnaire. Hence, it can be used for all LUTS associated with bladder, sphincter or urethra abnormalities.(111, 112)

4.2.5.2.2 Validity for women

The IPSS was developed initially for male LUTS associated with BPH. However, it was found to be a non-gender, non-disease specific questionnaire.(109) Further research has revealed that the IPSS is as useful in females as it is in males. It provides a similar outcome, despite the fact that males might have higher scores.(113-115)

4.2.5.2.3 Limitation of IPSS

The IPSS does not include a specific question about urinary incontinence, which is more common in women.(116) Thereby, this study did not assess urinary incontinence, despite the fact that it has been proven that urinary incontinence may affect IPSS.(117)

4.2.5.3 Benign Prostatic Hyperplasia Impact Index (BII)

The BII was also developed by the AUA, and it measures the impact of LUTS on urological QoL and its interference with patient's daily activities.(110) Appendix 8

4.2.5.3.1 BII Design

BII consists of four simple questions, which can be self or investigator administered. The total score for the questions range from 0 to 13, where higher scores means lower QoL.

4.2.5.3.2 Validity for women

BII was also found to a valid tool for measuring LUTS associated QoL in women.(118, 119)

4.2.6 Data Analysis

Statistical analysis for the data was performed using Statistical Analysis System (SAS) version 9.1 and the Statistical Package for Social Sciences (SPSS) version 15.0.

Each categorical variable was analysed for their frequencies and distribution amongst different groups. While test statistics, mean and standard deviation were performed for continuous variables. The relationship between LUTS IPSS and QoL scores, age, and other continuous variables were analysed using Pearson correlation. The Chi square test and Fisher's exact test were used to compare the categorical variables.

Multivariate analysis using logistic regression was used to determine if CAs were contributing to LUTS after adjusting for other risk factors. The odds ratios of each individual risk factor and for CAs were also estimated.

4.3 Results

4.3.1 Demographics

4.3.1.1 Study Sample

A total of 322 patients were approached of whom 32 declined to participate (or asked for an interview at a later stage) and 279 patients were recruited into the study. One female patient withdrew consent after speaking to her family, and subsequently, her

questionnaire was destroyed in her presence. All remaining 278 (99.7%) completed the study.

4.3.1.2 Age and Gender of Participants

4.3.1.2.1 Gender

There were 151 males (54.3%) and 127 females (45.7%) patients included in the study. This is slightly different from the West Australian demographic where, according to Australian Bureau of Statistics (2006), there are 49.1% males and 50.9% females. The latter figures are also consistent with the national data which shows that Australian male population is 49.4% and females are 50.6%.(120)

4.3.1.2.2 Age

The mean age of the participants was 72.06 ± 13.73 years, with the range from 42 to 96 years (95% CI: 70.44-73.68). The distribution for both genders amongst the different age groups is shown in Table 4-3.

The mean age for male and female participants was 70.68 ± 14.51 years and 73.7 ± 12.6 years, respectively. Despite the females appearing to be slightly older, there was no statistically significant difference between the two groups (Difference = 3.02 years; p= 0.68).

It is clear from the data presented in Table 4-3 that more than half of the females and about half of males were aged between 70 and 90. The data also show that there were more males aged younger than 50 years (11.3%) compared to females (4.7%). A similar distribution, to a lesser extent, is also obvious for patients above 90 years where there were 7.3% males compared to only 5.5% of females.

Table 4-3 Age Distribution by Gender

Age Range	Gender of the Participant n(%)		Total
	Male	Female	
below 50	17 (11.3%)	6 (4.7%)	23 (8.3%)
51-60	26 (17.2%)	16 (12.6%)	42 (15.1%)
61-70	23 (15.2%)	24 (18.9%)	47 (16.9%)
71-80	37 (24.5%)	34 (26.8%)	71 (25.5%)
81-90	37 (24.5%)	40 (31.5%)	77 (27.7%)
91-100	11 (7.3%)	7 (5.5%)	18 (6.5%)
Total	151	127	278

4.3.1.3 Types of Medical Wards

Patients were recruited from both long and short stay medical wards. A total of 96 patients (34.5%) were interviewed during their hospitalisation in the short stay ward. While the remaining 182 patients (65.5%) patients were recruited from long stay medical wards. The distribution is shown in Table 4-4.

Table 4-4 Patient Distribution by Ward Type

Type of Wards	Ward	Frequency	Percent (%)
Long Stay	1LS*	59	21.2
	2LS	58	20.9
	3LS	57	20.5
	4LS	8	2.9
Short Stay	1SS^	96	34.5
Total		278	100.0

*LS: Long stay. ^SS: Short stay.

4.3.1.4 Length of Stay before the Interview

The average patients' length of stay before being interviewed is 5.02 ± 4.14 days. The average length of stay for males is 5.11 ± 4.27 days, and for females is 4.91 ± 4 days. There is no statistically significant difference between the pre-interview length of stay of males and females p= 0.7.

The length of stay, as expected, was statistically significantly different between patients in long and short stay wards $p < 0.001$. The average length of stay for patients in short stay wards was 3.29 ± 2.04 days, and for patients in long stay it was 5.93 ± 4.65 days.

4.3.1.5 Reason for Admission

There were different reasons for patient admissions. For the purpose of analysis, reasons for admission were sub-classified into two main categories:

a) **Urinary related admission**: this included urinary symptoms, infection, and all other urinary related disorders/ diseases.
b) **Non-urinary related admissions**: for all other reasons.

Only 19 patients (6.8%) were admitted because of urinary related issues. This number is considered relatively small and is not expected to have an impact on the distribution of urinary symptoms.

4.3.1.6 Surgical History

About three quarters (74.4 %) of the participants had a history of surgery at the time of admission. However, only 12.9% of participants had had urinary related surgery. Table 4-5 shows the surgical history distribution for the participants.

Table 4-5 Patient's Surgical History

Surgical Procedure	Number of Patients	Percentage (%)
No	71	25.5
Urinary Related Surgery	36	12.9
Non-Urinary Related Surgery	171	61.5

4.3.1.7 Risk Factors

A number of risk factors which are known to cause LUTS were identified and analysed separately. These are discussed below.

4.3.1.7.1 Drugs

The patients were grouped into two broad categories with regards to their use of drugs that might cause LUTS: (i) Patients who took at least one drug (other than CAs) that is known to cause LUTS and (ii) Patients took no drugs that are known to cause LUTS.

About three quarters of the patients (74.1%) were taking at least one drug, other than CAs, that is known to cause LUTS.

4.3.1.7.2 Diseases and Surgical Procedures

A number of medical conditions and surgical procedures which are known to cause LUTS were analysed for their distribution in both genders and association with the severity of LUTS. More than a third of patients (36.3%) had diabetes, while just under a quarter (23%) had had a stroke/TIA. About one third of the patients were identified as obese. Figure 4-2 presents the ranking for the different risk factors

All non-gender-specific risk factors other than recurrent urinary tract infections were equally distributed between males and females with no statistically significant difference between them. Recurrent urinary tract infections were significantly more in prevalent females (11%) compared to males (2.6%), p = 0.005.

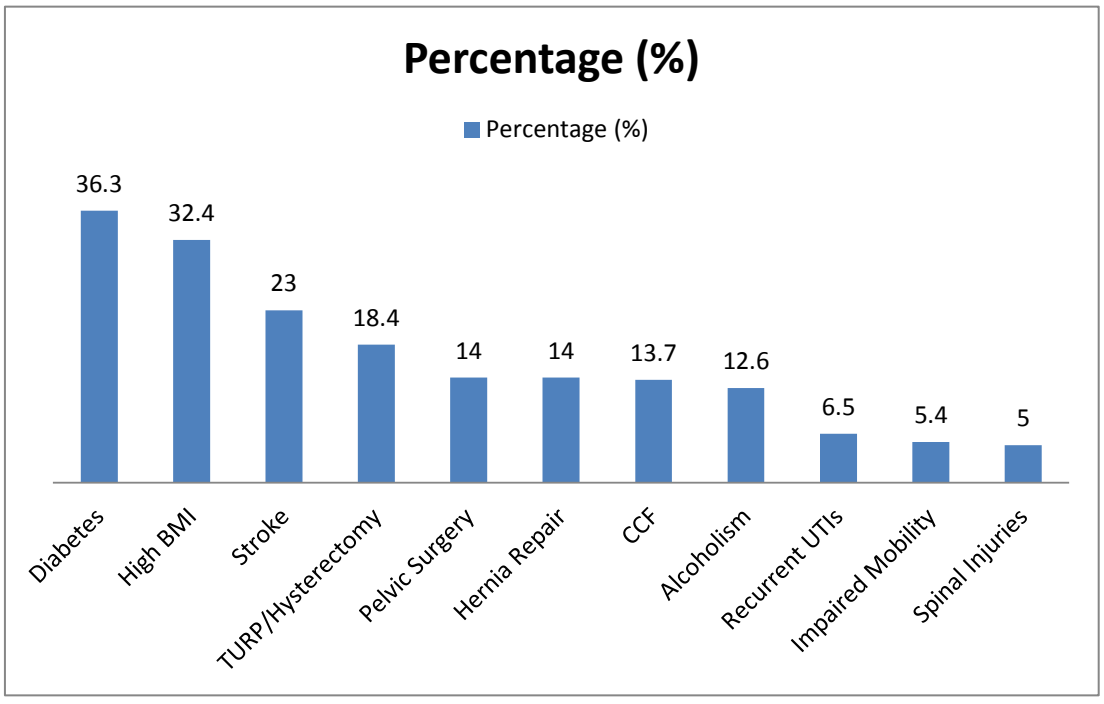

Figure 4-2 The Major Risk Factors' Distribution

4.3.1.8 Past Medical and Surgical History (Other than the Risk Factors)

The past medical and surgical history was obtained by direct patient interview and by review of patients' medical records.

4.3.1.8.1 Past Medical history

The most commonly reported medical condition was hypertension which affected 60.8% of participants. The second most commonly reported condition was ischaemic heart disease with 43.9% of patients suffering from this condition. Figure 4-3 shows the top 10 most commonly reported medical conditions.

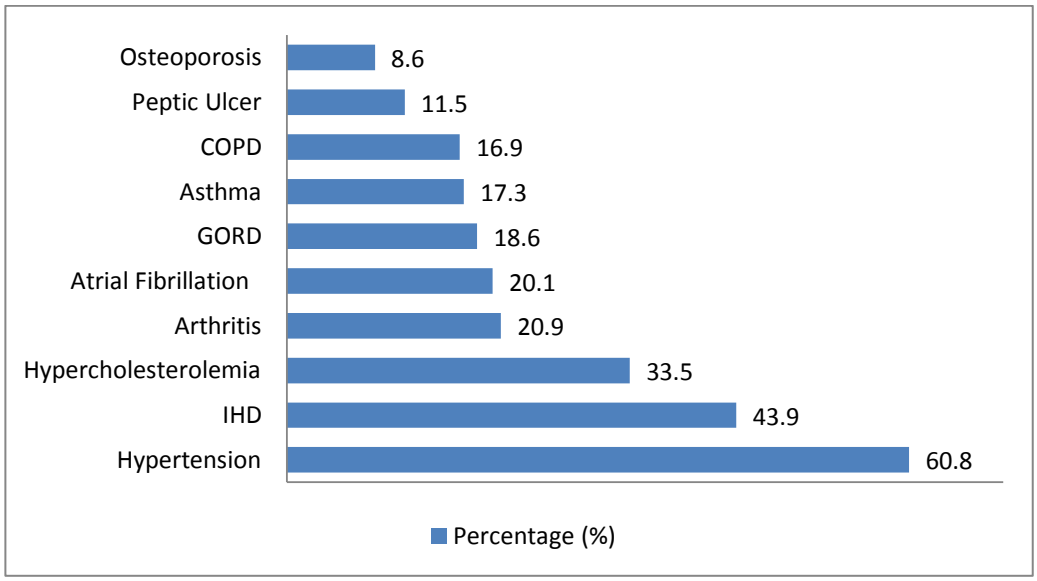

Figure 4-3 Top 10 Reported Medical Conditions

From the data presented in Figure 4-3, it is clear that the number of patients suffering from cardiovascular conditions was high. This might have increased the probability of the patients taking CAs.

4.3.1.8.2 Past Surgical History

Appendectomy was the most commonly reported surgical procedure (16.2%), followed by coronary bypass surgery (Percutaneous Coronary Intervention, PCI) (14.4%). Table 4-6 shows the ranking of the top 5 most commonly reported surgical procedures.

Table 4-6 Past Surgical History of Patients

Rank	Surgical Procedure	Percentage
1	Appendectomy	16.2
2	Coronary Bypass	14.4
3	Cholecystectomy	13.7
3	Knee Replacement	13.7
5	Tonsillectomy	5.8
5	Mitral Valve Replacement	5.8
5	Hip Replacement	5.8

4.3.2 Medication Use

4.3.2.1 Calcium Antagonists Distribution

A total of 85 patients (30.6%) were using at least one CA. The distribution was not equal between the two main classes (DHP and non-DHP) and individual drugs within each group. Two patients were using two CAs at the same time (one DHP and one non-DHP). About 13% of the participants were using non-DHP only, and 84.7% were using DHP. Table 4-7 shows the distribution of each individual drug and subclass.

Table 4-7 CAs Distribution

CA Subclass	CA	Number of Patients	Percentage (%)
DHP	Amlodipine	39	45.9
DHP	Felodipine	13	15.3
DHP	Lercanidipine	12	14.1
Non-DHP	Diltiazem	10	11.8
DHP	Nifedipine	8	9.4
Non-DHP	Verapamil	1	1.2
Mixed	Amlodipine / Diltiazem	1	1.2
Mixed	Felodipine / Verapamil	1	1.2
Total		**85**	**100**

Amlodipine was the most frequently prescribed CA amongst the participants. This high prescription rate is consistent with the Australian prescribing trends where amlodipine is the most commonly prescribed CA in Australia making up about one third of the total Australian CA prescriptions.(64) CA use was significantly higher for females, where 37.8% of females were on a CA (56.5% of the total CA-users) compared to 24.5% of males, $p = 0.017$.

4.3.2.2 Indication and Duration of CA Use

4.3.2.2.1 Duration of CA Use

The duration of CA use was obtained from patients during their interviews and later confirmed by reviewing their medical records. For cases where a patient was unable to remember the exact the duration of therapy and the data was not available in the medical records, the Primary Investigator asked the patient to specify if the duration was more

than or less than a year. The date of starting on the first CA was documented for patients who are taking more than one CA at a time.

More than 90% of the patients had been using a CA for more than one year, with about a third of those taking CAs for more than 5 years. Only one patient was just commencing his CA when interviewed (Figure 4-4).

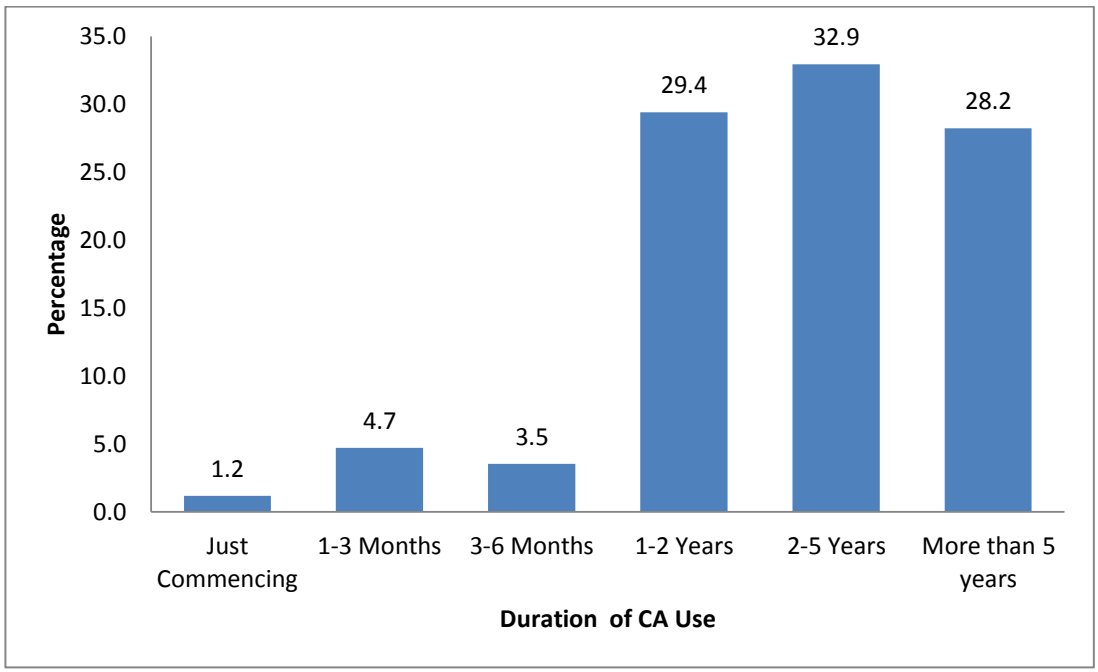

Figure 4-4 Duration of CA-Use before Interview

4.3.2.2.2 Indication for CA Use

The indication for CA use was documented only in few patients' medical records. This data was obtained primarily by direct patient interview and/or a review of their past medical history.

From the available data hypertension was the most commonly reported/documented indication for CA use (70.6% of patients). The second most commonly reported/documented indication for use was angina (27% of patients). About 18.8% of the total patients were using CA for both hypertension and angina. The proportion of

patients who used a CA for angina and also had hypertension was about 70% of total patients with angina, whereas only about 20% of patients with high blood pressure also had angina. For patients with heart failure and/or arrhythmia, the numbers were very low with only one patient in each category. Figure 4-5 shows the different reasons of CA use.

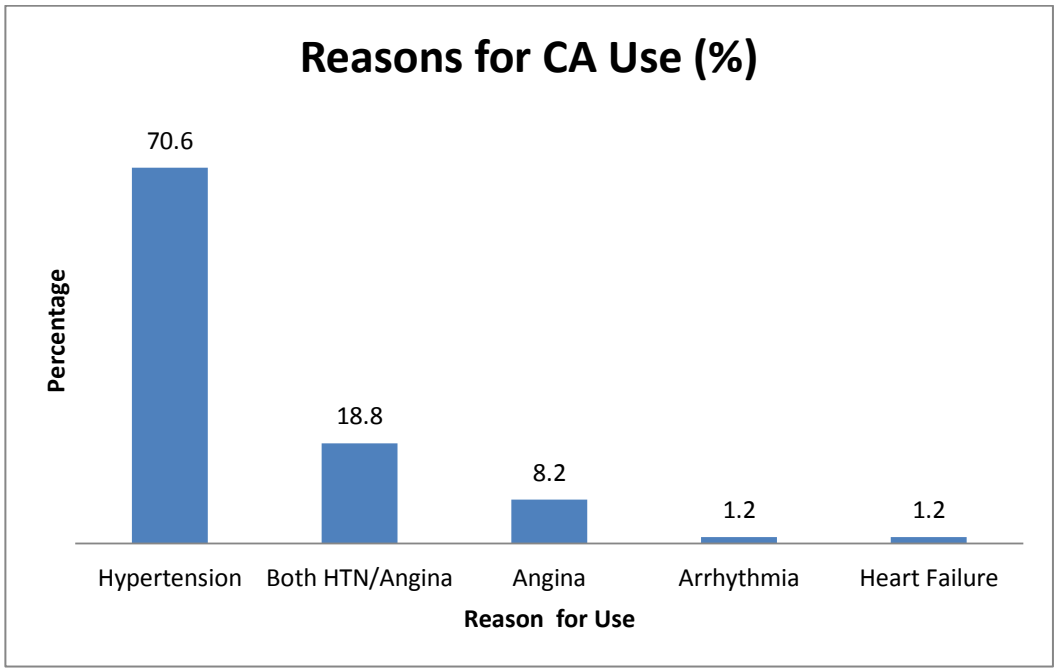

Figure 4-5 Reasons for CAs Use

4.3.2.3 Other Medications Distribution

Table 4-8 shows the distribution of other medications use amongst the patients. Antacids were the most commonly used drugs; where more than two third of the patients were using antacids. Lipid lowering drug and aspirin were used by about half of the participants. Other cardiovascular drugs including diuretics, angiotensin converting enzyme inhibitors, and beta blockers were also ranked on the top of the list. The high use of cardiovascular drugs, lipid lowering drugs and aspirin could be linked to the high prevalence of cardiovascular diseases amongst the sample.

Table 4-8 The Most Commonly Used Medication

Rank	Drugs	Percentage (%)
1	Antacids	68.6
2	Lipid Lowering	48.9
3	Aspirin	48.2
4	Diuretics (Thiazide/Loop)	47.5
5	Angiotensin Converting Enzyme Inhibitors	43.2
6	Beta Blockers	37.1
7	Paracetamol/ Narcotic Analgesics	36
8	Laxatives	28.8
9	Other Antiplatelets Aggregate	27
10	Inhaled Corticosteroid	25.6
11	Long Acting Beta Agonists	23.8
12	Short Acting Beta Agonists	20.9
13	Inhaled Anticholinergic drugs	20.9
14	Angiotensin Receptor Blockers	20.5
15	Biguanides	18.3

4.3.2.4 Seeking Treatment of LUTS

The relationship between CA use and genitourinary procedures was analysed. Medications for the treatment of overactive bladder and the use of alpha blockers for urinary retention was also analysed for their association with CA use. For the purpose of this analysis the CAs were further classified into the following three categories:

a) Non DHP: Verapamil/diltiazem.
b) High Vascular Selective DHP: Lercanidipine/felodipine.

c) Other DHP: Amlodipine/nifedipine.

4.3.2.4.1 Genitourinary Procedures

CA-users were also more likely to have had urogenital surgeries (16.5%) compared to non-CA-users (7.8%), Chi Square p= 0.029. Female patients who were receiving a CA were about nine times more likely to have urogenital surgeries (10.5%) than non-CA-users (1.2%), p=0.029. While, male CA-users were two times more likely to have urogenital surgeries (24.3%) compared to non-CA-users (12.3%), p= 0.07.

4.3.2.4.2 LUTS Treatment While on CA

The chances of being on treatment for LUTS (e.g. alpha blockers, oxybutynin) while using CAs were estimated using Pearson Chi Square Test or Fisher's Exact Test (if the expected value for one cell or more is less than 5).

An estimated 22.4% of the CA-users group were taking treatments for LUTS (obstructive and irritative) compared to 9.3% of the Non-CA-users group, p = 0.003.

This relationship was still statistically significant when analysis was performed separately for males (Pearson Chi Square, p = 0.03) and females (Fisher's Exact Test p = 0.006).

4.3.2.4.3 Use Alpha Blockers

The association between CA use and alpha blockers use was analysed in a similar way. Over three times as many CA-users (17.6%) were taking alpha blockers compared to non-CA-users (5.2%; Pearson Chi Square, p = 0.001).

About 27% of male CA-users were on alpha blockers compared to only 7.9% of non-CA-user, Fisher's Exact Test p = 0.004. Likewise, five out of six female CA-users were taking prazosin, which is uncommonly used for women as it is widely used for urinary retention (a problem usually linked to prostatism), Fisher's Exact Test p = 0.29.

The above relationship was not consistent among all CAs categories. There was no statistically significant association between non-DHP and high vascular selective DHP groups with alpha blockers use. However, the association was highly significant for patients who were taking other DHP (i.e. amlodipine or nifedipine) with 21.3% compared to 6.5%, Fisher's Exact test p= 0.003.

4.3.2.4.4 Use of Treatment for Overactive Bladder

None of the patients in Non-DHP or Other DHP groups were taking treatment for overactive bladder. Nevertheless, 16% of patients on high vascular selectivity DHP were on treatment for overactive bladder compared to 3.6% of non-CA-users, Fisher's Exact Test p = 0.021.

4.3.3 LUTS Prevalence and Distribution

4.3.3.1 IPSS Distribution

The average IPSS for all participants was 11.08 ± 7.59. Males had a statistically significantly higher mean IPSS 12.2 ± 8.19 compared to 9.74 ± 6.59 for females, p = 0.007.

4.3.3.1.1 Gender Distribution of Symptoms

LUTS were not equally distributed between males and females. Females were found to have experienced significantly lower prevalence of intermittence, weak stream, and straining compared to males, p = 0.001, 0.002, and <0.001, respectively. The graphical distribution is shown in Figure 4-6.

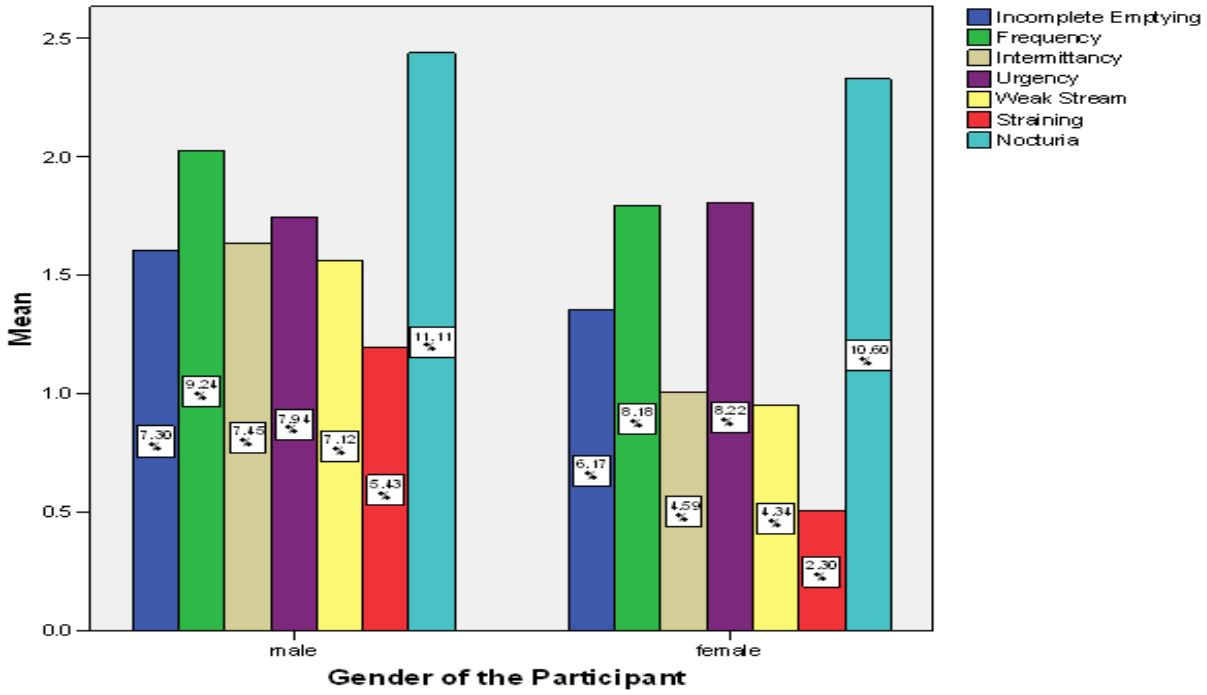

Figure 4-6 Symptoms Distribution by Gender
The mean represents the mean sore for every individual IPSS question on a scale (0-5)

4.3.3.1.2 CA and Symptoms Distribution

Patients on CAs had reported statistically significantly higher IPSS compared to non-CA-users. The mean IPSS was 15.22 ± 8.1 for CA-users and 9.25 ± 6.6 for non-CA-users, $p < 0.0001$. The significant increase was apparent in both men and women. For females, the mean IPSS was 7.4 ± 5.0 for non-CA-users and 13.7 ± 7.0 for CA-users, $p < 0.0001$. Similarly, the mean IPSS was significantly higher among male CA- users, 17.3 ± 8.9 compared to 10.6 ± 7.3 for non-CA-users, $p < 0.0001$

The distribution of each individual symptom was analysed using independent sample t-test. The analysis showed a statistically significant difference between CA-users and non-CA-users for all symptoms except straining (Table 4-9 and Figure 4-7).

Table 4-9 CA Use and the Difference in LUTS

Symptoms	Using CA	N	Mean IPSS	p- values
Incomplete emptying	No	193	1.306	0.005
	Yes	85	1.906	
Frequency	No	193	1.632	< 0.0001
	Yes	85	2.576	
Intermittency	No	193	1.036	< 0.0001
	Yes	85	2.059	
Urgency	No	193	1.311	<0.0001
	Yes	85	2.812	
Weak Stream	No	193	1.078	0.001
	Yes	85	1.753	
Straining	No	193	0.788	0.122
	Yes	85	1.082	
Nocturia	No	193	2.101	< 0.0001
	Yes	85	3.035	

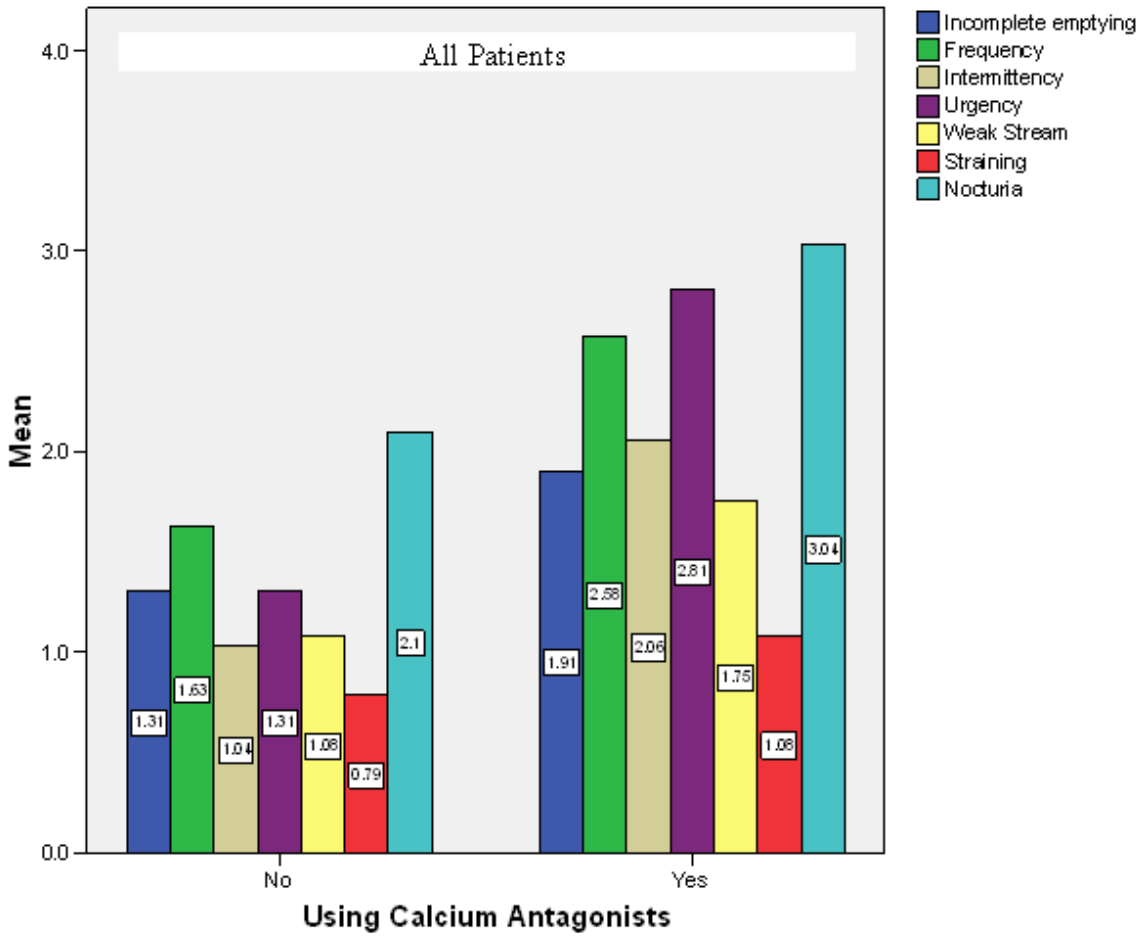

Figure 4-7 Distribution of Individual Symptoms by CA use
The mean represents the mean score for every individual IPSS question on a scale (0-5)

The increase in individual scores was significant for both genders. Table 4-10 and Figure 4-8 (A and B) show that females have a statistically significant increase for incomplete emptying and straining, while a similar increase was not significant for males.

Table 4-10 The Significance of Individual LUTS by Gender

	p Values						
Gender	**Incomplete emptying**	**Frequency**	**Intermittency**	**Urgency**	**Weak Stream**	**Straining**	**Nocturia**
Males	0.26	< 0.001	0.007	< 0.001	0.005	0.36	< 0.001
Females	0.002	< 0.001	<0.001	< 0.001	0.006	0.01	< 0.001

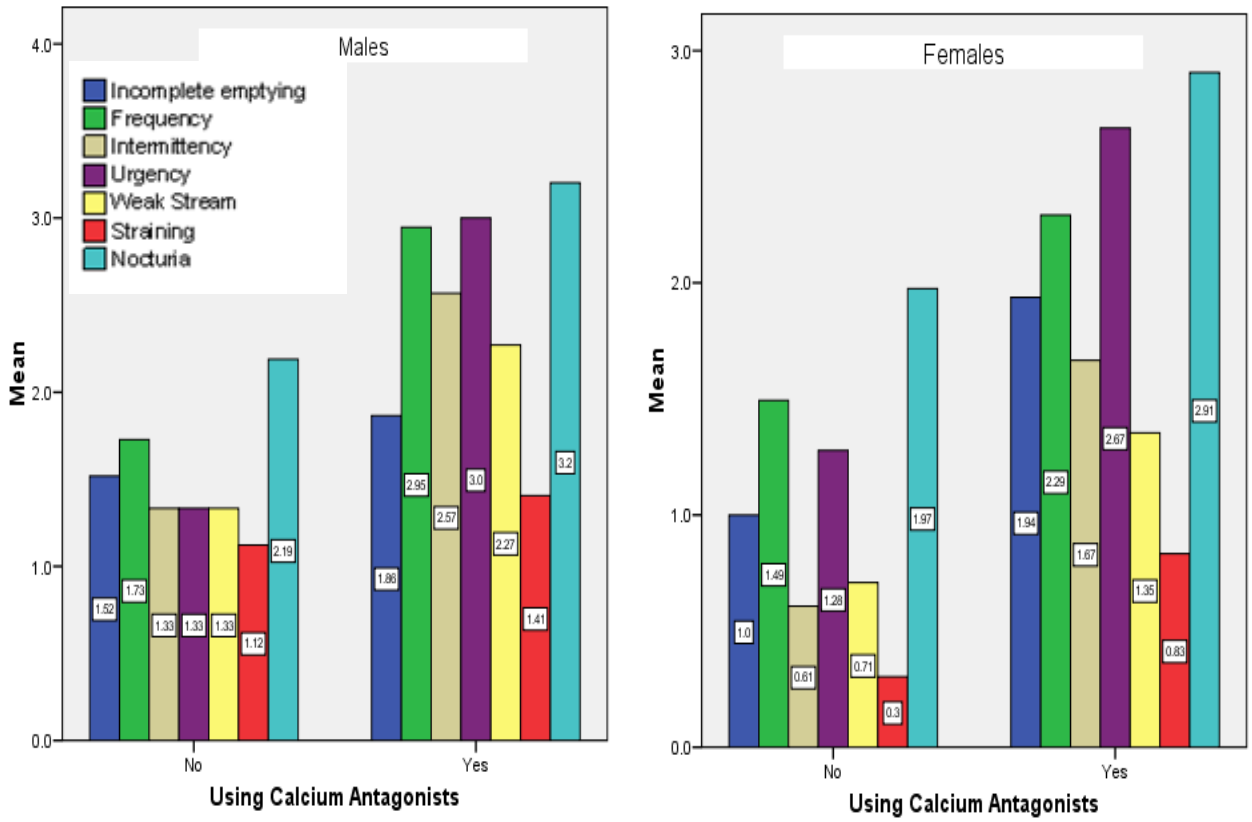

Figure 4-8 CA Use and LUTS by Gender
The mean represents the mean sore for every individual IPSS question on a scale (0-5)

4.3.3.1.3 Correlation between IPSS and Age

There is no statistically significant correlation between the increase in IPSS and age, Pearson Correlation r = 0.005, p = 0.94. The scattered graph below (Figure 4-9) shows

that the IPSS is independent of age for this study sample for both males and females. This finding is inconsistent with some other demographic data for general population where the increase is linked to ageing.(23, 121, 122) However, when we looked at the distribution LUTS within different age groups, there was an increase in the number of patients suffering from moderate-to-severe LUTS with age (Figure 4-10). Just over half the patients in their 40s were suffering from moderate-to-severe LUTS. This proportion was higher for older patients. About 53% of men and 50% of women have reported moderate-to-severe LUTS. The number increase to 65% for men in their 50s and about 73% for men older than 60 years. For women, the increase was not as steady (Figure 4-9).

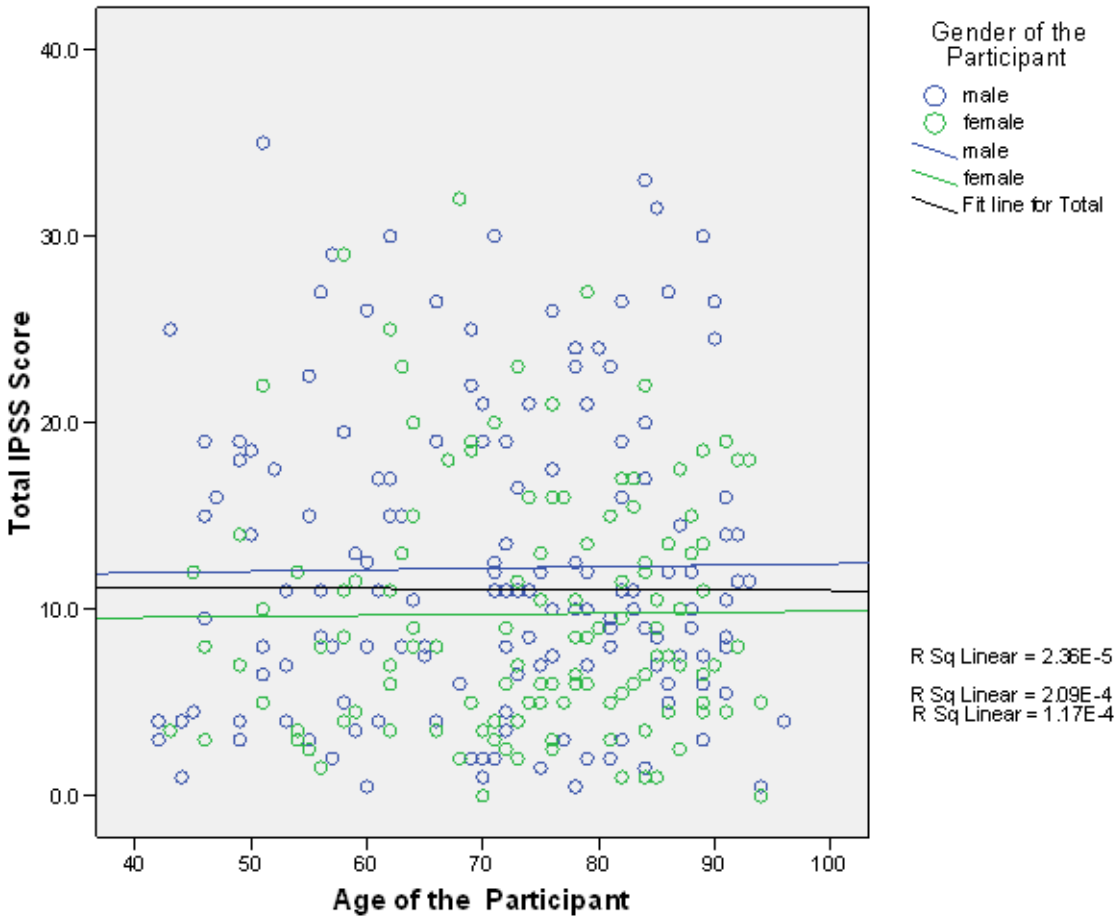

Figure 4-9 IPSS Correlation with Age

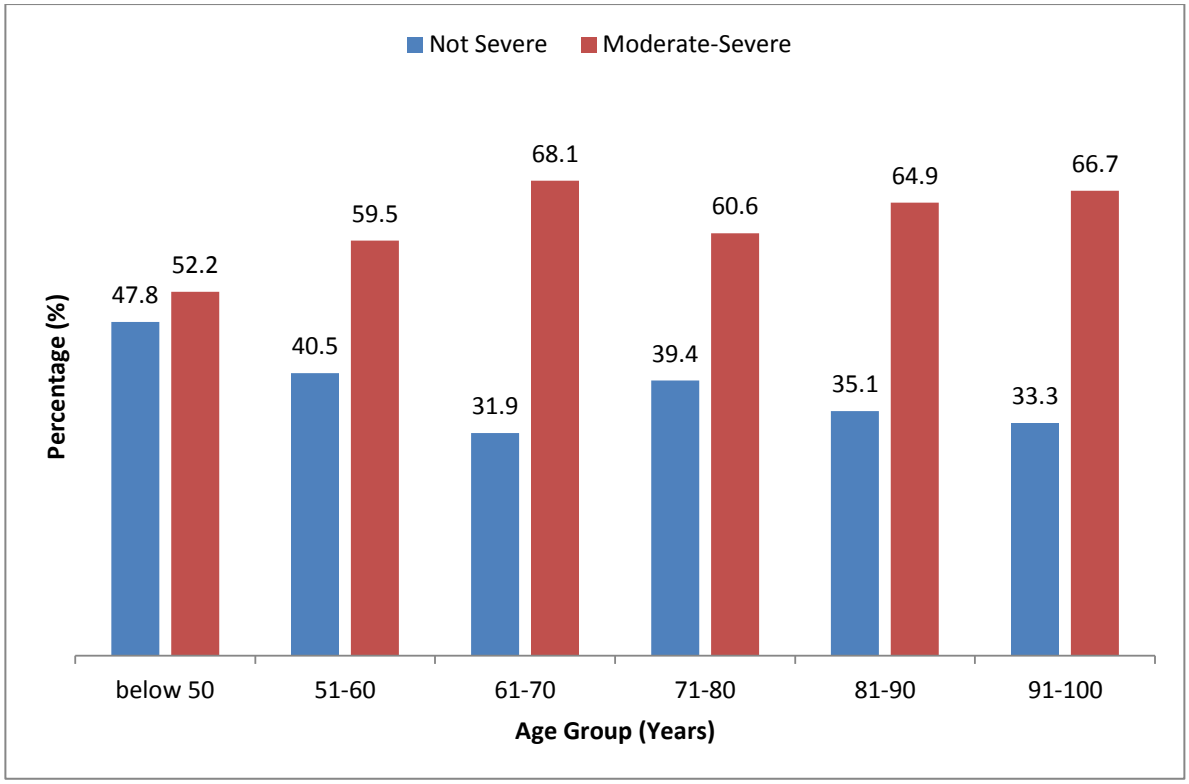

Figure 4-10 The Influence of Age and Gender on LUTS Severity

Table 4-11 Patients with Moderate-to-severe LUTS by Age

Age (years)	Patients with moderate-to-severe LUTS (%)	
	Male	Female
40-50	52.9	50.0
51-60	65.4	50.0
61-70	73.9	62.5
71-80	73.0	47.1
81-90	73.0	57.5
91-100	72.7	57.1

4.3.3.2 Severity of LUTS

The severity of LUTS was classified into three categories based on the patients' IPSS: mild (including no symptoms) for scores below 7, moderate (IPSS 7.5-19), and severe (IPSS 19.5- 35). Overall, 37.4% of patients were identified as mild, 48.2% as moderate, and 14.4% as severe.

4.3.3.2.1 The Effect of Gender on Severity of LUTS

A statistically significant difference was observed between genders with more males suffering from moderate and severe LUTS (p= 0.007) compared to females. Males, compared to females, were also more likely to suffer from severe LUTS, p= 0.013, and moderate-to-severe combined, p= 0.009 (Table 4-12).

Table 4-12 LUTS Severity by Gender

	Severity of LUTS		
	Mild	**Moderate**	**Severe**
Male	46 (30.5%)	76 (50.3%)	29 (19.2%)
Female	58 (45.7%)	58 (45.7%)	11 (8.7%)
Total	104 (37.4%)	134 (48.2%)	40 (14.4%)

4.3.3.2.2 Effect of CA use on Severity of LUTS

CA-users were more likely to suffer from moderate to severe LUTS (p <0.0001) compared to non-CA-users. CA-users were also more likely to suffer from severe LUTS, p= 0.001 and moderate-to-severe (p < 0.0001) than non-CA-users (Table 4-13).

Table 4-13 LUTS Severity by CA Use

	Severity of LUTS		
	Mild	**Moderate**	**Severe**
Non-CA-users	89 (46.1%)	85 (44.0%)	19 (9.8%)
CA-users	15 (17.6%)	49 (57.6%)	21 (24.7%)
Total	104 (37.4%)	134 (48.2%)	40 (14.4%)

The distribution of each individual CA is shown in Table 4-14.

Table 4-14 LUTS Severity for Individual CAs

	Severity of IPSS		
	Mild	**Moderate**	**Severe**
Amlodipine	2 (5.1%)	22 (56.4%)	15 (38.5%)
Diltiazem	-	7 (70%)	3 (30%)
Felodipine	7 (53.9%)	6 (46.2%)	-
Lercanidipine	6 (50%)	6 (50%)	-
Nifedipine	-	6 (75%)	2 (25%)
Verapamil	-	1 (100%)	-
Total	15	48	20

4.3.3.2.3 Length of Stay and Moderate/ Severe LUTS

Patients' length of stay before being interviewed did not seem to have an impact on the reporting of the symptoms with 63.5% of patients on short-stay and 62.1% of patients on long-stay wards reporting moderate-to-severe LUTS.

4.3.3.2.4 Effect of Other Risk Medication on LUTS

The data showed no significant association between using one or more drugs (other than CA) that are known to cause LUTS and severe or moderate-to-severe LUTS. About 13.6% of patients who were taking at least one risk drug compared to 16.1% of those who used none had suffered from severe LUTS, p =0.52. Similarly, 64.1% of patients on at least one risk drug suffered from moderate-to-severe LUTS compared to 58.3% of the non-CA-user, p = 0.39.

4.3.3.2.5 Effect of Other Risk Factors on LUTS

A number of risk factors including male gender had a significant contribution to LUTS among the study sample. Each factor were analysed for its contribution on both severe LUTS and the combination of moderate-to-severe LUTS. The list below shows the factors associated with severe LUTS and Moderate-to-severe LUTS.

i. **Severe LUTS:**
   1. Male Gender: p= 0.013
   2. Diabetes: p= 0.008
   3. BPH (males): p= 0.009
   4. TURP (males): p= 0.018
   5. Hysterectomy (females): p=0.003
   6. Hernia Repair Operation: p= 0.008

ii. **Moderate-to-severe LUTS**
   1. Male Gender: p= 0.009
   2. Hernia Repair Operation: p= 0.002

All the factors identified in the list above were reported previously in the literature to have some association with LUTS.

4.3.4 Logistic Regression for LUTS Severity

The significance of the association between each individual risk factor and LUTS was estimated using Chi square test and independent sample t-test statistics. Then multivariate analysis was performed after adjusting for risk factors that appear to have had a significant contribution to LUTS.

4.3.4.1 Logistic Regression for Severe Symptoms

CAs were analysed under three main categories: felodipine/lercanidipine (high vascular selective DHP), amlodipine/nifedipine (other DHP), and diltiazem/verapamil (non-DHP). None of felodipine/lercanidipine patients suffered from severe symptoms. Therefore, they were excluded from the analysis under severe symptoms category.

After adjusting for gender, alcoholism, gender specific genitourinary tract operations, and high BMI; patients who take amlodipine/nifedipine and diltiazem/verapamil had an adjusted odds ratios (AOR) for having severe LUTS of 9.8 (95% CI, 3.98-24.34) and odds ratios of 8.2 (95% CI, 1.93-34.92), respectively.

The significant association was apparent for both males and females; however, the contributing factors for LUTS were not the same across gender. Table 4-15 shows the AORs and the p-values for severe LUTS.

Table 4-15 Multivatiate Analysis for Severe LUTS

Variable	AORs (95% CI)	p-value
All patients with severe LUTS		
Gender (female)	0.24 (0.10-0.57)	0.001
Alcohol	3.28 (1.15-9. 36)	0.27
Gender specific operation (hysterectomy and TURP)	5.09 (2.10-12.35)	<0.001
Obesity	3.47 (1.49-8.07)	0.004
Amlodipine/nifedipine	9.84 (3.98-24.34)	<0.001
Diltiazem/verapamil	8.20 (1.93-34.92)	0.004
Males with severe LUTS		
Alcohol	6.72 (1.93-23.37)	0.003
BPH	5.34 (1.66-17.19)	0.005
Obesity	2.77 (1.01-7.58)	0.048
Amlodipine/nifedipine	7.34 (2.43-22.26)	<0.001
Diltiazem/verapamil	12.45 (1.57-98.63)	0.017
Females with severe LUTS		
Hysterectomy	5.92 (1.41-24.81)	0.039
Amlodipine/nifedipine	10.48 (2.23-49.19)	0.003
Diltiazem/verapamil	7.75 (0.94-63.94)	0.057

4.3.4.2 Logistic Regression For Moderate-to-Severe Symptoms

All patients on diltiazem/verapamil had reported moderate-to-severe LUTS. For the purpose of further analysis they were merged with amlodipine/nifedipine groups to form a new group called ‘Other CA’.

After adjusting for gender, gender specific operations, and high BMI; the AOR of having moderate to severe symptoms when using other CA was 37.45 (95% CI, 8.56-163.88). Patients on felodipine/lercanidipine were not shown to have a statistically significant increased risk of LUTS compared to non-CA-users, AOR 1.37 (95% CI, 0.55-3.36). Table 4-16 shows the different risk factors for moderate-to-severe LUTS and the corresponding AORs for males and females.

Table 4-16 Multivariate Analysis for Moderate-to-severe LUTS

Variable	AORs (95% CI)	p-value
All patients with moderate-to-severe LUTS		
Gender (female)	0.33 (0.19-0.59)	<0.001
Gender specific operation (hysterectomy and TURP)	2.12 (0.99-4.55)	0.053
Obesity	2.32 (1.27-4.26)	0.007
Felodipine/lercanidipine	1.37 (0.55-3.36)	0.499
Other CAs	37.45 (8.56-163.88)	<0.001
Males with moderate-to-severe LUTS		
Obesity	2.48 (1.07-5.76)	0.035
Felodipine/lercanidipine	0.95 (0.24-3.84)	0.945
Other CAs	17.43 (2.26-134.39)	0.006
Females with moderate-to-severe LUTS		
Felodipine/lercanidipine	1.21 (0.41-3.58)	0.725
Other CAs	47.80 (6.22-367.37)	<0.001

4.3.5 Quality of Life (QoL) of the Participants

4.3.5.1 Impact of LUTS on QoL

Figure 4-11 A and B show that an increase in IPSS leads to similar increases in both BII and IPSS-QoL score. This indicates a significant deterioration in QoL with the increase in IPSS.

The correlation between IPSS QoL score and the total IPSS was statistically significant ($p < 0.0001$) for both genders (Pearson Correlation for males $r= 0.64$ and for females $r= 0.5$).

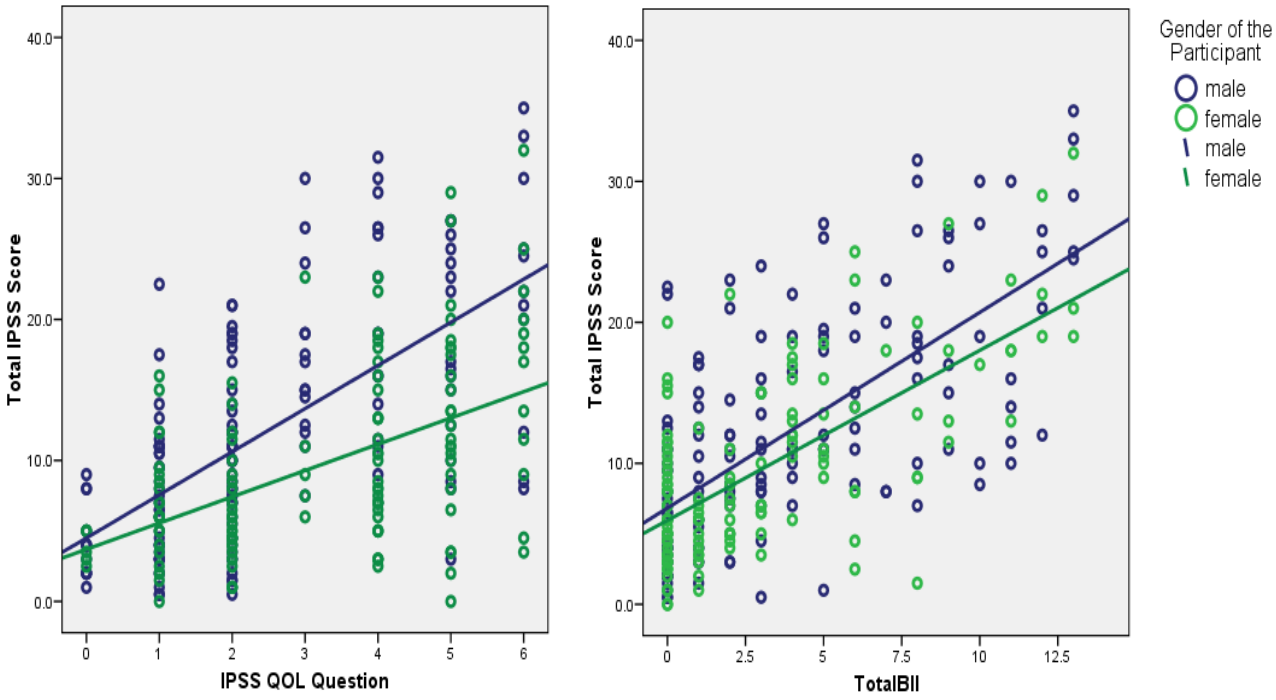

Figure 4-11 The Correlation between BII and IPSS-QoL with the Total IPSS

4.3.5.2 Age and QoL

QoL appears to be independent of age among the study sample. There was no statistically significant relationship between increase in age and either BII or IPSS QoL question scores.

4.3.5.3 Gender Difference in QoL Reporting

Dissatisfaction is derived from the IPSS QoL question where the score is 4 or more. Males had a lower tendency to report their dissatisfaction compared to females. Table 4-17 shows the percentage of patients who reported their dissatisfaction within each severity category by gender.

Table 4-17 Percentage of Dissatisfaction within IPSS Severity

	Dissatisfied/total (%)		
	Mild	**Moderate**	**Severe**
Males	2/46 (4.3%)	19/76 (25%)	22/29 (75.9%)
Females	19/58 (32.8%)	39/58 (67.2%)	10/11 (90.9%)

4.3.5.4 Relationship between CA Use on QoL

CA-users generally were more dissatisfied with their current urinary symptoms compared to non CA-users (55.3% vs. 33.2%, $p= 0.001$). The association was significant for women ($p < 0.0001$), but not for men ($p = 0.85$). Patients on CA showed statistically significantly higher BII scores ($p = 0.017$) and IPSS QoL question scores ($p < 0.0001$).

The correlation was statistically significant between total BII and total IPSS (Pearson Correlation $r= 0.67$ for either genders, $p < 0.0001$) (Figure 4-12).

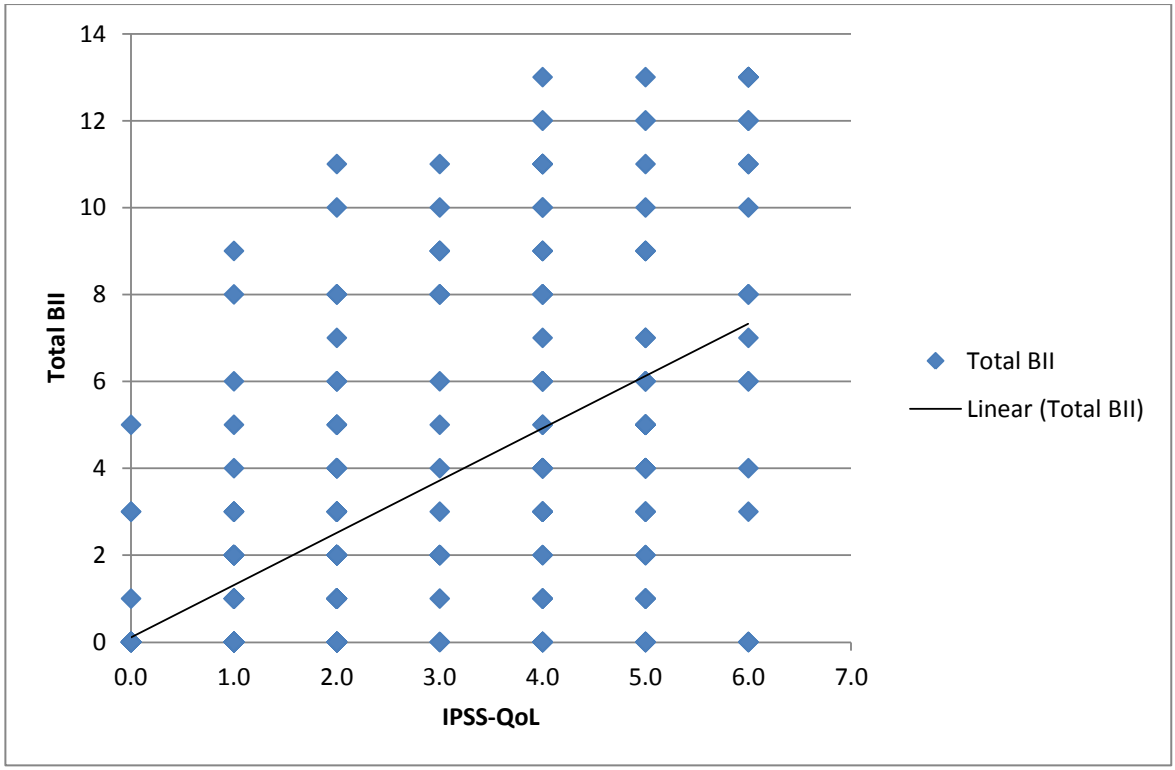

Figure 4-12 Correlation between IPSS-QoL and BII

4.3.6 Logistic Regression for QoL

Logistic regression was conducted for both IPSS-QoL and BII questionnaire responses. The cut-off point for dissatisfaction was not clear for BII as it is a sum of four questions (maximum 13). Thereby, we extrapolated the cut point for dissatisfaction from IPSS-QoL to estimate that by using Figure 4-12. The cut point was estimated to be 4, thus any scores higher than four were considered dissatisfaction.

The AORs were calculated for factors that appeared to have contributed to patients' dissatisfaction.

4.3.6.1 Logistic Regression for Dissatisfaction Using IPSS-QoL

Logistic regression was performed for the QoL reported using IPSS-QoL. The estimate for dissatisfaction was any score above the cut-off point three. After adjusting for other contributing risk factors, gender remained the only contributing factor to dissatisfaction, other than CA use, AOR 2.80 (95% CI: 1.68-4.68). For men, however, BPH was the

main contributor to dissatisfaction along with CA use, AOR 3.65 (95% CI: 1.52-8.74). Compared to other CAs, felodipine/lercanidipine use was associated with better QoL. Table 4-18 shows the AORs and p-values for dissatisfaction using IPSS-QoL.

Table 4-18 Multivariate Analysis for Dissatisfaction Using IPSS-QoL

Variables Contributing to Dissatisfaction	AORs (95% CI)	p-value
All Patients		
Gender (female)	2.80 (1.68-4.68)	<0.001
Amlodipine/nifedipine	2.95 (1.51-5.78)	0.002
Diltiazem/verapamil	3.65 (1.02-13.01)	0.046
Felodipine/lercanidipine	1.12 (0.47-2.67)	0.80
Males		
BPH	3.65 (1.52-8.74)	0.004
Felodipine/lercanidipine	-	-
Amlodipine/nifedipine	1.80 (0.69-4.72)	0.231
Diltiazem/verapamil	2.51 (0.40-15.97)	0.339
Females		
Felodipine/lercanidipine	2.50 (0.83-7.51)	0.102
Amlodipine/nifedipine	5.90 (2.01-17.32)	0.001
Diltiazem/verapamil	8.02 (0.92-69.92)	0.0597

4.3.6.2 Logistic Regression for Dissatisfaction Using BII Questionnaire

Unlike IPSS-QoL, the BII questionnaire has no clear cut-off point for dissatisfaction. To estimate a cut-off point we used the correlation plot (Figure 4-12) to extrapolate the corresponding cut point on the BII axis. The cut-off point was estimated to be 4.

Recurrent urinary tract infections (UTI) and amlodipine/nifedipine use appeared to have the most significant association with dissatisfaction. The other gender specific contributing factors and the AORs are displayed in Table 4-19.

Table 4-19 Multivariate Analysis for Dissatisfaction Using BII

Variables Contributing to Dissatisfaction	AORs (95% CI)	p-value
All Patients		
Recurrent UTIs	3.08 (1.08-8.77)	0.035
Amlodipine/nifedipine	11.26 (4.95-25.63)	<0.001
Diltiazem/verapamil	1.281 (0.37-4.47)	0.698
Felodipine/lercanidipine	0.29 (0.08-1.00)	0.049
Males		
Alcohol	2.58 (0.98-6.83)	0.060
BPH	7.71 (2.79-21.30)	<0.001
Felodipine/lercanidipine	-	-
Amlodipine/nifedipine	10.42 (3.17-34.24)	<0.001
Diltiazem/verapamil	0.86 (0.09-8.17)	0.896
Females		
Felodipine/lercanidipine	0.62 (0.16-2.37)	0.483
Amlodipine/nifedipine	16.21 (4.96-53.98)	<0.001
Diltiazem/verapamil	2.47 (0.51-11.96)	0.260

4.4 Discussion

4.4.1 Demographic Information

4.4.1.1 Age and Gender Distribution

The distribution of males and females was slightly different from the reported Australian and West Australian demographics.(120) The difference, however, was not expected to have an effect on the final LUTS scores as a separate analysis was conducted for males and females. In addition to that, necessary adjustments were made for gender, gender specific operations, and other related risk factors.

The distribution of age showed that over 80% of the males and 70% of the females were older than 60 years. Ageing have been often associated with high prevalence of LUTS in both males and females.(25, 27, 30) Thus, the higher percentage of patients suffering from both moderate and severe LUTS could be attributed to the increased mean age. Nevertheless, the age - IPSS correlation was not clear among the study sample. The association, however, did exist between the percentages of symptomatic patients (moderate-severe) within different age groups and the increase in age. A number of factors that could have contributed to the poor age - severity correlation including:

a) The uneven distribution of patients in different age groups and their higher mean age. About half the patients were aged between 70 and 90 years. While only small numbers are below 40 or over 90.

b) The setting of the study was targeted to hospitalised patients.

4.4.1.2 Admission Reasons and the Length of Stay

The target population was internal medicine patients not urology patients. Therefore, only a small percentage (6%) of the recruited patients was admitted because of urinary related complaints.

The significant difference between average length of stay before being interviewed of patients in long and short stay units was expected. The aim was to recruit the patient in

the shortest possible time to eliminate the impact of new drugs being administered in the hospital and the possible hospitalisation associated QoL deterioration. Patients generally transferred to the short stay units after being assessed in the Emergency Department and reassessed again in the Acute Assessment Unit (AAU). This made the first day interview impossible for the majority of cases. Apart from the delay in transfer within the hospital, patients in long stay units generally had poorer health conditions and the interview for many of them was possible only after their conditions had been stabilised. Such significant difference, however, did not have an effect on patients' LUTS scores. About the same proportions of patients in either side had reported moderate/ severe symptoms.

4.4.1.3 Risk Factors

Each individual risk factor was analysed for its association with the presence of severe or moderate-to-severe LUTS and their distribution by gender. Necessary adjustments were made by multivariate logistic regression for the factors that appear to have significant impact on LUTS and the odd ratios were calculated for them. Gender difference had an impact on both moderate and severe LUTS. Thus, it was considered as a risk factor and the odds ratio were adjusted for it. Similarly, gender specific operations (TURP and hysterectomy) had a significant association with the severity of LUTS and necessary adjustments were made.

In addition to the above risk factors, obesity appeared to have an impact on males moderate-to-severe and severe LUTS, while BPH had an impact on moderate-to-severe only. For females no risk factor appeared to have a significant impact on their severe LUTS, while gender specific operations had a significant association with moderate-to-severe symptoms.

Dates were not recorded along with the past medical and surgical history and medication history. Therefore, further analysis for the association between the causality and immediate/delayed effects with the severity of LUTS was not possible.

4.4.1.4 Past Medical/ Surgical History

The majority of patients were suffering from cardiovascular diseases with hypertension, atrial fibrillation, and ischaemic heart disease among the top five diseases reported. The high prevalence of cardiovascular diseases among the study sample could be due to the high average age of the participants. Ageing is associated with increased cardiovascular risk and disease.(123, 124)

The higher prevalence of cardiovascular diseases among the study sample is the most likely explanation for the high proportion of CA users (about one third). An earlier estimation based on the annual prescribing of CAs in Australia suggested that the ratio of 1:12 might exist in the general population above 40.(64) Considering the nature of the hospitalised participants, increased cardiovascular diseases, and their high mean age, such low ratio of 1:3 is not unexpected.

Despite the fact that three quarters of the participants had had at least one surgical procedure, only 13% had urinary related surgical procedures. About three quarters of the participants were using at least one drug (other than CA) that is known to cause LUTs. The effect of using one or more drugs that cause LUTs on the severity of LUTs was not clear and did not affect the symptoms distribution. This was unexpected findings and there is no clear explanation; the use of the medication could increase the prevalence and severity of LUTS, which was not true in this study.

4.4.2 Prevalence of LUTS

The prevalence of severe and moderate-to-severe symptoms appears to be higher than what had been reported in previous general demographic studies.(25, 27, 30) This increase could be due to the high mean age, the physical condition of the selected hospitalised cohort and the high level of CA use amongst the participants. The data however did not reflect an association between the severity of LUTS and age. The association was only present between the percentage of patients suffering from moderate-to-severe LUTS within each age category and the increase in age.

The high prevalence of LUTS in males is consistent with what has been reported in the literature.(1, 22-24, 125) The difference between males and females was evident for all the symptoms, males suffer from higher scores for all the symptoms but urgency. Statistically significance difference however was only clear for the obstructive symptoms of intermittency, weak stream, and straining. This could be due to the naturally higher prevalence of obstructive LUTS in elderly men.

4.4.3 CAs Induced LUTS

A very strong association was found between CA use and the change in the severity of symptoms. The average IPSS was significantly higher (about two folds increase) for CA-users regardless of their gender. This increase was significant for all the seven symptoms for women, while for males this was true with the exception of straining and incomplete emptying. By comparing the different CAs, patients on high vascular selective CAs had a distribution of symptoms (about 1:1) which was similar to those of non-CA-users. In addition to that, none of the patients on high vascular selective CAs had suffered from severe symptoms. The higher vascular selectivity of felodipine and lercanidipine appears to be associated with lower bladder selectivity. Lercanidipine has been reported to have 177 times higher vascular selectivity compared to its bladder selectivity.(92) The high selectivity of lercanidipine and its association with lower rates of LUTS was apparent within ADRAC reports where there was only one report of lercanidipine-induced LUTS. An intensive literature search and correspondence with the CA manufacturers have failed to locate any evidence on the bladder selectivity of felodipine.

The scarcity of the literature associating LUTS side-effects with CAs use may have lead to the negligence of such risk. Therefore, patients could be misdiagnosed and commence on drug treatment or operated on in order to resolve their symptoms. The data suggested that patients on CAs are more likely to have bladder-TURP (males) operations. The rate was nine times higher for females and two times for males. Furthermore, the percentage of patients who were taking alpha blockers was 3.5 times higher among CA-users. Five

out of the six female patients using an alpha blocker were also found to be taking a CA. However, none of these patients were taking high vascular selective DHP CAs.

Logistic regression confirmed the association between non-DHP (diltiazem, verapamil) and other DHP CAs (amlodipine, nifedipine) use and the existence of severe and moderate-to-severe LUTS. The odds ratio was statistically significant for both males and females. The logistic regression also showed that high vascular selective CAs (felodipine/lercanidipine) had an AOR which was not significantly greater than 1, potentially indicating that they are less likely to have an effect on LUTS.

Data from ADRAC (Chapter 3 page 32) and result from this study suggest that the other dihyropyridine CA (amlodipine and nifedipine) has a higher tendency to cause LUTS compared to non DHP. However, this is inconsistent with the finding in male patients of this study (as shown in section 4.3.4 page 72).

4.4.4 The Impact of LUTS on QoL

The significant correlation between IPSS and the deterioration in QoL was consistent with the previous literature.(23, 28, 30, 118, 126) The total IPSS and the QoL scores appears to be independent of age as there was no significant correlation between them. Gender reporting of the dissatisfaction was not consistent, with less men reporting their dissatisfaction. Although female patients had significantly lower IPSS, they had a higher dissatisfaction rate regardless of their IPSS severity. The proportion of dissatisfied males and females increased with the severity of LUTS. The high dissatisfaction rates among females could be another factor that might explain the high proportion of females amongst the ADRAC reports. The positive correlation with BII and the higher female scores were consistent with EPIC study results.(24)

4.4.5 CAs Use and the Deterioration in QoL

Patients on CA had statistically significantly higher dissatisfaction rates compared to the non-CA-users. This association was observed in both male and female patients. From the previous literature, it is clear that worsening QoL as a result of LUTS would make

more patients report their LUTS. Therefore, deterioration in QoL and worsening LUTS (measured by IPSS) could encourage the patients to seek medical advice.

4.4.6 Limitation of the study

This study had a number of limitations. There were no previous studies looking at CA and LUTS in females, therefore the sample size was calculated based on the available studies in males. The demographic questionnaire was not designed to collect dates for urogenital interventions and LUTS treatment commencement, thus causality could not be established. The study used the IPSS questionnaire which does not include a question for incontinence, therefore the prevalence of urinary incontinence and the impact that it may have on IPSS could not be assessed. The collection of the data by the primary investigator may have lead to a potential investigator bias.

4.4.7 Patient Comments

A considerable number of male patients who were suffering from LUTS expressed their acceptance of their worsening LUTS. Many male patients tend to justify their satisfaction with their current urinary symptoms “I’m getting old, what can I do about it?”, “It is okay for someone my age”, “I have friends who are far worse than me”, “damage done, what to do”.

From the patient comments provided during their interviews, men tended to accept changes to their LUTS as an inevitable part of ageing. From the ADRAC reports it was clear that the symptoms are reversible. Thus, cessation of CAs for patients suffering from LUTs side-effects might lead to a substantial improvement in their QoL due to the improvement of their LUTS scores.

Some other comments were suggesting an association between LUTS and CA use. A female patient indicated that her urinary retention started few months after commencement of verapamil. Another male patient indicated that he had suffered from

"very bad" obstructive symptoms while on verapamil for hypertension. During the last 4 years he has done prostate examination a number of times and his symptoms did not improve with prazosin use. After he had a sphincterectomy, before one year, his symptoms improved, but not completely. Three month after the interview his cardiologist switched verapamil with felodipine and his symptoms resolved completely.

4.4.8 Case study

A 68-year old female patient was admitted to Royal Perth Hospital medical wards on 21 October 2008 with exacerbation of asthma. Her past medical and surgical history included diabetes, hypertension, hypercholesterolemia, cholecystectomy, hysterectomy, cervical cancer, fistula, persistent urinary retention, and persistent urinary incontinence. The patient was allergic to perindopril (throat and mouth swelling). Her medication on admission included oxybutynin (for incontinence), prazosin (for hypertension and urinary retention), diltiazem (for more than 10 years), metoprolol, aspirin, atorvastatin, salbutamol nebuliser, ipratropium nebuliser, Symbicort®, folic acid, and pyridoxine. Her metoprolol was discontinued after admission. The patient was scheduled for cystoscopy to investigate her urinary symptoms on 8 December 2008.

Day two: The patient was interviewed by the primary investigator for the purpose of the study, her IPSS was 32 (severe LUTS) and she was very dissatisfied and "feel terrible".

Day three/four: She discussed the possibility of diltiazem discontinuation with her junior medical doctor. The doctor decided to put diltiazem on hold. Amazingly, her "leaking" stopped completely within 24 hours and her urinary symptoms improved. The primary investigator was contacted by the patient and re-interviewed again using IPSS using a modified IPSS (to cover the current symptoms after diltiazem cessation instead of a month period). Her new IPSS was 14 (moderate LUTS) and the patient was satisfied. The patient gave her consent to be followed up by the primary investigator to monitor the progress of her symptoms over time.

Day seven: Diltiazem was recommenced to manage her high blood pressure because there was no evidence to justify the cessation.

17 days post discharge: The patient was re-interviewed using the modified IPSS. The LUTS relapsed again and the IPSS was 33 and the patient was dissatisfied. The patient agreed to allow the primary investigator to contact her General Practitioner (GP) to discuss her LUTS. The GP had decided to let the patient go for the cystoscopy because she was on waiting list for over a year.

December 2008: The cystoscopy was conducted on the 8th of December and revealed no obvious cause for LUTS. A second cystoscopy was scheduled in March. The GP then decided to switch from diltiazem to lercanidipine following the investigator's advice.

January 2009: The patient was interview using IPSS questionnaire and her IPSS was 16 (moderate) with no leaking and the patient was satisfied. The GP had discontinued her oxybutynin and decided to leave prazosin for the control of hypertension.

The second cystoscopy was later cancelled.

4.5 Conclusions

This study demonstrated a significant association between CA use and LUTS. The problem was apparent for both males and females. The study also highlighted the strong relationship between increased LUTS and deterioration in urogenital QoL. Consequently, QoL deterioration was significant amongst CA-users. CA-users were more likely to be on a treatment for LUTS and to have had urogenital surgeries/intervention. The causality however could not be established.

The association between CAs and LUTS did not appear to be a class effect as users of highly vascular selective DHPs showed less severe LUTS. Suggesting that may be the preferred drugs amongst patients who require a CA and are at risk of or who have LUTS.

Chapter 5

5 Signals of CAs Association with LUTS amongst Veterans

5.1 Introduction

The evidence of the significant association between CA-use and LUTS from the ADRAC data and from the previous study has provided further evidence of the existence of a real problem. The second study especially as it also showed an increase in urogenital interventions and the use of LUTS treatments among CA-users. However, the relatively small sample size did not allow further analysis of the use of LUTS treatments for each individual CA.

Large prescription databases have been used before to detect or confirm the presence of potential adverse events.(127-136) Their use helped to create signals of possible/suspected adverse drug reactions and to confirm the presence of existing/known adverse drug reactions. The aim of this study was to investigate the presence of an association between CA-use and subsequent treatment of LUTS using the Australian Department of Veteran Affairs (DVA) database.

5.2 Method

5.2.1 Study Setting

The database used belongs to the DVA, Australia, which has been previously described in details in 2006.(136) In brief, DVA database contains information for 310 thousand veterans, which includes 80 million pharmacy records, 200 million medical and allied health service records, and more than six million hospital records. The database contains prescription medicines that are coded according to WHO anatomical and therapeutic chemical (ATC) classification and the Australian schedule of Pharmaceutical Benefits item codes. Hospitalisation records are classified according to the WHO International Classification of Disease (ICD-10) Australian modification.

5.2.2 Study Design

This study was performed using prescription sequence symmetry analysis for the DVA database. The prescription sequence symmetry analysis method was developed in 1996,

by J. Hallas to screen large prescription databases for evidence of potential/unknown adverse drug reaction.(127) The study methodology has been used previously in a number of publications.(127-135) When compared to normal cohort and nested case-control designs, prescription sequence symmetry analysis appears to have had a lower sensitivity.(132) Therefore, results from such studies are used to create signals or to highlight the possible existence of an adverse event.

Prescription sequence symmetry analysis is usually performed by identifying patients who have been commenced on the suspected index drugs (e.g. CAs) during the time frame for the study specified and have used a marker drug (e.g. LUTS treatment) or had an event (e.g. hospitalisation) within 12 months before or after. The method is designed to investigate any asymmetry in the distribution of either prescription of another medicine to treat the adverse drug reaction (prescription sequence symmetry) or other recorded events (prescription event symmetry).

5.2.3 Procedure

Prescription sequence symmetry analysis was carried out on data for the period between January 1st, 2004 and December 31st, 2008. Only individuals who started on LUTS treatment within one year of commencing of CAs for the first time were included in the study. Patients were then classified into two groups according to the temporal order of alternative sequence of prescription event. Patients who started on the index drugs (CAs) first and the marker drugs (LUTS treatments) second were classified as 'causal' group. Conversely, patients who started on the LUTS treatment first and CAs second were classified as 'non-causal'. The patients acted as their own controls in this study.

CAs group (index drugs) included the following drugs: amlodipine, felodipine, lercanidipine, nifedipine, verapamil, and diltiazem. LUTS Treatments (marker drugs) were studied under the following categories: urinary antispasmotics (ATC class G04BD), medicines for BPH (G04C), and prazosin.

5.2.4 Ethical Issues and Approvals

The study was approved by Curtin University Human Research Ethics Committee. The DVA data management team at the University of South Australia, Adelaide also approved the study.

The study had minimal risk for the patients. Researchers had access only to coded/grouped data, and only the data management team had access to the complete data. Curtin University researchers were provided only with grouped and analysed data.

5.2.5 Data Analysis

Data analysis was conducted with the help of the DVA's data management team. The sequence ratio (SR) was calculated by dividing the number of patients who commenced on a marker drug after an index drug by those who commenced the marker drug before the index drug ($n_{\text{Index} \rightarrow \text{Marker}} / n_{\text{Marker} \rightarrow \text{Index}}$). Under the null hypothesis these numbers should be equal. The SR was then adjusted for changes in prescribing trends over time to obtain the adjusted sequence ratios (ASR) and the corresponding confidence intervals.

5.3 Results

During the 5 years of the study, the data analysis showed that 1113 patients had used both CAs and prazosin within a 12 month period of each other. In total, 757 patients have started prazosin after commencing on CA, while 356 were taking prazosin when commenced on CAs with a crude SR of 2.13. The adjusted SR was calculated to be 1.91 (95% CI 1.69-2.17), which means about two fold (91%) increase.

The results for individual CAs are summarised in Table 5-1. It appears that there was a significant association between all CAs and prazosin use with a statistically significant ASR for all individual CAs.

Table 5-1 Symmetry Analysis of Individual CAs and Prazosin

Index Drug (CA)	n	Causal	Non-causal	Crude SR	Adjusted SR (95% CI)
Amlodipine	631	377	254	1.48	1.39 (1.18-1.63)
Felodipine	223	128	95	1.35	1.30 (1.00-1.69)
Lercanipidine	629	413	216	1.91	1.73 (1.47-2.04)
Nifedipine	248	153	95	1.61	1.49 (1.16-1.93)
Verapamil	216	135	81	1.67	1.56 (1.19-2.06)
Diltizaem	331	215	116	1.85	1.72 (1.38-2.16)

Prescription sequence symmetry in patients who received both CAs and prazosin

5.3.1 CAs and Urinary Antispasmodics

A total of 963 patients who had been prescribed both CAs for the first time and urinary antispasmodics within up to a year of each other were identified from the 5-year DVA data. The data included 562 causal and 401 non-causal cases with a crude SR of 1.40 and adjusted SR of 1.31 (95% CI 1.15-1.49). Despite showing an overall significant causal association between CA-use and subsequent urinary antispasmodics, the data did not provide such significance for individual CAs with the exception of verapamil as shown in Table 5-2.

Table 5-2 Symmetry Analysis of Individual CAs and Urinary Antispasmodics

Index Drug (CA)	n	Causal	Non-causal	Crude SR	Adjusted SR (95% CI)
Amlodipine	486	265	221	1.20	1.15 (0.96-1.37)
Felodipine	143	84	59	1.42	1.34 (0.96-1.86)
Lercanipidine	351	186	165	1.13	1.11 (0.90-1.37)
Nifedipine	154	87	67	1.30	1.22 (0.89-1.68)
Verapamil	154	98	56	1.75	1.64 (1.18-2.28)
Diltizaem	233	134	99	1.35	1.28 (0.99-1.67)

Prescription sequence symmetry in patients taking both CAs and urinary antispasmodics

5.3.2 CAs and BPH Medicines

Overall, there was no statistically significant association between CA-use and BPH medicines. For the 384 patients who started on both CAs and BPH treatment within up to 12 months apart (210 causal and 174 non-causal), the crude SR was 1.21 and the adjusted SR was 1.13 (95% CI 0.92-1.38). A statistically significant association was observed for lercanidipine and diltiazem, despite the absence of an overall association (Table 5-3).

Table 5-3 Symmetry Analysis of Individual CAs and BPH Medications

Index Drug (CA)	n	Causal	Non-causal	Crude SR	Adjusted SR (95% CI)
Amlodipine	215	111	104	1.07	1.02 (0.78-1.34)
Felodipine	68	36	32	1.13	1.09 (0.68-1.75)
Lercanipidine	151	94	57	1.65	1.48 (1.07-2.06)
Nifedipine	54	24	30	0.8	0.78 (0.46-1.34)
Verapamil	78	41	37	1.11	1.05 (0.67-1.64)
Diltizaem	109	70	39	1.79	1.51 (1.03-2.24)

Prescription sequence symmetry for CAs and medicines for BPH

5.4 Discussion

The results of this study demonstrated further evidence of existence of a significant association between CA use and obstructive LUTS. The likelihood of commencing on prazosin after taking CAs was increased by about two folds. This finding is consistent with previous finding for the hospitalised patients. Prazosin is an alpha blocker drug, which can be used to treat hypertension. It is more commonly used for the treatment of BPH and obstructive urinary symptoms like urinary retention. Further analysis for individual CAs, however, showed a statistically significant increase for all CAs. This finding is not consistent with the previous study where high vascular selective CAs have shown lesser association with obstructive symptoms. It is not clear, using this data, if the association is a true association because the data did not include other risk factors and other drugs in the analysis.

For urinary antispasmodic use, the results have shown a statistically significant association with CA use, while this significance was not reflected on each individual CA with the exception of verapamil. The results also failed to show an overall significance for BPH medication and also for individual drugs except lercanidipine and diltiazem. The above finding shows that the possible obstructive symptoms treated with prazosin could not be necessarily BPH related.

Prescription sequence symmetry analysis is a validated method for examining the association between a number of clinical issues and therapeutic classes of medicines.(127-136) On the contrary, this method has a number of limitations as it did not take in consideration other drugs or factors that may have caused the adverse event, it does not respond to non specific clustering of medicines, and it is difficult to control outcomes of exposure. There were a number of limitations to this study. The data obtained for all patients with no gender stratification, even though the previous study has shown a significant difference between males and females. The analysis for BPH medicines may have accidently included some females who are taking drugs like alpha blockers for some other medical condition.

5.5 Conclusion

Findings from this study have provided a strong signal of the association between CA use and obstructive symptoms. The study also has shown a potential association between some CAs and irritative urinary symptoms.

5.6 Prescription Event Symmetry Analysis

It was planned to conduct a prescription event symmetry analysis study to investigate the potential association between CA use and increased urogenital hospitalisation, procedures/operations, investigations, and urology related doctor visits. This study was not performed because of coding issues in the database. We managed to obtain only the hospitalisation data for bladder and prostate problems.

5.6.1 Hospitalisation and CA Use: A Prescription Event Symmetry Analysis

The data obtained showed that a total of 1011 veterans had bladder or prostate hospitalisation of whom 553 were causal and 458 were non-causal with a crude SR of 1.21 and adjusted SR 1.11 (95% CI, 0.98-1.25).

Chapter 6

6 Co-prescribing of LUTS treatment and CAs in Residential Aged Care Facilities

6.1 Introduction

Our previous studies assessing the association between CAs and LUTS have provided some useful information regarding the severity and the prevalence of LUTS amongst CA users. The DVA study has demonstrated a strong signal of association between CA use and LUTS through examining the ratios of patients subsequently prescribed LUTS treatment after commencing on a CA. While the study of hospitalised patients provided a quantitative measure of the prevalence and severity of CA associated LUTS, and their impact on QoL. Findings from both of these studies have shown a higher prevalence of LUTS treatment use amongst CA-users. The aim of this study was to investigate the co-prescribing of CAs and LUTS treatments amongst residents in Residential Aged Care Facilities (RACFs).

6.2 Methodology

This study involved a retrospective analysis for prescription records of residents from a number of RACFs in Australia.

6.2.1 Study Setting

Prescription data was obtained from Manrex Pty Ltd, which provides pharmaceutical services for a number of RACFs in Australia. Manrex Pty Ltd provides medications and medication administration aids for over 1,500 RACF residents.

6.2.2 Procedure

One year numerically coded prescription records (2009) were provided by Manrex Pty Ltd for the purpose of the study. The records included all medications supplied by Manrex Pty Ltd including OTC medicines. The data included a serial patient number, age, gender (incomplete), and the dispensing records. A statistical analysis was performed using the records to assess the likelihood of being on both CAs and

medication used to treat LUTS. The analysis was later expanded to investigate the association of all drugs with increased LUTS treatment use.

6.2.3 Ethical Issues and Approvals

The study has been approved by Curtin University Human Research Ethics Committee. The study had minimal risk for the patients. Researchers only had access to coded data.

6.2.4 Data Analysis

Statistical analysis was performed using SPSS version 17.0 and SAS version 9.1. Basic univariate analysis was performed for demographic information. Chi square test and logistic regression were used to identify drugs with a higher association with the use of LUTS treatments, and the AORs and CI were calculated.

6.3 Results

6.3.1 General Results

One year prescription records for 1,548 RACF residents were provided by Manrex Pty Ltd. The gender was missing for about 892 residents. Of the remaining 656 residents, there were 477 females and 179 males. The mean age of the residents was 89.61±11.97 years. There were about 224,000 dispensing records for 2009 in the data provided. When we divided the number of dispensing records by 12 month by the number of residents the average number of medication used by individual resident was estimated to be 12 medications.

6.3.2 CAs Distribution

A total of 297 (19.2%) of residents were dispensed at least one CAs during 2009. The distribution of these can be seen in Table 6-1.

Table 6-1 CAs Distribution for RACF Residents

CA	N	Percentage
Amlodipine	136	8.8%
Lercanidipine	55	3.6%
Diltiazem	41	2.6%
Felodipine	37	2.4%
Verapamil	27	1.7%
Nifedipine	23	1.5%
Total	319	20.6%

6.3.3 LUTS Treatments

Thirty nine residents (2.5%) were using alpha blockers and 42 residents (2.7%) were using BPH treatment. A total of 77 residents (5%) were using urinary antispasmodic drugs. The distribution of LUTS treatments can be seen in Table 6-2.

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Table 6-2 LUTS Treatment Distribution for RACF Residents

LUTS Treatment	N	Percentage
Prazosin	24	1.6%
Tamsulosin	15	1.0%
Terazosin	1	0.1%
Propantheline	6	0.4%
Solifenacin	21	1.4%
Darifenacin	1	0.1%
Finasteride	4	0.3%
Oxybutynin	54	3.5%
Tolterodine	3	0.2%
Desmopresin	1	0.1%
Total	130	8.7%

6.3.4 CAs and Alpha Blocker Use

CAs users were more likely to be on alpha blockers, AOR 2.11 (95% CI 1.05-4.26). Other drugs that appeared to have a significant association with increased alpha blockers user were atorvastatin, candesartan, dothiepin, gabapentin, indapamide, and antiepileptic drugs. Detailed information is illustrated in Table 6-3.

Table 6-3 Medications and Alpha Blocker Use

Variable	n/N (with drug)	n/N (without drug)	Odds Ratio	95% CI	p-value
All CAs	15/297 (5.0%)	24/1251 (1.9%)	2.11	1.05 to 4.26	0.0370
Atorvastatin	11/228 (4.8%)	28/1320 (2.1%)	2.36	1.13 to 4.94	0.0227
Candesartan	7/59 (11.9%)	32/1489 (2.2%)	4.88	1.90 to 12.48	0.0010
Dothiepin	2/15 (13.3%)	37/1533 (2.4%)	8.33	1.70 to 40.88	0.0090
Gabapentin	3/36 (8.3%)	36/1512 (2.4%)	4.13	1.16 to 14.72	0.0290
Indapamide	6/44 (13.6%)	33/1504 (2.2%)	7.08	2.60 to 19.27	0.0001
Antiepileptics	9/159 (5.7%)	30/1389 (2.2%)	3.70	1.65 to 8.28	0.0015

After examining individual CAs, diltiazem and verapamil were excluded from the analysis because none of the residents on them were using alpha blockers. Of the remaining DHP CAs, amlodipine was the only drug which had shown a statistically significant association with increased alpha blocker use. (Table 6-4)

Table 6-4 CAs and Alpha Blocker Use

Variable	n/N (with drug)	n/N (without drug)	Odds Ratio	95% CI	p-value
Amlodipine	10/136 (7.4%)	29/1412 (2.1%)	3.12	1.41 to 6.91	0.0050
Nifedipine	1/23 (4.4%)	38/1525 (2.5%)	1.34	0.15 to 12.01	0.7919
Felodipine	2/37 (5.4%)	37/1511 (2.5%)	2.73	0.59 to 12.52	0.1973
Lercanidipine	2/55 (3.6%)	37/1493 (2.5%)	1.02	0.21 to 4.98	0.9766

6.3.4.1 CAs and Prazosin Use

Factors associated with high prazosin use were almost the same to those of all alpha blockers. The most significant factors were use of: CAs (AOR 4.22; 95% CI 1.76-10.12), atorvastatin (AOR 3.27; 95% CI 1.31-8.18), candesartan (AOR 5.73; 95% CI 1.91-17.20), indapamide (AOR 7.73; 95% CI 2.35-25.49), rosuvastatin (AOR 9.0; 95% CI 1.33-60.87), and antiepileptic drugs (AOR 5.43; 95% CI 1.95-15.13). None of the patients on non-DHPs were using prazosin. Amlodipine was the only CAs with a statistically significant association with prazosin use, AOR 5.76; 95% CI 2.28-14.60.

6.3.5 CAs and Urinary Antispasmodics Use

Multivariate analysis demonstrated that CA users were more likely to be on urinary antispasmodic treatment, AOR 2.18 (95% CI 1.32-3.61). Neuroleptic drugs (imipramine and venlafaxine) were also associated with increased urinary antispasmodic use as shown in Table 6-5.

Table 6-5 Medications and Urinary Antispasmodic Use

Variable	n/N (with drug)	n/N (without drug)	Odds Ratio	95% CI	p-value
All CAs	26/297 (8.8%)	51.1251 (4.1%)	2.18	1.32 to 3.61	0.0022
Imipramine	3/10 (30%)	74/1538 (4.8%)	9.57	2.35 to 38.98	0.0016
Venlafaxine	11/90 (12.2%)	66/1458 (4.5%)	2.66	1.33 to 5.33	0.0059

After excluding nifedipine from the regression analysis for individual CAs, lercanidipine and diltiazem were significantly associated with greater urinary antispasmodic use. (Table 6-6)

Table 6-6 CA and Urinary Antispasmodic Use

Variable	n/N (with drug)	n/N (without drug)	Odds Ratio	95% CI	p-value
Amlodipine	10/136 (7.4%)	67/1412 (4.8%)	1.49	0.73 to 3.04	0.2744
Felodipine	4/37 (10.8%)	73/1511 (4.8%)	2.50	0.82 to 7.65	0.1078
Lercanidipine	8/55 (14.6%)	69/1493 (4.6%)	3.41	1.51 to 7.73	0.0033
Diltiazem	6/41 (14.6%)	71/1507 (4.7%)	3.33	1.32 to 8.38	0.0108
Verapamil	1/27 (3.7%)	76/1521 (5.0%)	0.67	0.08 to 5.46	0.7064

6.3.5.1 CAs and Oxybutynin use

Oxybutynin use was significantly higher amongst CA users. Atorvastatin again emerged as one of the most significant drugs associated with oxybutynin use. Other drugs which demonstrated statistically significant association are shown in Table 6-7.

Table 6-7 Medications and Oxybutynin Use

Variable	n/N (with drug)	n/N (without drug)	Odds Ratio	95% CI	p-value
All CAs	18/297 (6.1%)	36/1251 (2.9%)	2.17	1.20 to 3.93	0.0108
Atorvastatin	13/288 (5.7%)	41/1320 (3.1%)	1.95	1.01 to 3.78	0.0476
Baclofen	4/22 (18.2%)	50/1526 (3.3%)	4.09	1.11 to 15.08	0.0341
Digoxin	11/150 (7.3%)	43/1398 (3.1%)	2.96	1.45 to 6.05	0.0029
Imipramine	2/10 (20.0%)	52/1538 (3.4%)	5.35	1.03 to 27.83	0.0460

None of the residents on nifedipine, diltiazem, or verapamil were using oxybutynin and were not included for further analysis. Felodipine and lercanidipine were associated with a statistically significant increased prevalence of oxybutyinin use as shown in Table 6-8.

Table 6-8 CAs and Oxybutynin Use

Variable	n/N (with drug)	n/N (without drug)	Odds Ratio	95% CI	p-value
Amlodipine	7/136 (5.2%)	47/1412 (3.3%)	1.58	0.68 to 3.65	0.2897
Felodipine	4/37 (10.8%)	50/1511 (3.3%)	3.92	1.27 to 12.10	0.0175
Lercanidipine	5/55 (9.1%)	49/1493 (3.3%)	3.32	1.23 to 8.96	0.0175

6.4 Discussion

The high average age of the subjects was expected in RACF settings, where the majority of residents are elderly. As expected, the average number of medications used by residents was also high. This could be attributed to the high average age of the residents and associated changes to disability level of the residents. This could also be attributed to the high prevalence of medical conditions amongst the elderly and that such conditions often require multi-medication treatment as in the case of diabetes and cardiovascular disease. Previous studies have shown high medication use amongst RACF residents (average 5-7 medications/resident), however the number of medications used appeared to be higher than what had been previously reported.(137-139) This could be because the data received from Manrex Pty Ltd included all medications dispensed and we subsequently used the entire database including non-prescription medications in the study. Our data also listed individually the record of dispensing of all PRN medications and topically administered dermatological medications.

Our previous estimation for CA use in the general Australian population was 1 in every 10-12 Australians. This estimation appears to be inconsistent in some patient settings and age groups. In our Royal Perth Hospital study the ratio was 1 in 3 patients and the

number was again higher than the general population estimate in this study (1 in 5). Such a high prevalence of use of CAs was expected in elderly patients, because of their increased risk of cardiovascular disease and the associated increased need for medication use.

In line with our previous findings, results from this study confirmed the significant association between CA use and alpha blocker use. Amlodipine appeared to be the drug with the most significant association in this study as well, while lercanidipine was still the one with the least statistical association. Similar results were produced again for prazosin with highly statistically significant odds ratios.

LUTS have been reported as side effects of dothiepin, gabapentin, indapamide, and some antiepileptic drugs. Therefore, the significant association with increased alpha blockers use could be explained. The manufacturer's information for all HMG-CoA reductase inhibitors and ATRBs does not include any mention of LUTS amongst their adverse effects.

Urinary antispasmodic use was also found to be higher amongst CA users. Nonetheless, the only lercanidipine and diltiazem use was shown to have a statistically significant association. The association between lercanidipine and urinary antispasmodic was consistent with previous findings from the medical inpatients study. It is still not clear if this association is a direct association. It could be because lercanidipine has a minimal effect on the bladder, thus it does not treat the pre-existing overactive bladder.

Further analysis for oxybutynin use also showed a significant association between CA use and the use of oxybutynin. The results were consistent with our previous results for medical inpatients at Royal Perth Hospital where there was increased oxybutynin use amongst felodipine and lercanidipine users. Again, it is postulated that this is might be due to these agents lack of effect on the bladder, rather than a true adverse effects; i.e. their failure to reduce the symptoms overactive bladder.

The manufacturer's information for baclofen, digoxin, imipramine, and venlafaxine includes LUTS as a possible adverse effect of each of the drugs. However, no such information is available for HMG-CoA reductase inhibitors or ATRBs. Our extensive literature search failed to identify any possible explanation for the association between HMG-COA reductase inhibitors and LUTS, but one could postulate that it may be associated with some form of myopathy.

A paper published in the Bulgarian Journal of Veterinary Medicine discussed the potential interest in the role of angiotensin II in bladder contraction and the potential use for understanding and treating micturition disorders.(140) The interest was based on the *in vitro* evidence of a dose dependent bladder contractions induced by angiotensin II in rats, which are inhibited by losartan.

We contacted the Australian ADRAC to obtain any available reports for a possible association between LUTS and HMG-CoA reductase inhibitors and ATRBs. The ADRAC have thankfully provided us with all available reports. There were 28 reports (of 1924 reports; 1.46%) for ATRBs and 89 reports (of 6819 reports; 1.31%) for HMG-CoA reductase inhibitors; summary shown in Table 6-9. A number of these reports for both ATRBs and HMG-CoA reductase inhibitors involved drugs form each class as the sole agents.

Table 6-9 ADRAC Reports Summary: ATRBs and HMG-CoA Reductase Inhibitors with LUTS

Urinary Disorder	Angiotensin Two Receptor Blockers	HMG-CoA Reductase Inhibitors
Urinary tract disorder	1	1
Dysuria	1	11
Micturition disorder	3	6
Micturition urgency	0	2
Pollakiuria	8	24
Urinary incontinence	5	16
Urinary retention	2	6
Urinary flow decreased	1	1
Nocturia	1	15
Polyuria	6	7
Total	**28**	**89**
Total Reports	**1924**	**6819**

This study has some limitations. The large number of residents with missing gender prevented us from doing a gender specific analysis. Moreover, the high mean age of the residents may have increased the prevalence of LUTS amongst them, as may have their underlying medical conditions and their management.

6.5 Conclusions

Findings of this study add to the evidence of the possible association between CAs and LUTS. The study provided further evidence for the obstructive LUTS and amlodipine,

while it did not confirm previous findings for nifedipine and other non-DHP CAs. Lercandipine and felodipine were associated with increased oxybutynin use and possible urinary incontinence. Nevertheless, the causality could not be established.

This study revealed a number of drugs that may be associated with the use of agents to treat urinary symptoms. Amongst these the possible association of HMG-CoA reductase inhibitors and ATRBs were not expected based on their known mode of action and further studies are required to confirm this association and underlying mechanism.

Chapter 7

7 General Discussion, Conclusions, and Recommendations

7.1 General Discussion

The impact of CAs on LUTS appears to be higher than previously anticipated. The study of LUTS in hospitalised patients provided an estimate of the severity of LUTS amongst CA-users. It was clear that the association is significant and as is the associated deterioration in QoL. Despite showing a statistically significant deterioration of QoL that correlates with worsening LUTS, females appeared to have higher tendency to report their dissatisfaction with their LUTS. Many males, on the other hand, showed some acceptance of LUTS as a part of getting old. This finding could help in explaining the increased reporting LUTS amongst female CA users in the ACSOM database.

After examining the consequences of CA use on the patients, all the studies, except the first one (in which the necessary data to show the association was not available), have shown an increased risk of being on a treatment for LUTS while using CAs. The second and the third studies also showed an increased risk of having urogenital surgeries/procedures while using CAs.

The second study for hospitalised medical inpatients revealed some evidence of an interclass difference between CAs. Highly vascular selective CAs emerged as a safer option as they are likely to cause less/no obstructive symptoms. Amongst the two drugs, felodipine and lercanidipine, the evidence from our studies were to some extent consistent for lercanidipine. It was the drug with the lowest number of reports in ADRAC and the findings from the nursing home study have confirmed that results. Conversely, the prescription sequence symmetry analysis showed a strong signal of an association between lercanidipine and obstructive LUTS. The evidence for the association of felodipine, however, was inconsistent.

In spite of the possible role of the highly vascular selective CAs as a safer alternative for patients at risk of developing obstructive LUTS, the studies revealed a signal of their association with urinary incontinence. The use of oxybutynin was higher amongst patients on highly vascular selective CAs, but the association needs to be further

investigated to identify if it is a true association (a side effect) or indirect association (other CAs prevent incontinence by their action on bladder and lercanidipine/felodipine do not). If proven as an indirect association, this finding would assist in setting guidelines for which CAs to consider as a potential treatment for overactive bladder and explain the conflicting results produced by previous studies.

The ADRAC data provided evidence that cessation of CAs is generally associated with resolution of patients' LUTS. A rapid recovery would be predicted on the basis of the fact that the majority of CAs have short half-lives (2-8 hours), amlodipine being the exception (35-50 hours).

7.2 Conclusions

There was a high prevalence of LUTS in both males and females, with more males suffering from severe symptoms. Our results have revealed a strong association between the use of CAs and LUTS. This association does not appear to be a class effect.

The results have also shown that CA-users are more likely to suffer from moderate and severe LUTS, and they are more likely to be on a treatment for LUTS and/or to have undergone urogenital procedures (consequences of LUTS).

CA use was associated with a significant deterioration of urological QoL. This deterioration was correlated with increased IPSS. Although there were more males with severe symptoms, they have lower tendency to report their dissatisfaction, which could contribute to a possible underreporting in adverse drug reaction databases.

Theoretical evidence on the reversibility of LUTS after medication discontinuation and evidence from ADRAC and the patient case study, all suggest that the symptoms could be reversible.

7.3 Recommendations

It is important to educate doctors, pharmacists, and other healthcare professionals about the possible association between CA use and LUTS. Amongst CA users who develop LUTS, it would be valuable to consider them as a potential cause of LUTS and where possible consider a trial of withdrawing the CA to assess whether symptoms improve. A monitoring program for all CA users to assess their LUTS may help to prevent unnecessary investigations and treatment of their symptoms.

A prospective randomised control trial is needed to confirm the association between CA use and LUTS. The study could look at patients commencing CA and monitor the development of symptoms over time. Another easier way of investigating the association would be by simple discontinuation of CAs in symptomatic patients and to monitor the improvement of the symptoms.

Possible benefits of using CAs to treat overactive bladder may still exist. Future studies looking at such benefits should take in consideration the possible interclass difference and the tissue selectivity factors.

Further prospective studies are required to confirm and quantify the presence of an association between LUTS and HMG-CoA reductase inhibitors, ATRBs, and/or other drugs that are suspected to have an association with LUTS. The mechanism behind that association is yet to be investigated for some these drugs like HMG-CoA reductase inhibitors and ATRBs.

8 References

1. Chapple CR, Wein AJ, Abrams P, Dmochowski RR, Giuliano F, Kaplan SA, et al. Lower Urinary Tract Symptoms Revisited: A Broader Clinical Perspective. Eur Urol. 2008.

2. Walsh K, Stone AR. How is the lower urinary tract affected by gynaecological surgery? BJU Int. 2004;94(3):272-5.

3. Tewari A, Narayan P. Voiding dysfunction in men with lower urinary tract symptoms and benign prostatic hyperplasia. In: Unyime O. Nseyo, Edward Weinman, Lamm DL, editors. Urology for primary care physicians: W.B. Saunders; 1999. p. 197-207.

4. Martini F. Fundamentals of Anatomy and Physiology. fourth ed. New Jersey: Prentice Hall International; 1998.

5. Jacob S. Human Anatomy: A Clinically-Oriented Approach. Philadelphia: Elsevier Health Sciences; 2007.

6. McCorry LK. Essentials of Human Physiology for Pharmacy. Second ed. London: CRC Press; 2009.

7. Andersson K-E, Arner A. Urinary Bladder Contraction and Relaxation: Physiology and Pathophysiology. Physiol Rev. 2004 July 1, 2004;84(3):935-86.

8. Damaser MS, Kim K-B, Longhurst PA, Wein AJ, Levin RM. Calcium Regulation of Urinary Bladder Function. J Urol. 1997;157(2):732-8.

9. Nakayama S, Brading AF. Evidence for multiple open states of the Ca2+ channels in smooth muscle cells isolated from the guinea-pig detrusor. J Physiol. 1993 November 1, 1993;471(1):87-105.

10. Wiggins SA, Griebling T, Walling A. Urinary Incontinence. Kansas: University of Kansas; 2009 [updated March 20, 2009]; Available from: http://www2.kumc.edu/coa/Education/AMED900/UrinaryIncon.htm.

11. Hegde SS, Eglen RM. Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. Life Sci. 1999;64(6-7):419-28.

12. Ouslander JG. Management of overactive bladder. N Engl J Med. 2004 Feb 19;350(8):786-99.

13. Doughty DB. Urinary & fecal incontinence: current management concepts. Third ed. St. Louis: Elsevier Health Sciences; 2006.

14. Anderson KE. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev. 1993 Sep;45(3):253-308.

15. Goepel M, Wittmann A, Rübben H, Michel MC. Comparison of adrenoceptor subtype expression in porcine and human bladder and prostate. Urol Res. 1997;25(3):199-206.

16. Caine M. The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. J Urol. 1986 Jul;136(1):1-4.

17. Barry A OR, Alan H K, Gillian F K, Thomas K C, Anthony P.D.W F, Janice M R, et al. P2X receptors and their role in female idiopathic detrusor instability. J Urol. 2002;167(1):157-64.

18. Masters JG, Neal DE, Gillespie JI. The contribution of intracellular Ca2+release to contraction in human bladder smooth muscle. Br J Pharmacol. 1999;127(4):996-1002.

19. Godfraind T, Ertel E. Calcium Channel Blockers. Berlin: Birkhäuser; 2004.

20. Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol. 2003;4(7):517-29.

21. Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. International Union of Pharmacology. XLVIII. Nomenclature and Structure-Function Relationships of Voltage-Gated Calcium Channels. Pharmacol Rev. 2005 December 1, 2005;57(4):411-25.

22. Norman RW, Nickel JC, Fish D, Pickett SN. 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. Br J Urol. 1994 Nov;74(5):542-50.

23. Araki I, Zakoji H, Komuro M, Furuya Y, Fukasawa M, Takihana Y, et al. Lower Urinary Tract Symptoms in Men and Women Without Underlying Disease Causing Micturition Disorder: A Cross-Sectional Study Assessing the Natural History of Bladder Function. J Urol. 2003;170(5):1901-4.

24. Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs FDR, Fourcade R, et al. The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. BJU Int. 2003;92(4):409-14.

25. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006;50(6):1306-15.

26. Irwin DE, Milsom I, Kopp Z, Abrams P, Artibani W, Herschorn S. Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. Eur Urol. 2009 Jul;56(1):14-20.

27. Homma Y, Kawabe K, Tsukamoto T, Yamanaka H, Okada K, Okajima E, et al. Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. Int J Urol. 1997;4(1):40-6.

28. Pinnock CB, Marshall VR. Troublesome lower urinary tract symptoms in the community: a prevalence study. Med J Aust. 1997;167(2):72-5.

29. Guess HA, Chute CG, Garraway WM, Girman CJ, Panser LA, Lee RJ, et al. Similar levels of urological symptoms have similar impact on Scottish and American men--although Scots report less symptoms. J Urol. 1993 Nov;150(5 Pt 2):1701-5.

30. Terai AA, Matsui YY, Ichioka KK, Ohara HH, Terada NN, Yoshimura KK. Comparative analysis of lower urinary tract symptoms and bother in both sexes. Urology. 2004;63(3):487-91.

31. Hankey GJ. Stroke: your question answered. Second ed. Edinburgh: Elsevier; 2007.

32. Tibaek S, Gard G, Klarskov P, Iversen HK, Dehlendorff C, Jensen R. Prevalence of lower urinary tract symptoms (LUTS) in stroke patients: a cross-sectional, clinical survey. Neurourol Urodyn. 2008;27(8):763-71.

33. Ramsey EW. Benign prostatic hyperplasia: a review. Can J Urol. 2000 Dec;7(6):1135-43.

34. Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of transurethral resection of the prostate (TURP)--incidence, management, and prevention. Eur Urol. 2006 Nov;50(5):969-79; discussion 80.

35. Bauer RM, Bastian PJ, Gozzi C, Stief CG. Postprostatectomy Incontinence: All About Diagnosis and Management. Eur Urol. 2009;55(2):322-33.

36. Sekido N, Kawai K, Akaza H. Lower urinary tract dysfunction as persistent complication of radical hysterectomy. Int J Urol. 1997 May;4(3):259-64.

37. Rortveit G, Daltveit AK, Hannestad YS, Hunskaar S, the Norwegian Epincont Study. Urinary Incontinence after Vaginal Delivery or Cesarean Section. N Engl J Med. 2003 March 6, 2003;348(10):900-7.

38. Berger D, Bientzle M, Müller A. Postoperative complications after laparoscopic incisional hernia repair. Surg Endosc. 2002;16(12):1720-3.

39. Gianetta E, Cian FD, Cuneo S, Friedman D, Vitale B, Marinari G, et al. Hernia repair in elderly patients. Br J Surg. 1997;84(7):983-5.

40. Brewster S, Cranston D, Noble J, Reynard J. Urology: A handbook for medical students. London: Informa Health Care; 2001.

41. Takamichi Hattori KYKKKH. Voiding Dysfunction in Parkinson's Disease. Psychiatry Clin Neurosci. 1992;46(1):181-6.

42. Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry. 2000;68(4):429.

43. Simon R. Hill AMFGRJ. Diabetes mellitus and female lower urinary tract symptoms: A review. Neurourol Urodyn. 2008;27(5):362-7.

44. Kathleen FH, Katherine NM. Diabetes-associated bladder dysfunction in the older adult. Geriatr Nurs. 2003;24(3):138-45.

45. Lee W-C, Wu H-P, Tai T-Y, Liu S-P, Chen J, Yu H-J. Effects of diabetes on female voiding behavior. J Urol. 2004;172(3):989-92.

46. Brown JS, Wessells H, Chancellor MB, Howards SS, Stamm WE, Stapleton AE, et al. Urologic Complications of Diabetes. Diabetes Care. 2005 January 1, 2005;28(1):177-85.

47. Van Den Eeden SK, Sarma AV, Rutledge BN, Cleary PA, Kusek JW, Nyberg LM, et al. The Effect of Intensive Glycemic Control and Diabetic Complications on Lower Urinary Tract Symptoms (LUTS) in Men with Type 1 Diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care. 2009 Jan 26;26:26.

48. Prezioso D, Catuogno C, Galassi P, D'Andrea G, Castello G, Pirritano D. Life-Style in Patients with LUTS Suggestive of BPH. Eur Urol. 2001;40(Suppl. 1):9-12.

49. Arnfinn Seim CHTلLV. The prevalence and correlates of urinary tract symptoms in Norwegian men: The HUNT Study. BJU Int. 2005;96(1):88-92.

50. Brown CT, Emberton M. Could self-management challenge pharmacotherapy as a long-term treatment for uncomplicated lower urinary tract symptoms? Curr Opin Urol. 2004;14(1):7-12.

51. Schmidbauer J, Temml C, Schatzl G, Haidinger G, Madersbacher S. Risk Factors for Urinary Incontinence in Both Sexes. Eur Urol. 2001;39(5):565-70.

52. Nseyo ON, Weinman E, Lamm DL. Urology for Primary Care Physicians: W.B. Saunders Company; 1999.

53. Drake MJ, Nixon PM, Crew JP. Drug-induced bladder and urinary disorders. Incidence, prevention and management. Drug Saf. 1998;19(1):45-55.

54. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med. 2000 September 1, 2000;93(9):457-62.

55. Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry. 1992 Oct;149(10):1393-4.

56. Stallard S, Prescott S. Postoperative urinary retention in general surgical patients. Br J Surg. 1988 Nov;75(11):1141-3.

57. Petersen TK, Husted SE, Rybro L, Schurizek BA, Wernberg M. Urinary retention during i.m. and extradural morphine analgesia. Br J Anaesth. 1982 Nov;54(11):1175-8.

58. Tsakiris P, Oelke M, Michel MC. Drug-Induced Urinary Incontinence. Drugs Aging. 2008;25(7):541-9.

59. Diokno AC, Brown MB, Herzog AR. Relationship between use of diuretics and continence status in the elderly. Urology. 1991 Jul;38(1):39-42.

60. Marshall HJ, Beevers DG. Alpha-adrenergic blockade and urinary incontinence. J Hypertens. 1993;11(10):1152-3.

61. Ambrosini PJ. A pharmacological paradigm for urinary incontinence and enuresis. J Clin Psychopharmacol. 1984 Oct;4(5):247-53.

62. Van Putten T, Malkin MD, Weiss MS. Phenothiazine-induced stress incontinence. J Urol. 1973 Apr;109(4):625-6.

63. Landi F, Cesari M, Russo A, Onder G, Sgadari A, Bernabei R. Benzodiazepines and the risk of urinary incontinence in frail older persons living in the community. Clin Pharmacol Ther. 2002 Dec;72(6):729-34.

64. PBS. Australian Statistics on Medicines. Draft Report: Department of Health and Ageing2007.

65. Catterall WA, Striessnig J, Snutch TP, Perez-Reyes E. International Union of Pharmacology. XL. Compendium of voltage-gated ion channels: calcium channels. Pharmacol Rev. 2003 Dec;55(4):579-81.

66. Hughes J, Lockhart J, Joyce A. Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? Br J Clin Pharmacol. 2007;64(1):83-9.

67. Harari D, Gurwitz JH, Minaker KL. Constipation in the elderly. J Am Geriatr Soc. 1993;41:1130-40.

68. Geyskes GG, Van Schaik BA, Gaillard CA, Koomans HA. The diuretic effect of calcium entry blockade in normals and hypertensive patients. Tohoku J Exp Med. 1992 Jan;166(1):135-46.

69. Krusell LR, Jespersen LT, Schmitz A, Thomsen K, Pedersen OL. Repetitive natriuresis and blood pressure. Long-term calcium entry blockade with isradipine. Hypertension. 1987 Dec;10(6):577-81.

70. Sluiter HE, Huysmans FTM, Thien TA, van Lier HJJ, Koene RAP. Hemodynamic, hormonal, and diuretic effects of felodipine in healthy normotensive volunteers. Drugs. 1985;29(Suppl 2):26-35.

71. Krishna GG, Riley LJ, Jr., Deuter G, Kapoor SC, Narins RG. Natriuretic effect of calcium-channel blockers in hypertensives. Am J Kidney Dis. 1991 Nov;18(5):566-72.

72. Dietz JRPD, Davis JOPDMD, Freeman RHPD, Villarreal DMD, Echtenkamp SFPD. Effects of Intrarenal Infusion of Calcium Entry Blockers In Anesthetized Dogs. [Article]. Hypertension July/August. 1983;5(4):482-8.

73. Antonelli D, Koltun B. Excessive nifedipine diuretic effect. Br Med J. 1984;288(Mar 10).

74. Bauer JH, Reams G. Short- and long-term effects of calcium entry blockers on the kidney. Am J Cardiol. 1987 Jan 23;59(2):66A-71A.

75. Young MA, Watson RDS, Stallard TJ, Littler WA. Calcium channel blockers--are they diuretics? Br J Clin Pharmacol. 1985;20(Suppl 1).

76. Vetrovec GW. Hemodynamic and electrophysiologic effects of first- and second-generation calcium antagonists. Am J Cardiol. 1994 Jan 27;73(3):34A-8A.

77. Saito M, Kondo A. Effects of verapamil on bladder instability induced by partial outflow obstruction in rat. Int Urol Nephrol. 1998;30(5):543-52.

78. Andersson K-E, Fovaeus M, Morgan E, McLorie G. Comparative effects of five different calcium channel blockers on the atropine-resistant contraction in electrically stimulated rabbit urinary bladder. Neurourol Urodyn. 1986;5(6):579-86.

79. Badaw JK, Langbein S. Selective beta-adrenoceptor agonists, calcium antagonists and potassium channel openers as a possible medical treatment of the overactive bladder and urge incontinence. Pharmazie. 2006;61(3):175-8.

80. Badawi J, Li H, Langbein S, Kwon S-T, Kamp S, Bross S. Inhibitory effects of L- and T-type calcium antagonists on contractions of human detrusor muscle. Eur J Clin Pharmacol. 2006;62(5):347-54.

81. Faustini S, Salvini A, Pizzi P, Conti M, Magistretti MJ, Vescovini R. Experimental study on the action of diltiazem on detrusor muscle and clinical evaluation in patients with detrusor hyperactivity. Arzneimittelforschung. 1989 Aug;39(8):899-903.

82. Hamada K, Sasaki Y, Taniguchi N, Fukui H, Miyatsuka Y, Kimura Y, et al. Anticholinergic and calcium antagonistic activities of NS-21 contribute to the inhibition of rat urinary bladder contractions. Gen Pharmacol. 1997 Nov;29(5):771-8.

83. Hassouna M, Nishizawa O, Miyagawa I, Toguri A, Gotoh M, Elhilali M. Role of calcium ion antagonists of the bladder detrusor muscle: in vitro and in vivo study. J Urol. 1986 Jun;135(6):1327-31.

84. Hughes JD. Nifedipine and urinary retention. Aust J Hosp Pharm. 1991;21(Feb):45-6.

85. Mattiasson A, Ekstrom B, Andersson KE. Effects of intravesical instillation of verapamil in patients with detrusor hyperactivity. J Urol. 1989 Jan;141(1):174-7.

86. Parmley WW. New calcium antagonists: Relevance of vasoselectivity. Am Heart J. 1990;120(6, Part 1):1408-13.

87. Ljung B. Vascular selectivity of felodipine: experimental pharmacology. J Cardiovasc Pharmacol. 1990;15 Suppl 4(4):S11-6.

88. Thomas P, Sheridan DJ. Vascular selectivity of felodipine: clinical experience. J Cardiovasc Pharmacol. 1990;15 Suppl 4(4):S17-20.

89. Godfraind T, Salomone S, Dessy C, Verhelst B, Dion R, Schoevaerts JC. Selectivity scale of calcium antagonists in the human cardiovascular system based on in vitro studies. J Cardiovasc Pharmacol. 1992;20(Suppl 5):S34-41.

90. Nordlander M, Abrahamsson T, Akerblom B, Thalen P. Vascular versus myocardial selectivity of dihydropyridine calcium antagonists as studied in vivo and in vitro. Pharmacol Toxicol. 1995 Jan;76(1):56-62.

91. Angelico P, Guarneri L, Leonardi A, Testa R. Vascular-selective Effect of Lercanidipine and other 1,4-Dihydropyridines in Isolated Rabbit Tissues. J Pharm Pharmacol. 1999;51:709-14.

92. Guarneri L, Angelico P, Ibba M, Poggesi E, Taddei C, Leonardi A, et al. Pharmacological in vitro studies of the new 1,4-dihydropyridine calcium antagonist lercanidipine. Arzneimittelforschung. 1996 Jan;46(1):15-24.

93. Meredith PA. Lercanidipine: a novel lipophilic dihydropyridine calcium antagonist with long duration of action and high vascular selectivity. Expert Opin Investig Drugs. 1999;8(7):1043-62.

94. Li JH. Pharmacology of ZM244085: A Novel Bladder-Selective Dihydropyridine KATP Channel Activator. Cardiovasc Drug Rev. 1997;15(3):220-31.

95. Anonymous. New indications are predicted for calcium channel blockers. American Druggist. 1983;188(Aug).

96. Zar MA, Iravani MM, Luheshi GN. Effect of nifedipine on the contractile responses of the isolated rat bladder. J Urol. 1990 Apr;143(4):835-9.

97. Andersson, Appell, Cardozo, Chapple, Drutz, Finkbeiner, et al. The pharmacological treatment of urinary incontinence. BJU Int. 1999;84(9):923-47.

98. Edwards C. Management of urinary incontinence. Hosp Pharm Prac. 2000;10(Sep):264-6.

99. Holroyd-Leduc JM, Straus SE. Management of Urinary Incontinence in Women: Scientific Review. JAMA. 2004 February 25, 2004;291(8):986-95.

100. Naumann G, Koelbl H. Pharmacological Treatment of Urinary Incontinence. In: Becker H-D, Stenzl A, Wallwiener D, Zittel TT, editors. Urinary and Fecal Incontinence An Interdisciplinary Approach. 1st ed. Berlin, Heidelberg: Springer-Verlag Berlin Heidelberg; 2005. p. 176-80.

101. Srikrishna S, Robinson D, Cardozo L, Vella M. Management of overactive bladder syndrome. Postgrad Med J. 2007 July 1, 2007;83(981):481-6.

102. Drake MJ. Emerging drugs for treatment of overactive bladder and detrusor overactivity. Expert Opin Emerg Drugs. 2008;13(3):431-46.

103. Frohlich G, Burmeister S, Wiedemann A, Bulitta M. Intravesical instillation of trospium chloride, oxybutynin and verapamil for relaxation of the bladder detrusor muscle. A placebo controlled, randomized clinical test. Arzneimittelforschung. 1998 May;48(5):486-91.

104. Naglie G, Radomski SB, Brymer C, Mathiasen K, O'Rourke K, Tomlinson G. A randomized, double-blind, placebo controlled crossover trial of nimodipine in older persons with detrusor instability and urge incontinence. J Urol. 2002 Feb;167(2 Pt 1):586-90.

105. Liu HP, Chen GL, Liu P, Xu XP. Amlodipine alone or combined with terazosin improves lower urinary tract disorder in rat models of benign prostatic hyperplasia or detrusor instability: focus on detrusor overactivity. BJU Int. 2009 Dec;104(11):1752-7.

106. Liu H, Liu P, Mao G, Chen G, Wang B, Qin X, et al. Efficacy of combined amlodipine/terazosin therapy in male hypertensive patients with lower urinary tract symptoms: a randomized, double-blind clinical trial. Urology. 2009 Jul;74(1):130-6.

107. Baker EC, Hughes J. Calcium Antagonists and Acute Urinary Retension [B. Pharm (Hons)]. Perth: Curtin University of Technology; 2002.

108. Coles M, Hughes J. Use of Calcium Antagonists May Not Be Appropriate in Males Over 50 Years of Age with Medical Conditions that are Associated with Urinary Obstruction [M Pharm]. Perth: Curtin University of Technology; 2007.

109. Kakizaki HH, Matsuura SS, Mitsui TT, Ameda KK, Tanaka HH, Koyanagi TT. Questionnaire analysis on sex difference in lower urinary tract symptoms. Urology. 2002;59(1):58-62.

110. AUA Guideline on the management of benign prostatic hyperplasia: diagnosis and treatment recommendations. 2006 [cited 2008]; Available from: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chapt_1_appendix.pdf.

111. Ameda K, Sullivan MP, Bae RJ, Yalla SV. Urodynamic characterization of nonobstructive voiding dysfunction in symptomatic elderly men. J Urol. 1999;162(1):142-6.

112. Chancellor MB, Rivas DA, Keeley FX, Lotfi MA, Gomella LG. Similarity of the American Urological Association Symptom Index among men with benign prostate hyperplasia (BPH), urethral obstruction not due to BPH and detrusor hyperreflexia without outlet obstruction. Br J Urol. 1994;74(2):200-3.

113. Chai TC, Belville WD, McGuire EJ, Nyquist L. Specificity of the American Urological Association voiding symptom index: comparison of unselected and selected samples of both sexes. J Urol. 1993;150(5 Pt 2):1710-3.

114. Lepor H, Machi G. Comparison of AUA symptom index in unselected males and females between fifty-five and seventy-nine years of age. Urology. 1993;42(1):36-40.

115. Roberts RO, Jacobsen SJ, Jacobson DJ, Reilly WT, Talley NJ, Lieber MM. Natural history of prostatism: high American Urological Association Symptom scores among community-dwelling men and women with urinary incontinence. Urology. 1998;51(2):213-9.

116. Diokno AC, Brock BM, Brown MB, Herzog AR. Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalized elderly. J Urol. 1986;136(5):1022-5.

117. Terai A, Ueda N, Utsunomiya N, Kouhei N, Ichioka K, Yoshimura K. Effect of urinary incontinence on lower urinary tract symptoms in Japanese women. Urology. 2004;64(6):1139-43.

118. Donovan JL. Measuring the impact of nocturia on quality of life. BJU Int. 1999;84(Suppl.1):21-5.

119. Vandoninck V. The prevalence of urinary incontinence in community-dwelling married women: a matter of definition. BJU Int. 2004;94(9):1291.

120. 2006 Census QuickStat: Australia. In: Statistics ABo, editor. Canberra2007.

121. Schatzl G, Temml C, Waldmuller J, Thurridl T, Haidinger G, Madersbacher S. A comparative cross-sectional study of lower urinary tract symptoms in both sexes. Eur Urol. 2001 Aug;40(2):213-9.

122. Stenzelius K, Westergren A, Mattiasson A, Hallberg IR. Older women and men with urinary symptoms. Arch Gerontol Geriatr. 2006;43(2):249-65.

123. Lakatta EG. Age-associated cardiovascular changes in health: impact on cardiovascular disease in older persons. Heart Fail Rev. 2002 Jan;7(1):29-49.

124. Priebe HJ. The aged cardiovascular risk patient. Br J Anaesth. 2000 Nov;85(5):763-78.

125. Naslund MJ, Gilsenan AW, Midkiff KD, Bown A, Wolford ET, Wang J. Prevalence of lower urinary tract symptoms and prostate enlargement in the primary care setting. Int J Clin Pract. 2007;61(9):1437-45.

126. Chapple CR, Wein AJ, Abrams P, Dmochowski RR, Giuliano F, Kaplan SA, et al. Lower urinary tract symptoms revisited: a broader clinical perspective. Eur Urol. 2008 Sep;54(3):563-9.

127. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. Epidemiology. 1996 Sep;7(5):478-84.

128. Hallas J, Bytzer P. Screening for drug related dyspepsia: an analysis of prescription symmetry. Eur J Gastroenterol Hepatol. 1998 Jan;10(1):27-32.

129. Lindberg G, Hallas J. Cholesterol-lowering drugs and antidepressants--a study of prescription symmetry. Pharmacoepidemiol Drug Saf. 1998 Nov;7(6):399-402.

130. Bytzer P, Hallas J. Drug-induced symptoms of functional dyspepsia and nausea. A symmetry analysis of one million prescriptions. Aliment Pharmacol Ther. 2000 Nov;14(11):1479-84.

131. Hersom K, Neary MP, Levaux HP, Klaskala W, Strauss JS. Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. J Am Acad Dermatol. 2003 Sep;49(3):424-32.

132. Corrao G, Botteri E, Bagnardi V, Zambon A, Carobbio A, Falcone C, et al. Generating signals of drug-adverse effects from prescription databases and application to the risk of arrhythmia associated with antibacterials. Pharmacoepidemiol Drug Saf. 2005 Jan;14(1):31-40.

133. Hallas J. Drug utilization statistics for individual-level pharmacy dispensing data. Pharmacoepidemiol Drug Saf. 2005 Jul;14(7):455-63.

134. Tsiropoulos I, Andersen M, Hallas J. Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis. Pharmacoepidemiol Drug Saf. 2009 Jun;18(6):483-91.

135. Caughey GE, Roughead EE, Pratt N, Shakib S, Vitry AI, Gilbert AL. Increased risk of hip fracture in the elderly associated with prochlorperazine: is a prescribing cascade contributing? Pharmacoepidemiol Drug Saf. 2010 Sep;19(9):977-82.

136. Roughead EE, Ramsay EN, Pratt NL, Ryan P, Gilbert AL. Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia. Med J Aust. 2009 Feb 2;190(3):114-6.

137. Sloane PD, Zimmerman S, Brown LC, Ives TJ, Walsh JF. Inappropriate medication prescribing in residential care/assisted living facilities. J Am Geriatr Soc. 2002 Jun;50(6):1001-11.

138. Tjia J, Rothman MR, Kiely DK, Shaffer ML, Holmes HM, Sachs GA, et al. Daily medication use in nursing home residents with advanced dementia. J Am Geriatr Soc. 2010 May;58(5):880-8.

139. Snowdon J, Day S, Baker W. Audits of medication use in Sydney nursing homes. Age Ageing. 2006 Jul;35(4):403-8.

140. Ilieva GS, Tolekova AN, Sandeva RV, Trifonova KJ, Tsokeva ZI, Ganeva MG, et al. Role of transmembrane calcium current in angiotensin ii-mediated contraction of detrusor organ strips from rat urinary bladder. BJVM. 2008;11(2):89−94.

Appendices

Appendix 1: Medications Known to Cause LUTS

The list is obtained from Nseyo et al. Urology for Primary Care Physicians book (52)

Drug-Induced Bladder Overactivity

Drugs that cause urgency, frequency, and incontinence by inducing bladder overactivity are:

Anticholinesterase: Neostigmine

Beta adrenergic blockers: Atenolol, carvedilol, labetolol, metoprolol, oxprenolol, pindolol, and propranolol

Smooth muscle stimulants: Oxytocin, prostaglandins, and vasopressin

Ganglion stimulants: Nicotine

Opioid antagonists: Methadone

Parasympathomimetics: Bethanecol and carbachol

Others: Digoxin, frusemide, metoclopramide, metronidazole, testosterone, thioridazine, and sodium valproate

Drug-Induced Urinary Outlet Relaxation:

Drugs which are reported to cause urgency, frequency, and incontinence by inducing urinary outlet relaxation are:

Alpha adrenergic blockers: Methyldopa, clonidine, guanethidine, phenoxybenzamine, phentolamine, and prazosin

Beta adrenergic agonists: Isoproterenol and terbutaline

Smooth Muscle Relaxants: Diazepam

Striated muscle relaxants: Baclofen and dantrolene

Others: Bromocriptine, levodopa, lithium, phenothiazines, phenytoin, and progesterone

Brain's Higher Centres Inhibitors:

Obstructive symptoms and urinary retention can be caused by drugs that inhibits the higher centres in the brain.

Antiepileptic: Carbamazepine, clonazepam, narcotic analgesics, and phenytoin

Polysynaptic Inhibitors - Spinal Cord Level:

Baclofen is an example of drugs that can cause obstructive symptoms and urinary retention by acting on the spinal cord and acting as a polysynaptic inhibitor.

Bladder Level - Detrusor Inhibitors:

A number of drugs are known to cause detrusor muscle inhibition/relaxation and hence they cause obstructive symptoms and urinary retention.

Psychiatric drugs: Phenothiazines and tricyclic antidepressants

Antiparkinsonism drugs: Benztropine, biperidine, levodopa, and procyclidine

Skeletal muscle relaxants: Diazepam and oxybutynin

Others: Bromocriptine, theophylline, isoniazid, hydralazine, prostaglandin inhibitors, diuretics, beta adrenergic blockers, anticholinergics, antihistamines, and ganglion blockers

Bladder Outlet Level

The following drugs affect the bladder outlet and cause obstructive symptoms and urinary retention:

Alpha-adrenergic agonists, beta adrenergic blockers, amphetamines, levodopa, and imipramine

Appendix 2: RPH Study Protocol

Calcium Antagonist-Induced Lower Urinary Tract Symptoms Amongst Medical Patients

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Protocol Approval Signatures

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_____

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_____

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Study Approval / Acknowledgements

By signing this protocol, the Investigator(s) acknowledge and agree:

The protocol contains all necessary information for conducting the study. The investigator will conduct this study as detailed, in compliance with the applicable regulatory requirements.

Samantha Hilmi

_____

____/____/_____

Signature Date

Abstract

Background

Lower urinary tract symptoms (LUTS) and disorders are prevalent and bothersome in the rapidly growing ageing Australian population. Calcium antagonists (CA) are amongst a number of drugs that have been reported to cause LUTS. CA acts on the bladder by affecting the ability of the detrusor muscle to create enough contractile force to overcome obstruction to normal voiding. CA also can increase the production of urine and cause constipation through their muscle relaxation and anti-cholinergic activity. The contribution of CA to LUTS in male patients were investigated and confirmed by two studies conducted by Baker et al (10) and Coles et al (11) through the School of Pharmacy, Curtin University of Technology. However, there have been no studies to evaluate the relationship between CA and LUTS in females.

Objective

To determine the relationship between CA use and LUTS in medical inpatients (both males and females) aged 40 years or older.

Method

An observational study will be conducted involving patients aged 40 years or older admitted to two medical wards at Royal Perth Hospital. Patients will be invited to participate in the study after its aims and their involvement in the study have been explained to them. The target number of patients required to detect a difference of 13.75% in LUTS scores is 50 CA-users and 200 non-users. A standard questionnaire will be used to collect the following data: patient demographics, past medical history, current medications and history of LUTS. The International Prostate Symptoms Score (IPSS) and Benign Prostate Hyperplasia Impact Index (BII) will be used to assess the severity of symptoms and their impact on the patient's quality of life, respectively. The latter two questionnaires were both developed for males, but have

been validated for use with females. The two groups will be compared to evaluate the relationship between CA usage and LUTS. Adjustment will be made for natural progression of LUTS with age and the presence of other medical conditions and/or drugs known to contribute to LUTS. Pearson correlation, independent sample t-test and ANOVA will be used for the analysis of the data. Multivariate analysis will be undertaken to evaluate whether CA are likely to contribute to LUTS after correction for other risk factors.

Background

Lower urinary tract symptoms (LUTS) and disorders are prevalent and bothersome in the rapidly growing ageing Australian population. Patients may experience different lower urinary tract symptoms which can be classified as obstructive symptoms (e.g. urinary retention, nocturia and pollakiuria) and non obstructive symptoms (e.g. polyuria, dysuria).

Ageing is associated with structural and physiologic changes of the lower urinary tract. LUTS caused by benign prostatic hypertrophy (BPH) are highly prevalent in older men (1); however, the development of increased LUTS is not gender specific as women develop incontinence as a result of menopause. There are other factors that may lead to LUTS such as constipation and drugs. A number of drugs have been found to have an effect on bladder and the micturition process. One such group is the calcium antagonists (CA) where LUTS have been reported amongst their side effects. (2) CA also can increase the production of urine and cause constipation through their muscle relaxation and anti-cholinergic activity. (3)

There are three main chemical groups of CA available in Australia – phenylalkylamines (verapamil), benzothiazepines (diltiazem) and dihydropyridines (nifedipine, amlodipine, felodipine, lercanidipine). CA are one of the most frequently prescribed groups of drugs in Australia. In the year 2005 there were more than 9 million prescriptions for CA dispensed in Australia of which 2.6 millions were for amlodipine. (4) They are used in the treatment of a range of cardiovascular disorders including hypertension, atrial arrhythmias and angina pectoris. Their effects on the cardiovascular system include depression of mechanical contraction of myocardial and smooth muscle, and depression of both impulse formation (automaticity) and conduction velocity. The different pharmacological profiles for these agents are in part based on their ability to bind to different receptor sites at the calcium channel. Dihydropyridines are strong vasodilators acting via relaxation of vascular smooth muscle cells. They have little direct effect on myocardial contractility or SA/AV nodal conduction. The non-dihydropyridines (diltiazem and verapamil) have an increased effect on AV nodal conduction compared to that of the dihydropyridines

and although they also cause vasodilatation via relaxation of vascular smooth muscle, they are less potent vasodilators than the dihydropyridines.

The inhibition of calcium channels is not limited to vascular or cardiac muscles only, as other smooth muscles such as the bladder's destrusor muscle also depend on the rise of intracellular calcium to integrate contractions. Therefore, the blockage of calcium channel in the bladder may affect the ability of the detrusor muscle to create enough contractile force to overcome obstruction to normal voiding, in the same way CA may also suppress involuntary bladder contractions experienced with detrusor muscle instability. (5-9)

Two previous studies were conducted through the School of Pharmacy (10, 11), Curtin University of Technology to assess the relationship between CA use and LUTS in males. The first study by Baker et al (10) investigated the relation between CA use and acute urinary retention (AUR) in males aged over 60 years. The use of CA was found to be associated with a statistically significant increased risk of AUR where bladder disorders (OR=4.38) or Type II Diabetes Mellitus (OR=3.0) existed. CA were also found to significantly increase the risk of AUR when used in combination with tricyclic antidepressants (OR=6.5). Similar distribution of symptoms was found in the presence and absence of calcium antagonists. Further, it was found that males taking a CA were statistically more likely to be commenced on prazosin or for the dose of this drug to be increased. Outcomes including death post-discharge and AUR recurrences were also significantly more likely to occur where CA were used. The second study by Coles et al (11) involving 40 males aged above 45 years was undertaken to determine the influence of CA use on LUTS. Despite the small sample size of the study, it demonstrated that the use of CA may result in urinary obstruction causing a significant worsening of LUTS. The mean International Prostate Symptoms Score (IPSS) increased from 3.13 (95% CI 2.09-4.17) before commencement of CA to 9.82 (95% CI 7.83-11.80) after commencement. This increase remained significant even after adjustment for natural progression of LUTS with time, with the mean increase of IPSS being 5.85 (95% CI 4.09-7.72; $p< 0.001$). The mean quality of life (QOL) score changed significantly from 1.42 (95% CI 0.86-1.99) to 3.66 (95% CI 2.49-3.66) after commencement of CA. That shows a highly significant increase in the mean QOL score after commencement of CA (2.27; 95%

CI 1.40-3.15; p< 0.001) indicating a significant worsening in QOL. The changes in IPSS and QOL scores showed significant correlation (Pearson correlation coefficient = 0.595; p< 0.001) indicating the worsening of QOL was closely correlated with their worsening of LUTS after commencement of CA. Based on their findings Coles et al (11) recommended a LUTS monitoring program should be introduced for male patients above 45 years of age receiving CA.

A review of the reports and case studies forwarded to Australia's Adverse Drug Reactions Advisory Committee (ADRAC), from 1988 to December 2007, revealed 78 reports of calcium antagonists induced LUTS. The most interesting finding from the data was 56% of the reported cases involved females. Males are more likely to suffer from moderate to severe LUTS naturally. (1) Thus, the high reported female incidence may not necessary be a true reflection of LUTS prevalence, with potential for under reporting in males. The data also showed that approximately 17% males and 22% of females who had experienced these symptoms were below 50 years of age. This indicates the importance of including females in this study, as it is clear that the effect of CA on the bladder is not limited only to males. Furthermore, the data indicates that both males and females might experience symptoms at a younger age, so this study will involve patients from 40 years of age. Finally, the ADRAC data indicated that the symptoms are reversible in most of the cases follow drug withdrawal.

Aim

The aim of this study is to determine the relationship between CA use and LUTS in medical inpatients (both males and females) aged 40 years or older.

Significance

CA are a commonly prescribed group of drugs in Australia and around the world. Evidence from two previous studies suggests that LUTS associated with these drugs may be more common and severe than previously reported. (10,11) Given that LUTS associated with CA use are generally reversible, recognition of these agents' potential role in symptoms in both males and females may contribute a significant

reduction in unnecessary investigations and interventions, resulting in improved patient outcomes and reduced health care costs.

Research Method

This will be an observational study involving patients aged 40 years or older admitted to medical wards in Royal Perth Hospital.

1.1. **Sample**

All patients of either gender, aged 40 years and above, who are admitted to two medical wards during the study period will be invited to participate in the study after its objectives and design have been explained to them. The current admission pattern in the hospital indicates that the sample will be assured of including both males and females. Patients who agree to participate will be required to give written informed consent. Patients will be excluded from the study if they do not give consent, are unable to read and converse in English or are deemed to be too unwell by their doctor to do so. (Appendix 1 and 2)

In 2005 it is estimated that there was around 750,000 patients on CA in Australia (based on the number of prescriptions per year divided by 12 months).(4) This number represents 6-10% of Australians aged 40 years or older. Thus, the number of CA users and non-users admitted to the medical wards are not expected to be equal (i.e. less patients on CA) with an estimated allocation ratio of 1:10 or higher. However, the ratio could be smaller because the study will involve only hospitalised patients.

No study has been conducted to evaluate the relationship between CA use and LUTS in females. Therefore the sample size has been calculated based on the study by Baker et al (10) where only males studied. Based on this study, the estimated sample size required to detect a difference of at least 13.75% and produce a study power of 83% at 5% level of significance, is 50 CA-users and 200 non-users (Appendix 6). The estimated sample size may not represent the true prevalence as males experience more LUTS than females.(1) This number of CA-users is expected to be recruited over a period of 8-12 weeks.

1.2. Instrumentation

1.2.1. Demographic Questionnaire: This questionnaire will be used to collect general patient information including their current medical condition and past medical history, medical conditions or procedures which may have affected LUTS, and medications currently in use or which have been used up to 6 months prior to the time of admission to hospital.(11) This questionnaire will be completed by the investigator using information obtained from the patient's medical records and via patient interview. (Appendix 3)

1.2.2. International Prostate Symptoms Score (IPSS): The validated seven symptoms IPSS questionnaire will be used to assess patient's LUTS with increasing scores being associated with worsening of symptoms.(12) It also includes questions for assessing the QOL of the patients. Although the questionnaire was developed to evaluate prostate symptoms in men, it is a useful tool for detecting voiding symptoms in women.(1,13) This questionnaire will be completed by the investigator via patient interview. (Appendix 4 and question 1 in Appendix 5)

1.2.3. Benign Prostate Hyperplasia (BPH) Impact Index (BII): The American Urological Association (AUA) Benign Prostate Hyperplasia (BPH) Impact Index will be used with IPSS to assess the QOL of patients. (14) Although BII was constructed for assessing LUTS in men, it is considered valid for measuring disease specific QOL of women.(15) This questionnaire will be completed by the investigator via patient interview. (Appendix 5)

2. Data Collection and Analysis

This research will involve CA users and non-users who are admitted on to two medical wards with subsequent evaluation for the existence of LUTS. The two groups will be compared to identify the relationship between CA usage and LUTS. Adjustment will be made for natural progression of LUTS with age and the presence of other medical conditions and/or drugs known to contribute to LUTS.

After completion of the data collection process a statistical analysis for each variable based on its frequencies will be undertaken. Pearson correlation will be used to identify the relationship between LUTS scores and other factors and precipitants, and independent sample t-tests and ANOVA will be also used in the analysis of the data. Multivariate analysis will be undertaken to evaluate whether CA are likely to contribute to LUTS after correction for other risk factors.

Ethical issues

All patients and their corresponding data will be assigned an alphanumeric code ensuring the de-identification of study data after completion of data collection. Further, all patient data will be grouped for the purpose of analysis to ensure the confidentiality of the participants.

Data Storage

During the study all data collection forms will be kept in a locked cupboard in the primary researcher's office. Electronic data will be password protected and the access will be limited to authorised personnel only. At the completion of the study all collected data and questionnaires will be stored in locked archive at the School of Pharmacy for a period of 5 years.

Facilities and Resources

The research will be carried out in Royal Perth Hospital medical wards. Office accommodation, computer, work desk, and all the support and miscellaneous items (e.g. printing) will be provided by the School of Pharmacy, Curtin University of Technology.

Budget

The budget will be minimal for the study as the data collection and analysis will be done by the primary researcher. Any expenses incurred (e.g. stationary, printing) will be contributed by the School of Pharmacy, Curtin University of Technology. These extra costs are expected to be minimal.

7. Time Schedule:

Month	Task
February – May 2008	Review the available literature Write the research proposal and submit candidacy
June – August 2008	Patient recruitment and data collection
September – November 2008	Data analysis
December 2008 – February 2009	Write the thesis

References

1. Terai AA, Matsui YY, Ichioka KK, Ohara HH, Terada NN, Yoshimura KK. Comparative analysis of lower urinary tract symptoms and bother in both sexes. Urology. 2004; 63: 487-91.
2. Tewari A, Narayan P. Voiding Dysfunction in Men with Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia. Urology for Primary Care Physicians. Philadelphia: W.B. Saunders Company; 1999: 197-207.
3. Harari D, Gurwitz JH, Minaker KL. Constipation in the elderly. J Am Geriatr Soc 1993; 41: 1130-40.
4. PBS. Australian Statistics on Medicines. Draft Report: Department of Health and Ageing; 2007.
5. Carl A, Lee HK, Sanders KM. Regulation of ion channels in smooth muscle by calcium. Am J Physiol Cell Physiol. 1996; 40: C9-C34.
6. Miljanich GP, Ramachandran J. Antagonists of Neuronal Calcium Channels: Structure, Function, and Therapeutic Implications. Annual Review of Pharmacology and Toxicology. 1995; 35:707-34.
7. Ehlert J, Rennolds S, Sawyer GW, Sawyer O. Subtypes of the Muscarinic Receptor in Smooth Muscle. Life Sciences 1997; 61: 1729- 40.
8. Masters JG, Neal DE, Gillespie JI. The contribution of intracellular Ca2+ release to contraction in human bladder smooth muscle. Brit J Pharmacol. 1999; 127: 996-1002.

9. Wu C, Fry CH. The rise of intracellular Ca2+ in human detrusor muscle via activation of muscarinic and purigenic receptors. Brit J Urol. 1996; 78(1):155.
10. Baker EC, Hughes J, James A. Calcium Antagonists and Acute Urinary Retention [B. Pharm (Hons)]. Perth: Curtin University of Technology; 2002.
11. Coles M, Hughes J. Use of Calcium Antagonists May Not Be Appropriate in Males Over 50 Years of Age with Medical Conditions that are Associated with Urinary Obstruction [M Pharm]. Perth: Curtin University of Technology; 2007.
12. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992; 148: 1549-57.
13. Password F, Yu. High prevalence of voiding symptoms in Taiwanese women. BJU Int. 1998; 82: 520.
14. Barry MJ, Williford WO, Chang Y, et al. Benign prostatic hyperplasia specific health status measures in clinical research: How much change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is perceptible to patients? J Uro. 1995; 154:1770-4.
15. Vandoninck V. The prevalence of urinary incontinence in community-dwelling married women: a matter of definition. BJU Int 2004; 94: 1291.

Appendix

Power and Sample Size Calculations

Based on a previous study conducted through the School of Pharmacy, Curtin University of Technology by Baker et al (1), to assess the relationship between calcium antagonists (CA) use and lower urinary tract symptoms (LUTS) in males. The study investigated the relationship between CA use and acute urinary retention (AUR) in males aged over 60 years. The use of CA was found to be associated with a statistically significant increased risk of AUR where bladder disorders (OR=4.38) or Type II Diabetes Mellitus (OR=3.0) existed. CA were also found to significantly increase the risk of AUR when used in combination with tricyclic antidepressants (OR=6.5).

The study also revealed that 18.75% of CA users experienced LUTS compared to 5% of non- users. This study was however conducted on male patients above the age of 60 years.

The proposed study will assess the impact of CA use on both males and females above the age of 40 years. In the absence of prior information regarding the percentage of bladder disorders in the CA and non-CA groups, the results of the previous study were used to calculate the sample size. The current admission pattern in the hospital will ensure that the sample collected will include both males and females.

In 2005 it was estimated that there were around 750,000 patients on CA in Australia (based on the number of prescriptions per year divided by 12 months). (4) This number represents 6-10% of the Australians aged 40 years or older. Thus, the number of CA users and non-users admitted to the medical wards are not expected to be equal (i.e. the number of patients on CA is less than the number of non-users) with an estimated allocation ratio of 1:10 or higher. However, the ratio could be smaller because the study will involve only hospitalised patients.

A sample size is made of 250 patients (50 CA-users and 200 non-CA- users) is required to detect a difference of 13.75 in LUTS score with a power of 83% power at 5% level of significance.

The sample sizes were calculated using Pass 2008 software (NCSS Statistical & Power Analysis Software, 329 North 1000 East, Kaysville, Utah, 84037, USA).

Reference:

Baker EC, Hughes J, James A. Calcium Antagonists and Acute Urinary Retention [B. Pharm (Hons)]. Perth: Curtin University of Technology; 2002.

Two Proportions Power Analysis

Numeric Results

Null Hypothesis: P1=P2 Alternative Hypothesis: P1<>P2.

			Allocation			Odds	
Power	**N1**	**N2**	**P1**	**P2**	**Ratio**	**Alpha**	**Beta**
0.82987	50	200	0.18750	0.05000	0.228	0.05000	0.17013
0.84838	50	250	0.18750	0.05000	0.228	0.05000	0.15162

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

Ni is the size of the sample drawn from the ith population.

Allocation Ratio is N2/N1 so that N2 = N1 x R.

Alpha is the probability of rejecting a true null hypothesis. It should be small.

Beta is the probability of accepting a false null hypothesis. It should be small.

P1 is the proportion for group one.

P2 is the proportion for group two under the alternative hypothesis.

Odds Ratio is [P2/(1-P2)] / [P1/(1-P1)].

Summary Statements

Group sample sizes of 50 and 200 achieve 83% power to detect a difference of 0.13750 between

the null hypothesis that both group proportions are 0.18750 and the alternative hypothesis that

the proportion in group 2 is 0.05000 using a two-sided Chi-square test without continuity

correction and with a significance level of 0.05000.

Two Proportions Power Analysis

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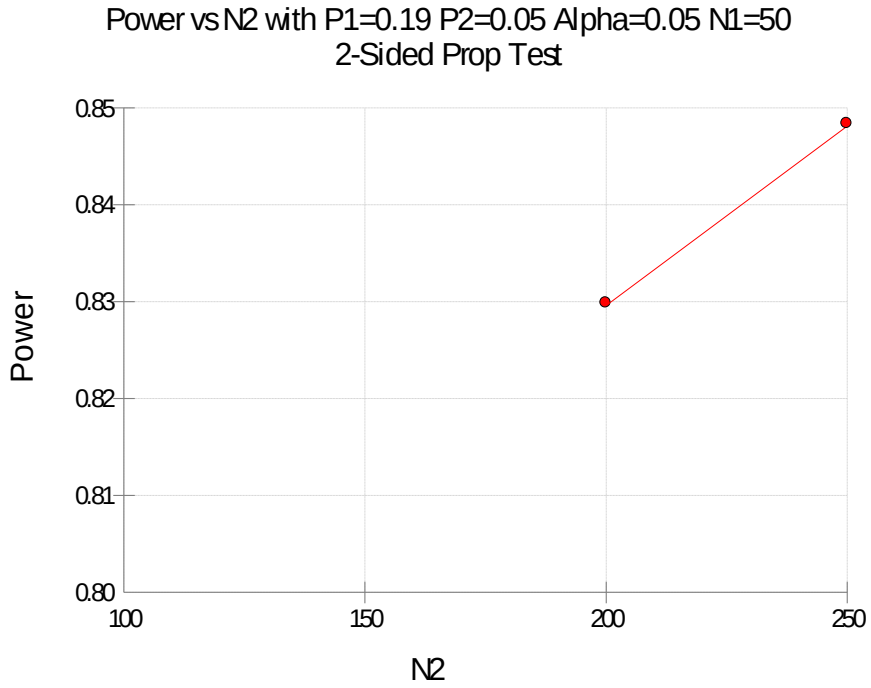
Chart Section



Appendix 3: Study Summary

Study Summary: Antagonist-Induced Lower Urinary Tract Symptoms amongst Medical Patients

Investigators

Ms Samantha Hilmi, Coordinator, Clinical Pharmacy services, Royal Perth Hospital (08 9224 2225)

Mr Elsamaul Elhebir, School of Pharmacy, Curtin University of Technology (0432399752)

A/Prof. Jeff Hughes, School of Pharmacy, Curtin University of Technology (08 9266 7367)

Background

Lower urinary tract symptoms (LUTS) and disorders are prevalent and bothersome in the rapidly growing ageing Australian population. Patients may experience different lower urinary tract symptoms which can be classified as obstructive symptoms (e.g. urinary retention, nocturia and pollakiuria) and non obstructive symptoms (e.g. polyuria, dysuria).

There are number of factors that may lead to LUTS such as benign prostatic hypertrophy, menopause, constipation and drugs. A number of drugs have been found to have an effect on bladder and the micturition process. One such group is the calcium antagonists (CA) also known as calcium channel blockers (CCB) where LUTS have been reported amongst their side effects. CA can affect the production of urine and cause constipation through their muscle relaxation and anti-cholinergic activity.

CA are one of the most frequently prescribed groups of drugs in Australia. In the year 2005 there were more than 9 million prescriptions for CA dispensed in Australia

of which 2.6 million were for amlodipine. The different pharmacological profiles for these agents are in part based on their ability to bind to different receptor sites at the calcium channel. The inhibition of calcium channels is not limited to vascular or cardiac muscles only, as other smooth muscles such as the bladder's destrusor muscle also depend on the rise of intracellular calcium to integrate contractions. Therefore, the blockage of calcium channel in the bladder may affect the ability of the detrusor muscle to create enough contractile force to overcome obstruction to normal voiding, in the same way CA may also suppress involuntary bladder contractions experienced with detrusor muscle instability.

Two previous studies were conducted through the School of Pharmacy, Curtin University of Technology to assess the relationship between CA use and LUTS in males. The first study by Baker et al investigated the relation between CA use and acute urinary retention (AUR) in males aged over 60 years. The use of CA was found to be associated with a statistically significant increased risk of AUR where bladder disorders (OR=4.38) or Type II Diabetes Mellitus (OR=3.0) existed. The second study by Coles et al involving 40 males aged above 45 years was undertaken to determine the influence of CA use on LUTS. Despite the small sample size of the study, it demonstrated that the use of CA may result in urinary obstruction causing a significant worsening of LUTS. The mean International Prostate Symptoms Score (IPSS) increased from 3.13 (95% CI 2.09-4.17) before commencement of CA to 9.82 (95% CI 7.83-11.80) after commencement. This increase remained significant even after adjustment for natural progression of LUTS with time, with the mean increase of IPSS being 5.85 (95% CI 4.09-7.72; $p< 0.001$). The mean quality of life (QOL) score changed significantly from 1.42 (95% CI 0.86-1.99) to 3.66 (95% CI 2.49-3.66) after commencement of CA.

A review of the reports and case studies forwarded to Australia's Adverse Drug Reactions Advisory Committee (ADRAC), from 1988 to December 2007, revealed 78 reports of calcium antagonists induced LUTS. The most interesting finding from the data was 56% of the reported cases involved females. Males are more likely to suffer from moderate to severe LUTS naturally. The ADRAC data also indicated that the symptoms are reversible in most of the cases follow drug withdrawal.

Aim

The aim of this study is to determine the relationship between CA use and LUTS in medical inpatients (both males and females) aged 40 years or older.

Research Method

This will be an observational study involving patients aged 40 years or older admitted to medical wards in Royal Perth Hospital.

1.1. **Sample**

All patients of either gender, aged 40 years and above, who are admitted to two medical wards during the study period will be invited to participate in the study after its objectives and design have been explained to them. Patients who agree to participate will be required to give written informed consent. Patients will be excluded from the study if they do not give consent, are unable to read and converse in English or are deemed to be too unwell by their doctor to do so.

No study has been conducted to evaluate the relationship between CA use and LUTS in females. Therefore the sample size has been calculated based on the study by Baker et al where only males studied. Based on this study, the estimated sample size required to detect a difference of at least 13.75% and produce a study power of 83% at 5% level of significance, is 50 CA-users and 200 non-users. The estimated sample size may not represent the true prevalence as males experience more LUTS than females. This number of CA-users is expected to be recruited over a period of 8-12 weeks.

1.2. Instrumentation

1.2.1. Demographic Questionnaire: This questionnaire will be used to collect general patient information including their current medical condition and past medical history, medical conditions or procedures which may have affected LUTS and medications currently in use or which have been used up to 6 months prior to the time of admission to hospital.

1.2.2. International Prostate Symptoms Score (IPSS): The validated seven symptoms IPSS questionnaire will be used to assess patient's

LUTS with increasing scores being associated with worsening of symptoms. It also includes questions for assessing the QOL of the patients. Although the questionnaire was developed to evaluate prostate symptoms in men, it is a useful tool for detecting voiding symptoms in women.

1.2.3. Benign Prostate Hyperplasia (BPH) Impact Index (BII): The American Urological Association (AUA) Benign Prostate Hyperplasia (BPH) Impact Index will be used with IPSS to assess the QOL of patients.(14) Although BII was constructed for assessing LUTS in men, it is considered valid for measuring disease specific QOL of women.

Feel free to contact the investigators for any further enquiries regarding the study

This study has been approved by Ethics Committees in both Royal Perth Hospital (EC LR.2008/125) and Curtin University of Technology (REG NO: 43/2008).

Appendix 4: Patient Information Sheet

Patient Information Sheet

Calcium Antagonist-Induced Lower Urinary Tract Symptoms amongst Medical Patients

Investigators

Ms Samantha Hilmi, Coordinator, Clinical Pharmacy services, Royal Perth Hospital (08 9224 2225)

Mr Elsamaul Elhebir, School of Pharmacy, Curtin University of Technology (0432399752)

A/Prof. Dr. Jeff Hughes, School of Pharmacy, Curtin University of Technology (08 9266 7367)

Why are we doing this study?

Lower urinary tract symptoms (LUTS) a significant problem for many ageing Australians. They include urinary retention (inability to pass urine), urinary hesitancy (difficulty in starting passing urine), nocturia (the need to pass urine during the night), urinary frequency (increased need to pass urine), polyuria (passing large volumes of urine) and dysuria (painful or difficult urination). These symptoms may be caused by a number of factors, including prostate enlargement, constipation, menopause and the use of some medications. One group of medications which may cause LUTS are the calcium antagonists (calcium channel blockers) which include nifedipine (Adalat), verapamil (Isoptin) and diltiazem (Cardizem).These medications are used to lower blood pressure, control the heart rhythm and treat angina.

In this study we want to determine if calcium antagonist use is associated with the development or worsening of LUTS in people aged 40 years or older.

This study has been approved by the ethics committees of both Royal Perth Hospital and Curtin University of Technology.

What you will be asked to do

If you agree to participate in the study you will be asked to do the following:

1. Complete a questionnaire that is designed to collect general information about you (age, gender, weight) and specific information about any lower urinary tract symptoms, your current and past health conditions and your current and past medication history. This should take about 10-15 minutes.

2. If necessary, approve the review of your medical record by the primary investigator to obtain additional information regarding your past medical history and medication histories.

You do not have to enter this study if you do not want to. If you decide against entering the study, you will be given the usual care and your future treatment will be unaffected. If you do agree to participate, you may withdraw from the study at any point without prejudice by contacting the investigators.

Side Effects and Risks

No direct risks are expected from participation in the study.

How your personal information will be handled

Special arrangements are in place to ensure that your data is handled in strict confidence and in compliance with all privacy laws (in Australia, this is the Privacy Act 1988). Your name will not appear on study documents and only duly authorised persons will have access to your data. Your name will not appear on any document or publication. Your identifiable data will be available for the researcher only during the data collection and will be 'coded' immediately after finishing the collection of data.

Cost of participation in the study

Participation in the study will be at no cost to you.

Further information

There are several sources of additional information:

1. Feel free to contact the investigators and ask any questions you like about the study (contact details above). During the study you can phone Elsamaul Elhebir during normal business hours (0432399752) if other questions occur to you.

2. For questions related to ethical approval, contact the Chairperson of the RPH Ethics Committee, Associate Professor Frank van Bockxmeer (9224 2244) or the Manager Research Ethics Curtin University of Technology on (08) 9266 2784.*"*

If after reading this information sheet you are interested in enrolling in the study you should now sign the CONSENT FORM.

Thank you for considering participating in this study.

Appendix 5: Consent Form

Consent Form

I,..... agree to participate in the above study. I have read and understood the patient information sheet and I have been given a copy of it. I have been given the opportunity to ask questions about the study. I understand that I may withdraw from the study at any time without affecting my future medical treatment, or the treatment of the condition which is the subject of the study.

I understand that the investigator and sponsor of the study will adhere to usual standards of confidentiality in the collection and handling of my personal information and that the standards of the Privacy Act 1988 will apply to the way my information is handled.

Signed..... Date.....

Signature of Investigator..... Date.....

Appendix 6: Demographic Questionnaire

To be completed via interview/ medical record by the investigator:

Patient's Label	**Date: ___/____/_____** **DD/MM/YYYY**
	Ward:_____
	Date of Admission: ___/____/_____ **DD/ MM/ YYYY**
Alphanumeric Code:	
Reason(s) for admission: _____ **_____**	

1. Have you any of the following medical conditions? (☒ appropriate box/s and fill if unavailable)

Stroke	☐	Congestive heart failure	☐
Parkinson's Disease	☐	Anterior spinal artery syndrome in thoracic aortic aneurysm	☐
Shy-Draper Syndrome	☐	Recurrent urinary tract infections	☐
Dementia	☐	Impaired mobility	☐
Spinal spondylosis	☐	Recurrent cough	☐
Spinal stenosis	☐	Respiratory acidosis	☐
Normal-pressure hydrocephalus	☐	Cor pulmonale	☐
Spinal cord injury (above T6)	☐	Tuberculosis of genitourinary tract	☐
Spinal cord injury (above L1)	☐	Herpes zoster – viral neuritis of sacral dermatoses	☐
Sacral Spinal cord injury	☐	Herpes zoster – viral prostatitis	☐
Multiple sclerosis	☐		☐
Diabetic autonomic cystopathy	☐		☐
Disc Disease	☐		☐
Alcoholism	☐		☐
	☐		☐

2. Have you had any surgical procedure before?

☐ **NO (go to question 3)**
☐ **Yes (Specify): _____**

_____

Are you taking any calcium antagonist (calcium channel blocker) ?

☐ **No (go to question 5)**
☐ **Yes (☒ the appropriate box/s)**
☐ **Nifedipine (Adalat, Nifecard)**
☐ **Lercanidipne (Zanidip)**
☐ **Felodipine (Plendil, Felodur, Agon)**
☐ **Amlodipine (Norvasc)**
☐ **Verapamil (Isoptin, Veracaps, Anpec, Cordilox)**
☐ **Diltiazem(Auscard, Cardizem, Cardizem CD, Chem mart Diltiazem, Coras, DBL Diltiazem Diltahexal, Diltiazem-BC, Dilzem, GenRxDiltiazem, Healthsense, Diltiazem SBPA Diltiazem, Terry White Chemists Diltiazem, Vasocardol CD)**

4. Medication History

A. Calcium Antagonists

Drug (Generic/Trade)	Strength	Dose	Reason/s for (select I to V as per note 1*)	Duration of use (select A-H as per note 2**)

*** Note 1: Reasons for taking calcium antagonists:**

I. Hypertension

High blood pressure

II. Angina

Pain in the chest, (may radiate down left ar,), Caused by lack of oxygen supply to heart muscles

III. Disorders of heart rhythm

Otherwise referred to as atrial fibrillation or supraventricular tachycardia - characterised by a fast, heavy heartbeat (palpitations), and variation in the rhythm of the heart (arrhythmia)

IV. Heart failure

Characterised by shortness of breath particularly with exercise, due to an inability of the heart to pump sufficient blood around the body (this differs to the shortness of breath associated with asthma or chronic obstructive airways disease).

V. Other reason/s

Please specify: _____

**** Note 2: Duration for calcium antagonist use:**

A. Just commencing
B. < 1 month
C. 1-3 months
D. 3-6 months
E. 6-12 months
F. 1-2 years
G. 2-5 years
H. > 5 years

5. Medications History

B. Other drugs (for the past 6 months)

(Including over the counter and alternative therapy medicines)

Drug (Generic/Trade)	Strength	Dose	Reason/s for Prescribing	Are you still taking?	Date Ceased DD/MM/YYYY
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	
				☐ Yes ☐ No	

6. Are there any medical conditions for which you are not taking medication? ***(Please list below)***

i. _____

ii. _____

iii. _____

The above section is to be answered only once

Appendix 7: International Prostate Symptom Score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month or so, how often have you had the sensation of not emptying your bladder completely after you have finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
2. Over the past month or so, how often have you had to urinate again less than two hours after you have finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	**0**	**1**	**2**	**3**	**4**	**5**
4. Over the past month or so, how often have you found it difficult to postpone urination?	**0**	**1**	**2**	**3**	**4**	**5**
5. Over the past month or so, how often have you had a weak urinary stream?	**0**	**1**	**2**	**3**	**4**	**5**
6. Over the past month or so, how often have you had to push or strain to begin urination?	**0**	**1**	**2**	**3**	**4**	**5**
7. Over the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	Once	Twice	3 times	4 times	5 times or more
	0	**1**	**2**	**3**	**4**	**5**

Appendix 8: QUALITY OF LIFE QUESTIONNAIRES

A. **IPSS Quality of Life Question:** If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	Delighted	Pleased	Mostly satisfied	Equally satisfied & dissatisfied	Mostly dissatisfied	Unhappy	Terrible
	0	**1**	**2**	**3**	**4**	**5**	**6**

B. **Benign Prostate Hyperplasia Impact Index (BII):**	None	Only a little	Some	A lot			
1. Over the past month, how much physical discomfort did any urinary problems cause you?	**0**	**1**	**2**	**3**			
2. Over the past month, how much did you worry about your health because of any urinary problems?	**0**	**1**	**2**	**3**			
3. Overall, how bothersome has any trouble with urination been during the past month?	Not bothersome at all	Bothersome a little	Bothersome some	Bothersome a lot			
	0	**1**	**2**	**3**			
4. Over the past month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?	None of the time	A little of the time	Some of the time	Most of the time	All the time		
	0	**1**	**2**	**3**	**4**		